Pohybové ústroji

Pokroky ve výzkumu, diagnostice a terapii

Vydává
Společnost pro pojivové tkáně ČLS J. E. Purkyně z.s.
Ortopedicko-protetická společnost ČLS J. E. Purkyně z.s.
Ambulantní centrum pro vady pohybového aparátu, s.r.o.

ročník 30 / 2023 číslo 1

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ORLING

ZALOŽENO ROKU 1992

BIOAKTIVNÍ KOLAGENNÍ PEPTIDY REGENERUJÍ

Kolagen je nezbytný pro pohyblivost kloubů, stabilitu kostí, odolnost a pevnost vazů a šlach a také pro zdravé svaly a hojně se vyskytuje i v cévách, meziobratlových ploténkách, hematoencefalické bariéře a rohovce, dentinu a střevní stěně – kolagen je životně důležitá složka celého těla.

Kolagenní peptidy zvyšují syntézu kloubního kolagenu a proteoglykanů

Nejen sportovci jsou ve zvýšené míře náchylní ke kloubním problémům a léčba se u nich nijak neliší od jejího zvládání u běžné populace. Hlavním cílem je minimalizovat bolestivost a zlepšit funkčnost kloubů. Klinická studie provedená v Penn State University testovala účinek kolagenních peptidů na studenty sportovních škol, kteří trpěli kloubními problémy v důsledku mechanické zátěže. V porovnání s kontrolní skupinou došlo u studentů, kteří užívali kolagenní peptidy, k **výraznému snížení kloubních potíží a také ke zlepšení pohyblivosti.** Tyto pozitivní účinky byly patrné zejména u účastníků s problémy kolenních kloubů pocházejících z mechanické zátěže. *(Clark K. , Sebastianelli W., Flechsenhar K., Aukermann D., Meza F., Millard R., Deitch J., Sherbondy P., Affiliations A., 24-Week study on the use of collagen hydrolysate as a dietary supplement in athletes with activity-related joint pain, Curr Med Res Opin, 2008 May;24(5):1485-96)*

Významný je i vliv kolagenních peptidů na hustotu kostí, zejména u osob s osteoporózou či osteopenií, potvrzeno už v roce 2010 pilotní studií s doplňkem stravy Calcidrink®.

V této studii se řešil „Vliv suplementace kolagenními peptidy, vápníkem a vitaminem D, resp. Calcidrinkem® na úbytek kostní hmoty a remodelaci kosti u postmenopauzálních žen s osteopenií“ *(Ortopedie 2010, Gabriela Šimková, Revmatologická ambulance 1. PP Kladno)*. Výsledky byly velmi nadějné. U žádné pacientky se nevyskytly během sledovaného období jednoho roku žádné nové nízkozátěžové zlomeniny. Cílem bylo prokázat účinek pravidelného užívání přípravku Calcidrink (vitamin D, kalcium a kolagenní peptidy) na snížení úbytku kostní hmoty u postmenopauzálních žen s osteopenií. Výsledky studie tento efekt potvrdily.

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Prof. MUDr. Milan Adam, DrSc. byl první, kdo objevil obrovský potenciál kolagenních peptidů a v průběhu let jej další vědci a lékaři opakovaně prokázali a ještě rozšířili oblasti použití, pro které jsou kolagenní peptidy vhodné.

Prof. MUDr. Milan Adam, DrSc. Dr.h.c.
český revmatolog, zakladatel kloubní výživy Geladrink®

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POHYBOVÉ ÚSTROJÍ

ročník 30, 2023, číslo 1 | datum vydání: 30. 9. 2023

Pohybové ústrojí. Pokroky ve výzkumu, diagnostice a terapii.

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Vydává Společnost pro pojivové tkáně ČLS J. E. Purkyně z.s.
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& Ambulantní centrum pro vady pohybového aparátu, s. r. o.
Excerpováno v Excerpta Medica a Bibliographia medica Čechoslovaca.
Návrh a grafická úprava obálky Pavel Lorenc.
Časopis je na Seznamu recenzovaných neimpaktovaných periodik vydávaných v České republice. Dvě čísla časopisu vycházejí v elektronické verzi jako ročník s průběžným vydáváním příspěvků po recenzi.
Při příležitosti sympozií je dvakrát ročně vydáváno supplementum.

Pro současné odběratele časopisu PÚ a další zájemce doporučujeme přihlásit se na http://www.pojivo.cz/en/newsletter/, zadat jméno a e-mailovou adresu, na kterou bude časopis posílán. Na webové doméně SPT ČLS JEP http://www.pojivo.cz/cz/pohybove-ustroji/ naleznete ve formátu PDF všechna jednotlivá čísla a dvojčísla časopisu (včetně Supplement) vydaná od roku 1997.
Rukopisy zasílejte na adresu *profesor MUDr. Ivo Mařík, CSc., Olšanská 7, 130 00 Praha 3, (ambul_centrum@volny.cz)* ve formátu doc. Vydavatel upozorňuje, že za obsah inzerce odpovídá výhradně inzerent. Časopis, jakožto nevýdělečný, neposkytuje honoráře za otištěné příspěvky.

LOCOMOTOR SYSTEM

Advances in Research, Diagnostics and Therapy

Published by The Society for Connective Tissues, Czech Medical Association of J. E. Purkyně, Prague, Society for Prosthetics and Orthotics, Czech Medical Association of J. E. Purkyně, Prague, Czech Republic and Centre for Defects of Locomotor Apparatus Prague, Czech Republic.

Call for papers

Support this journal by sending in your best and most interesting papers. The issue of the journal is published during whole year after proof acceptation of the reviewers. In occasion of the symposia (twice a year) is published the supplement.

Submitted papers: Locomotor System will review for publication manuscripts engaged in diagnostics and interdisciplinary treatment of genetic and metabolic skeletal disorders, limb anomalies, secondary osteoporosis, osteo/spondyloarthritis and another disorders that negatively influence development and quality of locomotor apparatus during human life. Both papers on progress in research of connective tissue diagnostics, medical and surgical therapy of multiple congenital abnormalities of skeleton mainly in the fields of paediatric orthopaedic surgery and plastic surgery, orthotics and prosthetics treatment, and papers dealing with biomechanics, clinical anthropology and paleopathology are appreciated.

The journal has an interdisciplinary character which gives possibilities for complex approach to the problems of locomotor system. The journal belongs to clinical, preclinical and theoretical medical branches which connect various up-to-date results and discoveries concerned with locomotor system. You can find the volumes of Locomotor System journal at http://www.pojivo.cz/cz/pohybove-ustroji/ since 1997 (free of charge). Since 2013 only electronic edition of the journal is available. That is why we recommend to all subscribers and those interested apply at http://www.pojivo.cz/en/newsletter, enter personal data, titles and e-mail address where the journal will be mailed.

Abstracts of presented papers are excerpted in EMBASE/Excerpta Medica (from the year 1994) and in the Bibliographia medica Čechoslovaca (from the year 2010). We prefer the manuscripts to be prepared according to Uniform Requirements for Manuscripts Submitted to Biomedical Journals (Vancouver Declaration, Brit med J 1988; 296, p. 401–405).

30. ročník časopisu Pohybové ústrojí – pokroky ve výzkumu, diagnostice a terapii je věnován jubilantům, čestným členům Společnosti pro pojivové tkáně České lékařské společnosti J.E. Purkyně (SPT ČLS JEP), členům redakční rady časopisu Pohybové ústrojí a držitelům pamětní Zlaté medaile ČLS JEP

panu

prof. MUDr. Josefovi Hyánkovi, DrSc. (90 let)

a panu

prof. MUDr. Ctiborovi Povýšilovi, DrSc. (80 let)

a také dalším jubilantům a čestným členům SPT ČLS JEP, kteří se zasloužili o činnost Společnosti pro pojivové tkáně ČLS JEP od jejího vzniku v roce 2004:

Ing. Haně Hulejové (65 let)

MUDr. Olze Hudákové, Ph.D. (50 let)

a

RNDr. Martinovi Braunovi, Ph.D. (50 let)

The 30th edition of Locomotor System journal – Advances in Research, Diagnostics and Therapy is dedicated to the jubilarians, honorary members of the Society for Connective Tissues of the Czech Medical Association J.E. Purkyně (SCT CMA JEP), members of the editorial board of the journal and holders of the commemorative Gold Medal of the CMA JEP

Mr.

Professor Josef Hyánek, DSc. (90 yrs.)

and Mr.

Professor Ctibor Povýšil, DSc. (80 yrs.)

and also other jubilarians and honorary members of Society for Connective Tissues of the Czech Medical Association J.E. Purkyně who have contributed to the activities of this Society since its establishment in 2004:

Ing. Hana Hulejová (65 yrs.)

Olga Hudáková, MD, PhD (50 yrs.)

and

RNDr. Martin Braun, PhD (50 yrs.)

**POHYBOVÉ ÚSTROJÍ –
POKROKY VE VÝZKUMU, DIAGNOSTICE A TERAPII, 30, 2023, č. 1**

Datum vydání: 10. 10. 2023

OBSAH

KASUISTIKY

ZPRÁVY

LOCOMOTOR SYSTEM –
ADVANCES IN RESEARCH, DIAGNOSIS AND THERAPY, 30, 2023, No. 1

Date of issue: 10. 10. 2023

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SLOVO ČTENÁŘŮM

Vážení čtenáři, autoři a inzerenti!

Děkujeme za Vaši nezastupitelnou pomoc při tvorbě mezioborového odborného recenzovaného časopisu *„Pohybové ústrojí – pokroky ve výzkumu, diagnostice a terapii* (dále PÚ).“

Všechna čísla časopisu (včetně Supplement) vydaná od roku 1997 najdete ve formátu PDF na webové doméně Společnosti pro pojivové tkáně ČLS JEP z.s.
http://www.pojivo.cz/cz/pohybove-ustroji/ (bezplatný přístup).

Časopis PÚ byl v roce 2008 zařazen Radou pro výzkum, vývoj a inovace vlády ČR na Seznam recenzovaných neimpaktovaných periodik vydávaných v České republice. Od roku 2013 je časopis PÚ vydáván pouze v elektronické formě (v roce 2014 bylo přiděleno nové ISSN 2336-4777). V souvislosti se změnou v elektronickou formu vydávání v roce 2013 časopis nedopatřením vypadl z tohoto Seznamu. Od roku 2015 je elektronická forma Pohybového ústrojí opět na Seznamu recenzovaných neimpaktovaných periodik.

Od roku 2016 vydáváme v časopisu PÚ příspěvky přijaté po recenzi jako číslo 1 a 2, dále dvě Suplementa obsahující souhrny nebo abstrakta ze symposií Kubátovy dny a mezinárodního symposia.

Nedostatek příspěvků je příčinou zpožděného vydání i tohoto čísla 1 časopisu PÚ, 30, 2023. Čtenář se dozví o Aktuálních trendech v růstu českých dětí v kontextu sekulárních změn, poučí se o pokroku v molekulárně genetické diagnostice, který vedl k radikálním změnám uveřejněným v Nozologii genetických poruch skeletu – Revize 2023. Čtenáři si také udělají představu o onemocněních, kterými trpěli naši předkové v 9. století, jak vyplývá z paleopatologického výzkumu panonského avarského pohřebišti Terehegy-Marfa v dnešním Maďarsku. Nepochybně je zaujmou raritní případové studie demonstrující komplexní léčení doplněné rozsáhlou diskusí týkající se jednak Makrodaktylie ruky v kombinaci s Polandovým syndromem a jednak molekulární diagnostiky vrozené arachnodactylie s kontrakturami (tzv. Bealsův-Hechtův syndrom), jak ze vzorku krve tak z kostní tkáně.

Toto číslo časopisu je věnováno jubilantům, čestným členům Společnosti pro pojivové tkáně (SPT) ČLS JEP a držitelům Zlatě pamětní medaile ČLS JEP panu prof. MUDr. Josefovi Hyánkovi, DrSc. (90 let) a panu prof. MUDr. Ctiborovi Povýšilovi, DrSc. (80 let) a dalším čestným členům SPT ČLS JEP Ing. Haně Hulejové (65 let), RNDr. Martinovi Braunovi, Ph.D. (50 let) a MUDr. Olze Hudákové, Ph.D. (50 let). Odborné životopisy všech jubilantů byly publikovány v Suplementu 1 časopisu PÚ, 30, 2023, které bylo vydáno při příležitosti tradičního symposia 28. Kubátův den. 28. Suplementum s abstrakty příspěvků a video záznam přednášek velmi úspěšného symposia, jsou dostupné na webových stránkách obou symposium organizujících společností www.pojivo.cz a www.ortoprotetika.cz.

Do redakční rady časopisu Pohybové ústrojí byli navrženi a schváleni tito členové Společnosti pro pro pojivové tkáně ČSLS JEP: Ass. MUDr. Josef Kraus, CSc. (dětský neurolog) a MUDr. Veronika Krulišová, Ph.D. (klinická genetička). Oba kolegové jsou aktivní jednak jako přednášející na sympoziích pořádaných

Společností pro pojivové tkáně ČLS JEP a Ortopedicko-protetickou společností ČLS JEP, jednak jako autoři a spoluautoři publikací v časopise PÚ.

Posláním časopisu PÚ je, jako v minulých letech, uveřejňovat vědecké práce zabývající se diagnostikou a mezioborovým léčením genetických kostních chorob, vrozených defektů končetin, sekundární osteoporózy, osteo/spondylartrózy, ale i jiných chorob, které ve svých důsledcích negativně ovlivňují růst, vývoj a kvalitu pohybového ústrojí v průběhu lidského života. Ceněny jsou práce vycházející z výzkumu pojivových tkání na všech úrovních poznání, práce orientované na biochemickou, morfologickou, genetickou a molekulární diagnostiku chorob pohybového ústrojí. Zvláštní pozornost je přikládána pracím z oblasti ortopedické a antropologické biomechaniky, neuroadaptačním změnám skeletu v období růstu, řízené remodelaci pojivových tkání, studiím muskuloskeletálních a neuronálních interakcí v závislosti na léčebných metodách (kalciotropní léky, rehabilitace, ortoticko-protetické a operační léčení aj.) a v neposlední řadě studiím antropologickým a paleopatologickým. Oceňujeme především interdisciplinárně zaměřené práce. V anglickém jazyce jsou publikována sdělení zahraničních i našich autorů. Žádaným doplněním obsahu časopisu jsou zprávy ze sjezdů a konferencí. Zveřejňujeme oznámení o životním výročí členů RR časopisu, SPT ČLS JEP z.s., OPS ČLS JEP z.s. a významných osobností, sdělení o prioritních pozorováních, ze studijních a poznávacích cest aj.

V každém ročníku najdete směrnice pro autory příspěvků, kterým věnujte prosím pozornost při tvorbě Vašich vědeckých sdělení. Souhrny prací publikovaných v časopisu jsou excerpovány v EMBASE / Excerpta Medica (od r. 1994) a v Bibliographia medica Čechoslovaca (od r. 2010).

K prosazení časopisu Pohybové ústrojí mezinárodně přispívá citovat práce publikované v našem časopisu v příspěvcích posílaných do zahraničních impaktovaných časopisů. Pro zvýšení mezinárodního zájmu o časopis PÚ je žádoucí získávat původní kvalitní práce a kazuistiky v angličtině. Souhrny všech prací doporučujeme psát co nejvýstižněji, strukturovaně, česky a anglicky (objectives, methods, results and discussion), s klíčovými slovy.

Těšíme se na Vaši spolupráci a tvůrčí připomínky v roce 2023.

Redakční rada

A WORD TO READERS

Dear readers, authors and advertisers!

Thank you for your indispensable help in the creation of the interdisciplinary peer-reviewed journal *Locomotor System – Advances in Research, Diagnosis and Therapy* (journal LS).

All issues of the journal (including the Supplement) published since 1997 can be found in PDF format on the web domain of the Society for Connective Tissues of the Czech Medical Association J.E. Purkynje http://www.pojivo.cz/cz/pohybove-ustroji/ (free access).

In 2008, the journal was included by the Council for Research, Development and Innovation of the Government of the Czech Republic in the List of peer-reviewed non-impacted periodicals published in the Czech Republic. Since 2013, the journal has been published only in electronic form (in 2014, a new ISSN 2336-4777 was assigned). In connection with the change to electronic publication in 2013, the journal inadvertently dropped from this List. Since 2015, the electronic form of the journal Locomotor System is again on the List of peer-reviewed non-impacted journals.

Since 2016, we have been publishing papers accepted after peer review as Issues 1 and 2, as well as two Supplements containing summaries or abstracts from the Kubát Days and International Symposia.

The lack of contributions is the reason for the delay in the publication of this issue 1 of the journal PÚ, 30, 2023. The reader will learn about the Current trends in the growth of Czech children in the context of secular changes; he will learn about the advances in molecular genetic diagnostics that led to the radical changes published in the Nosology of genetic skeletal disorders – Revision 2023; the readers will get an idea of the diseases from which our ancestors suffered in the 9th century, as revealed by paleopathological research at the Pannonian Avar burial site of Terehegy-Marfa in present-day Hungary; they will undoubtedly be interested in rare case studies demonstrating complex treatments, accompanied by extensive discussion of both Macrodactyly of the hand in combination with Poland's syndrome and the molecular diagnosis of congenital arachnodactyly with contractures (the so-called Beals-Hecht syndrome), from both blood and bone tissue samples.

This issue of the journal is dedicated to the jubilarians, honorary members of the Society for Connective Tissues (SCT) of the CMA JEP and holders of the Gold Commemorative Medal of the CMA JEP, Prof. Josef Hyánek, M.D., DrSc. (90 years) and Prof. Ctibor Povýšil, M.D., DrSc. (80 years) and other honorary members of the SCT of the CMA JEP, Ing. Hana Hulejová (65 years), RNDr. Martin Braun, Ph.D. (50 years) and MUDr. Olga Hudáková, Ph.D. (50 years). The professional biographies of all the jubilarians were published in Supplement 1 of the journal PÚ, 30, 2023, which was published on the occasion of the traditional symposium Kubat Days 28. The supplement with abstracts of the papers and video recording of the lectures of the very successful symposium are available on the websites of both symposium organizing companies www.pojivo.cz and www.ortoprotetika.cz.

The following have been nominated and approved for the editorial board of the journal Locomotor System, Ass. MUDr. Josef Kraus, Ph.D. (pediatric neurologist) and MUDr. Veronika Krulišová, Ph.D.

(clinical geneticist). Both colleagues are active both as lecturers at symposia organized by the Society for Connective Tissues CMA J.E. Purkyně and the Orthopaedic and Prosthetic Society CMA J.E. Purkyně and authors of publications in the journal LS.

The mission of the journal is to publish scientific papers dealing with the diagnosis and interdisciplinary treatment of genetic bone diseases, congenital defects of the limbs, secondary osteoporosis, osteo/spondylarthritis, as well as other diseases that adversely affect the growth, development and quality of the musculoskeletal system during human life. Works based on research on connective tissues at all levels of knowledge, works oriented on biochemical, morphological, genetic and molecular diagnostics of musculoskeletal diseases are valued.

Particular attention is paid to works in the field of orthopaedic and anthropological biomechanics, neuroadaptive changes of the skeleton during the growth period, controlled remodelling of connective tissues, studies of musculoskeletal and neuronal interactions in relation to therapeutic methods (calciotropic drugs, rehabilitation, orthotic-prosthetic and surgical treatment) and, last but not least, anthropological and palaeopathological communications. We particularly appreciate the interdisciplinary work. Communications by foreign and national authors are published in English. Reports from congresses and conferences are a welcome addition to the content of the journal. In the news section, we publish announcements of life anniversaries of members of the editorial board of the journal, Society for Connective Tissues CMA JEP & Society for Prosthetics and Orthotics CMA JEP and important personalities, announcements of priority observations, study and discovery trips, etc.

In each edition, you will find guidelines for authors of papers, which please pay attention to when drafting your scientific communications. Summaries of papers published in the journal are excerpted in EMBASE / Excerpta Medica (since 1994) and in Bibliographia medica Čechoslovaca (since 2010).

The citation of papers published in our journal in papers sent to foreign impacted journals contributes to the promotion of the journal Locomotor System internationally. In order to increase the international interest in the journal of Locomotor System, it is desirable to obtain original high quality papers and case reports in English. Abstracts of all papers are recommended to be written as concisely as possible, structured, in Czech and English (objectives, methods, results and discussion), with key words.

We look forward to your cooperation and creative comments in 2023.

Editorial Board

OBRÁZEK NA TITULNÍ STRANĚ ČASOPISU: ANALÝZA VZORKŮ DNA MASIVNÍM PARALELNÍM SEKVENOVÁNÍM

OBRÁZEK NA TITULNÍ STRANĚ ČASOPISU znázorňuje postup přípravy vzorků DNA pro analýzu sekvenováním nové generace (next-generation sequencing, NGS) za pomoci kitu Clinical Exome Solutions (Sophia Genetics) – sekvenování klinického exomu. Jedná se o panelové sekvenování vybraných genů, jejichž narušení je příčinou rozvoje vzácných vrozených onemocnění a syndromů, včetně onemocnění pohybového ústrojí.

Prvním krokem je izolace DNA ze vstupního materiálu, kterým je ideálně periferní krev, může být použit i bukální stěr, část tkáně nebo kosti. Izolace probíhá pomocí automatizované pracovní stanice MagCore® (RBC Bioscience) za využití technologie magnetických kuliček. Dostatečná kvalita a množství získané DNA je následně fluorometricky ověřena (**obr. 1a**).

Následuje příprava sekvenační knihovny, tedy souboru všech vzorků, které budou analyzovány. DNA je nejprve chemicky naštěpena na jednotlivé sady molekul/fragmentů o definované délce,

Obrázek 1a–d. Analýza vzorků DNA masivním paralelním sekvenováním (MPS)

tzv. amplikony. Ty jsou v dalším kroku označeny speciálními indexovacími adaptory, což jsou krátké oligonukleotidy navázané na konce jednotlivých fragmentů, které umožňují vzorky vzájemně odlišit. Do jedné sekvenační reakce je proto možné zahrnout vzorky více pacientů. Automatizace procesu přípravy sekvenační knihovny je provedena za využití robotického přístroje Bravo (Agilent Technologies) (**obr. 1b**).

V případě sekvenování klinického exomu jsou pro zachycení požadovaných genomických oblastí využívány hybridizační sondy, které se vážou pouze na specifické úseky genomu ve kterých leží geny, jež chceme analyzovat. SOPHiA DDM™ Clinical Exome Solution v3 pokrývá kódující oblasti (±5 bází intronových oblastí) 4,727 genů, celý mitochondriální genom a přibližně 200 nekódujících variant se známým patogenním dopadem, a to i v rámci hlubokých intronů/enhancerů/promotorů spojených se vzácnými a dědičnými poruchami. Po přečištění je vytvořená knihovna amplifikována, tedy jednotlivé fragmenty jsou namnoženy na tisíce přesných klonů, což je důležité pro zvýšení přesnosti identifikace jednotlivých bází během procesu sekvenování. Sekvenace probíhá na přístroji NextSeq 550 (Illumina) (**obr. 1c**). Značené fragmenty DNA jsou přichyceny pomocí adaptorové sekvence na flow-cell sekvenátoru (skleněná deska s miliony fixovaných oligonukleotidů komplementárních k adaptorovým sekvencím). Následnou replikací DNA (tj. tvorba kopie DNA) s fluorescenčně značenými deoxyribonukleotidtrifosfáty (dNTPs) přístroj opticky zaznamenává barevné signály pro jednotlivé báze v přesně definovaném pořadí a postupně tak sestavuje vznikající sekvenci DNA.

Bioinformatické zpracování dat zahrnuje kontrolu kvality a odstranění nekvalitních sekvencí, artefaktů či kontaminací. Základním principem je mapování osekvenované DNA (tzv. readů) k referenčnímu genomu a odhalení odlišností, což mohou být jednonukleotidové varianty (single nucleotide variant, SNV), krátké delece a inzerce (INDELs) či strukturní varianty (delece/duplikace celých exonů, copy number variation, CNV). Pro vizualizaci nalezené kauzální varianty c.3724+2T>C (rs863223570) *FBN2* genu v intronu 28 slouží software Alamut Visual Plus (Sophia Genetics) (**obr. 1d**).

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THE FIGURE ON THE TITLE PAGE OF THE JOURNAL: NEXT-GENERATION SEQUENCING (NGS) ANALYSIS

The cover page of the journal displays a visual representation of the protocol for preparing DNA samples for next-generation sequencing (NGS) analysis using the Clinical Exome Solutions kit (Sophia Genetics) for clinical exome sequencing. This technique involves sequencing a panel of chosen genes, the interruption of which may be responsible for the onset of rare inborn disorders and syndromes, including those affecting the locomotor system.

The initial stage involves extracting DNA from the input sample which ideally should be peripheral blood; however, a buccal swab, part of tissue or bone could also be considered. The automated MagCore® workstation (RBC Bioscience) utilises magnetic bead technology for isolation. Verification for sufficient quantity and quality of DNA is conducted using fluorometric analysis (**Fig. 1a**).

Consequently, sequencing libraries are prepared, comprising all samples slated for analysis. The DNA is initially chemically fragmented into specific sets of molecules/ fragments with predeter-

Figure 1a–d. Analysis of DNA samples using the next-generation sequencing (NGS)

mined lengths referred to as 'amplicons'. Following this, they are labelled with special indexing adapters, which are short oligonucleotides attached to the ends of the individual fragments to differentiate the samples from one another. Therefore multiple patients' samples can be included in a single sequencing reaction. The sequencing library preparation process is automated using the robotic device Bravo (Agilent Technologies) (**Fig. 1b**).

In clinical exome sequencing, hybridisation probes are utilized to specifically target genomic regions, binding solely to the desired section of the genome in which the genes of interest are located. SOPHiA DDM™ Clinical Exome Solution v3 covers the coding regions (±5 bases of intronic regions) of 4,727 genes, the entire mitochondrial genome, and around 200 non-coding variants with established pathogenic impact, which includes those observed within deep introns/enhancers/promoters linked to rare and hereditary conditions. After purification, the library undergoes amplification, resulting in thousands of identical clones of individual fragments. This process is crucial for precise identification of individual bases during sequencing. The sequencing process is conducted on NextSeq 550 device (Illumina). Labeled DNA fragments are attached with adapter sequences on a flow-cell, a glass plate containing millions of fixed oligonucleotides complementary to the adapter sequences. Through DNA replication (the copying of DNA) with fluorescently labeled deoxyribonucleotide triphosphates (dNTPs), the device optically records colour signals for individual bases in a precisely defined order and thereby reveals the emerging DNA sequence (**Fig. 1c**).

Bioinformatics data processing involves conducting quality control to remove low-quality sequences, artifacts and contaminations. The primary principle is to map sequenced DNA (known as reads) to the reference genome, detecting differences such as single nucleotide variants (SNVs), short deletions and insertions (INDELs), or structural variants such as deletion/duplication of entire exons (copy number variation, CNV). The Alamut Visual Plus software (Sophia Genetics) has been used for the visualisation of the discovered causal variant c.3724+2T>C (rs863223570) of the *FBN2* gene, which is located in intron 28 (**Fig. 1d**).

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AKTUÁLNÍ TRENDY V RŮSTU ČESKÝCH DĚTÍ V KONTEXTU SEKULÁRNÍCH ZMĚN

CURRENT TRENDS IN THE GROWTH OF CZECH CHILDREN IN THE CONTEXT OF SECULAR CHANGES

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ABSTRAKT

Růst a vývoj dítěte je ovlivňován řadou environmentálních faktorů, které se v průběhu generací mění. V populačním profilu tělesných charakteristik pak hovoříme o sekulárních změnách. Problémem současného životního stylu je zejména nedostatek pohybové aktivity od raného věku a nesprávné stravování. Dochází tak k poruchám vývoje struktur pohybového aparátu a postupně k rozvoji nadváhy a obezity. Zatímco v předškolním věku převládá typ skryté, latentní obezity, od prepuberty se zvyšuje prevalence obezity zjevné, spojené s nárůstem hmotnosti. Hormonální a enzymatická aktivita tukové tkáně je pak příčinou pubertálních změn v dnešní dětské populaci. U dívek dochází k dřívějšímu nástupu puberty a tím snižování věku dosažení reprodukční zralosti. U chlapců je naopak vlastní pubertální vývoj alterován, dochází k významnému uplatnění estrogenů v jejich vývoji. Výsledkem je typická výrazná feminizace postavy dnešních mladých mužů.

ABSTRACT

A child´s growth and development is influenced by a number of environmental factors that change over generations. In the population profile of body characteristics, we are talking about secular changes. The problem of the current lifestyle is mainly the lack of physical activity from an early age and improper diet. This leads to disorders in the development of the structures of the locomotor system and gradually to the development of overweight and obesity. While the type of hidden, latent obesity predominates in preschool age, the prevalence of obvious obesity, associated with weight gain, increases from prepuberty. Hormonal and enzymatic activity of adipose tissue is the cause of pubertal changes in the current child population. In girls, there is an earlier onset of puberty and thus a reduction in the age at which reproductive maturity is reached. In boys, on the other hand, the pubertal development itself is altered, there is a significant use of estrogens in their development. The result is a typical strong feminization of the character of current young men.

Klíčová slova / Key words: Sekulární trend, nadváha a obezita, děti, puberta, pohybová aktivita
Secular trend, overweight and obesity, children, puberty, physical activity

ÚVOD

Růst dítěte je kontinuální proces, který začíná splynutím gamet a končí uzavřením epifyzárních růstových plotének kostí v období adolescence. Jedná se o složitý děj, v jehož regulaci se uplatňuje řada faktorů. Dominantní roli v růstovém profilu dítěte a jeho finální výšce hraje genetický růstový potenciál, jehož uplatnění je limitováno vlivem prostředí, ve kterém dítě žije. Změny socioekonomických faktorů se výrazně promítají do životního stylu, a to již od dětského věku. Způsob života rodiny je určujícím prvkem zdravého růstu dítěte. Negativní trendy životního stylu ovlivňují nejen uplatnění genetického růstového potenciálu, ale jsou určujícím faktorem zdravotního stavu a kvality celého dalšího života jedince. Aktuální trendy – nedostatek pohybu a nesprávná výživa, negativně ovlivňují zdravotní stav celé populace.

Nedostatek pohybové aktivity (hypokineze) a její následky se stávají v současné době nejvýznamnějším problémem populace napříč všemi věkovými skupinami. Za nejzávažnější však považujeme hypokinezi v dětském a adolescentním věku, neboť nedostatek pohybu negativně ovlivňuje růst dítěte i všechny aspekty jeho fyziologického vývoje.

Záměrem článku je připomenout nejznámější trendy v růstu a vývoji české populace druhé poloviny dvacátého století a v jejich kontextu podat přehled současných nejvýraznějších změn, které jsou primárně podmíněné negativními prvky v životním stylu populace, zejména nedostatkem pohybové aktivity od raného věku a špatnými stravovacími návyky.

SEKULÁRNÍ ZMĚNY, SEKULÁRNÍ TREND

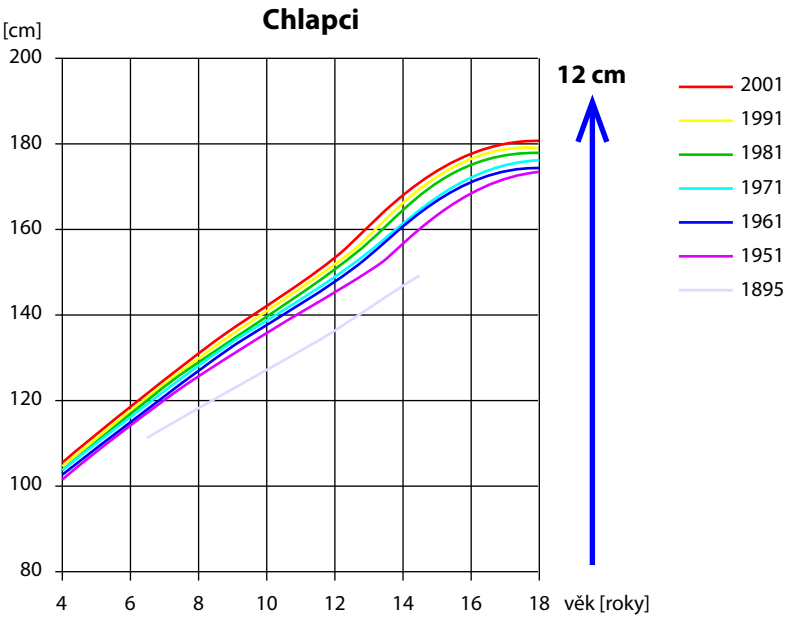
Dlouhodobé změny v somatickém profilu populace jsou označovány jako sekulární. Termín „sekulární trend" se začal v antropologické literatuře objevovat ve druhé polovině 20. století. Má základ v latinském slově saeculum, což v překladu znamená generace či století. Jedná se o dlouhodobý proces, při kterém se mění velikostní a tvarové parametry jedinců určité populace v mezigeneračním srovnání (**6, 11**). Zvyšování socioekonomické úrovně, pokroky ve zdravotnictví a vyšší dostupnost zdravotní péče vedly postupně k výraznějšímu uplatnění genetického růstového potenciálu, což se projevilo zvyšováním průměrné výšky populace (**12**). Tento trend je u české populace dobře zachycen a popsán díky datům z Celostátních antropologických výzkumů dětí a mládeže (CAV), které se v bývalém Československu konaly od roku 1951 v desetiletých intervalech až do roku 2001 (**5**). Průměrná hodnota nárůstu tělesné výšky českých mužů byla za 50leté období +8 cm, u žen o +6 cm (**76, 77**).

Ve vztahu k tělesné výšce podléhají pozitivním sekulárním změnám všechny lineární tělesné parametry. Intenzita jejich růstové akcelerace je však různá, dochází tak ke změnám proporcionality.

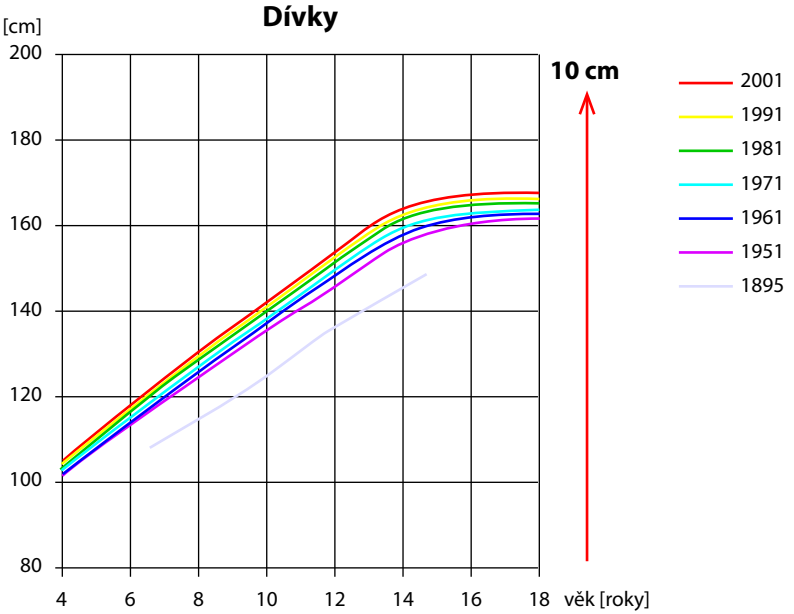
Jak uvádí studie Meadows et Jantz, 1995 (**46**), která hodnotila změny délky a proporcí dlouhých kostí končetin americké populace v časovém období 1800 až 1970, liší se proporcionalita růstu horní a dolní končetiny. Zatímco horní končetina vykazuje k tělesné výšce izometrický růst a tedy se v tomto vztahu proporcionalita nemění, růst dolní končetiny je pozitivně alometrický. Délka dolních končetin se tak v průběhu sekulárního nárůstu tělesné výšky prodlužuje. Uvedená studie potvrdila i výraznější sekulární akceleraci růstu distálních segmentů končetin, zejména na dolní končetině. Pozitivní alometrie je tak ve vztahu k tělesné výšce vyšší u tibie (i fibuly) než u femuru. Ke stejnému závěru dospěli i Auerbach a Sylvester, 2011 (**3**). Studie Holliday and Ruff, 2001 (**32**) už předtím u distálního segmentu dolní končetiny, resp. tibie zjistila nejvyšší hodnotu relativní variance ze všech segmentů lidských končetin.

Dolní končetiny také vykazují výraznější sekulární trend než končetiny horní. Byly nalezeny rozdíly mezi pohlavím a etnicitou (**3, 47**). Uvedená zjištění tak ukazují na primární vliv akcelerace růstu kostí dolní končetiny v procesu sekulárního nárůstu tělesné výšky.

Spolu s trendem nárůstu výšky postavy docházelo k postupnému snižování věku nástupu puberty. Došlo rovněž ke zvýšení průměrných hodnot růstové rychlosti v akcelerační fázi pubertálního spurtu. Průměrná růstová rychlost ve vrcholu pubertálního spurtu (peak height velocity) byla u chlapců v roce 1951 6,5 cm/rok, v roce 2001 7,3 cm/rok, u dívek 5,6 cm, resp. 6,6 cm/rok (**78**). Tělesný růst



Obr. 1a. Sekulární vývoj průměrné tělesné výšky českých chlapců.
Data 1895 Matiegka, 1927 (**45**), 1951–2001 Celostátní antropologické výzkumy dětí a mládeže.
Upraveno dle Vignerová et al. , 2006 (**78**).

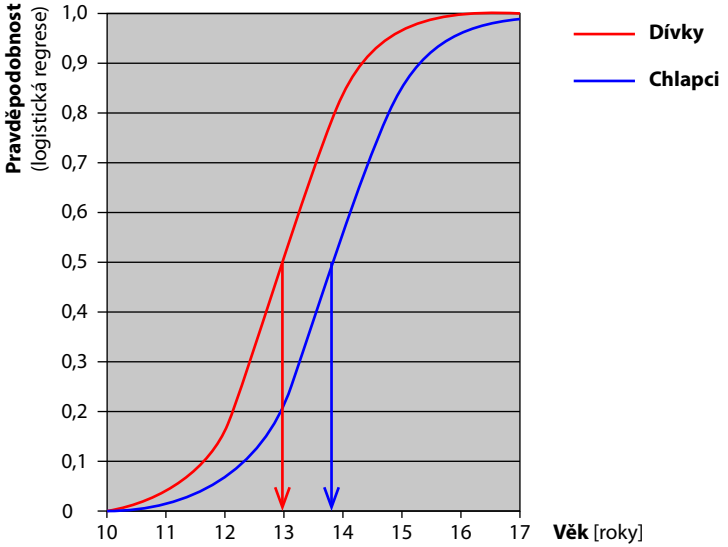


Obr. 1b. Sekulární vývoj průměrné tělesné výšky českých dívek.
Data 1895 Matiegka, 1927 (**45**), 1951–2001 Celostátní antropologické výzkumy dětí a mládeže.
Upraveno dle Vignerová et al. , 2006 (**78**).

chlapců byl před 100 lety ukončen po 20. roce, v současnosti již před 18. rokem. U dívek je období ukončení růstu proporcionálně posunuto o 2 roky do dřívějšího věku (**76**). Ve stoletém horizontu sledování byli 18letí chlapci v roce 2001 o 12 cm vyšší než jejich vrstevníci z konce 19. století, dívky o 10 cm (**obr. 1a, 1b**) (**76, 78**).

Od 80. let 20. století se začaly objevovat první zmínky o „vyznívání" sekulárního trendu nárůstu výšky, nejprve v předškolních věkových kategoriích (**58**), později i u prepubertálních dětí a pubertálních dívek (**77**). U posledních dvou CAV (1991 a 2001) bylo doloženo zpomalování trendu zvyšování postavy u obou pohlaví, které bylo u dívek mnohem výraznější než u chlapců. Porovnáme-li rozdíly průměrné tělesné výšky chlapců z let 1991 a 2001, rozdíly vyšší než 1 cm nacházíme pouze ve věkových kategoriích nad 12 let s maximem 1,8 cm v kategorii třináctiletých. U dívek činí nejvyšší diference pouze 0,7 cm v kategorii dvanáctiletých (**76, 77**).

Vyznívání sekulárního trendu, zvyšování tělesné výšky a urychlování nástupu puberty dokládala i stagnace středního věku menarche u českých dívek, která se dlouhodobě prakticky nezměnila a setrvávala až do roku 2001 na hodnotě 13 let. U chlapců určitá akcelerace pubertálního vývoje a tím i nárůst průměrné výšky v pubertálních věkových skupinách ještě probíhala, což dokládá pokles středního věku nástupu mutace u českých chlapců z hodnoty 14,5 roku v roce 1991 na 13,8 roku v roce 2001 (**obr. 2**) (**77, 78**).



Obr. 2. Věk pravděpodobnosti menarche u dívek a mutace u chlapců v daném věku z dat CAV 2001. Upraveno dle Vignerová et al., 2006 (**78**).

AKTUÁLNÍ STAV

Pohybový aparát

Správný vývoj všech složek pohybového aparátu je primárně podmíněn mechanickou stimulací (**21, 22**). Nedostatek pohybové aktivity, a to zejména v raném dětství a pubertálním věku vede k negativnímu ovlivnění nejen růstu a formování kostry, ale postiženy jsou i měkké tkáně – svaly a šlachy. Insuficietní skeletální vývoj představuje jednak poruchy formování skeletálních struktur, které přímo souvisí s bipedální lokomocí (**64**), zejména esovité zakřivení páteře a formování podélné nožní klenby, odráží se ale i velmi výrazně ve vytváření kvality kostní tkáně (denzity kosti) (**39, 56, 57**).

Studie českých předškolních dětí, která začala pilotním projektem sledování dětí v mateřských školách v roce 2013 a probíhá dosud, již ve svých prvních výsledcích doložila až u 2/3 dětí ve věku tří až šesti let nesprávné držení těla (sledováno na základě posturálních standardů dle Mathiase) (**29**). Dalším závažným zjištěním bylo nedostatečné formování podélné nožní klenby spojené s laterálním vyosením pat (**44**). Důsledky jsou pak nejvíce patrné na skeletální postuře, kdy dochází k porušení osy dolních končetin ve smyslu valgózního postavení v kolenních kloubech, šikmému postavení pánve vůči frontální rovině (vlevo hřeben lopaty kyčelní kosti je posunut distálněji) a averznímu postavení, tzv. protrakci ramen. To, společně s nedostatečnou tonizací hlubokých zádových svalů vede ke kyfoskoliotickému držení těla v proximálním hrudním segmentu páteře, což se projevuje bolestivostí zad. V současné době probíhá vyhodnocování souboru plantogramů a návazná studie,

která rozšiřuje sledování dětí až do prepubertálního věku (kategorie 7 a 8letých). Má tak za úkol zodpovědět otázku, zda se v důsledku nižší mechanické stimulace chodidla prodlužuje doba formování podélné nožní klenby a posunuje se tak období její fixace z předškolního věku do prepuberty, nebo se nožní klenba fixuje v nedostatečné kvalitě a představuje trvalý handicap.

Dalším obdobím s limitujícím vlivem na pohybový aparát a zejména kvalitu svalové tkáně je puberta. V období pubertální růstové akcelerace dochází i k výrazným změnám v tělesném složení. U dívek se fyziologicky zvyšuje podíl tuku, u chlapců dochází v důsledku anabolického působení testosteronu k dynamickému nárůstu svalové tkáně. I zde je ale k využití růstového potenciálu potřeba mechanické stimulace. Je potřeba si uvědomit, že proliferace tkáňových struktur je časově omezena. Každá tkáň má svoji geneticky naprogramovanou proliferační schopnost a po dosažení finálního stavu se její růstová aktivita omezuje na regenerační procesy (**15, 55**). Pokud tedy jedinec nevyužije proliferační potenciál tkáně její správnou stimulací, je po dosažení limitního stavu handicap v jejím vývoji již trvalý. To platí zejména o svalové a kosterní tkáni. Sportovní a posilovací aktivity mladých mužů, ve snaze o formování postavy pak tento nedostatek nejsou schopny kompenzovat, naopak dochází k mikrotraumatizaci úponových struktur, které se manifestují např. jako epikondylopatie humeru, achillodynie nebo dokonce rupturou tendo calcanei. Nedostatečná mineralizace kostní tkáně a tím i nízká hodnota tzv. peak bone mass (PBM) jsou příčinou osteoporózy v časné dospělosti. Důsledkem metabolické poruchy kostní tkáně vznikají mikrofraktury, přestavbové zlomeniny a fraktury v predilekčních oblastech kostry (**34**).

Motorická zdatnost

Insuficientní rozvoj aktivní tělesné hmoty a nízká fyzická zdatnost jsou hlavními příčinami nedostatečné motorické výkonnosti dnešních dětí a adolescentů. Jak ukázal projekt Ministerstva školství, mládeže a tělovýchovy (**13**), který sledoval na základě baterie standardizovaných testů hlavní aspekty motorické zdatnosti dětí ve vybraných ročnících základních a středních škol, výkonnost a tělesná zdatnost jsou v porovnání s normativy z 90. let 20. století na velmi nízké úrovni. Zejména vytrvalostní schopnosti, testované na základě člunkového běhu, nedosáhly u chlapců dokonce ani střední hodnoty dívčí normy. Propad výkonnosti u dívek byl také velmi výrazný (**13**).

Nízká motorická zdatnost má však svůj počátek již v předškolním věku. Jak dokládají studie českých předškolních dětí (**66**), nedostatečný rozvoj svalstva, zejména na dolních končetinách, vede k nízké výkonnosti v silových a vytrvalostních aktivitách. Jednoznačně výraznější propad motorických schopností byl doložen u dětí se skrytou (latentní) formou obezity, u kterých je výraznější handicap v rozvoji muskulatury než u dětí zjevně obézních (**48**).

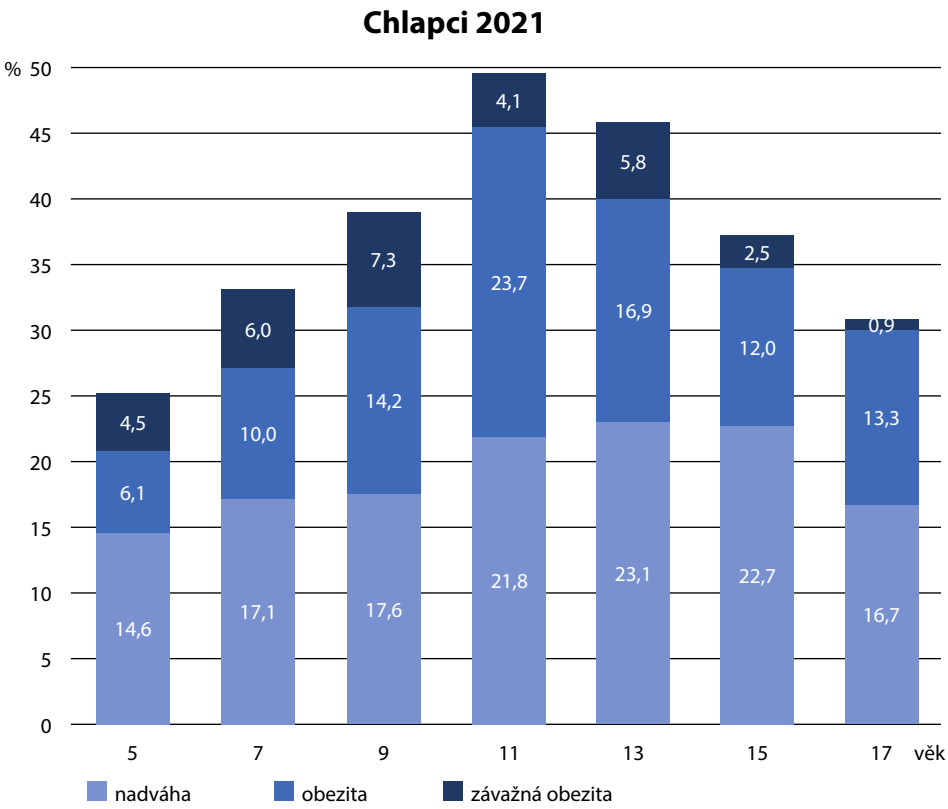
Všechny tyto aspekty významně ovlivňují celý další život jedince, zejména pak i možnost jeho pohyblivosti ve stáří, která je často limitujícím faktorem kvality života v pozdním věku.

Nadváha a obezita

S negativními trendy v životním stylu, tedy primárně s nedostatkem pohybu a nesprávným stravováním souvisí i výrazný nárůst nadváhy a obezity v dětské populaci. Tento vysoce aktuální sekulární fenomén s celospolečenským dopadem zásadně ovlivňuje růst a vývoj dítěte, a to již od raného věku (**54**). Od druhého roku života se dynamicky rozvíjí zejména svalová soustava dítěte a dochází k fyziologickému poklesu podílu tukové tkáně. Tento trend dokládá i vývoj Body mass indexu (BMI), jehož křivka v tomto období klesá. Zlom v průběhu křivky BMI, tedy dosažení minimální hodnoty, od které pak křivka kontinuálně narůstá, se označuje jako adipozity rebound (AR) (**79**). Časný AR je silně asociován s rozvojem obezity v pozdějším věku (**35, 61**) a s rozvojem závažných metabolických komplikací (**28, 40, 60**). Trend nedostatečné pohybové aktivity (**52**), kdy již předškolní děti tráví u obrazovek a mobilních zařízení čím dál více času (**53**), posouvá věk rozvoje nadváhy a obezity do tohoto exponovaného období (**54, 62**). Řada studií přináší jasné důkazy, že hlavní příčinou zvyšování prevalence nadváhy a obezity v raném věku je právě nedostatek pohybové aktivity (**31, 37, 51, 66, 74**). Specifika motorického a somatického vývoje v předškolním věku odrážejí i doporučení Světové zdravotnické organizace (WHO) z roku 2020, která pro děti do 5 let uvádí minimální limit 180 minut pohybové aktivity denně, z toho jedna hodina by měla být v zóně střední až vysoké intenzity (**81**).

Nejnovější údaje o prevalenci nadváhy a obezity v české dětské populaci přináší studie Vážná et al., 2022 (**75**), která hodnotila efekt lockdownu v průběhu pandemie Covid-19 na základě matematického modelování růstových dat. Studie přinesla alarmující výsledky nárůstu prevalence nadváhy, obezity a zejména závažné formy obezity (BMI > + 3 SD), a to nejvíce v peripubertálním věku. U 9, 11 a 13letých dětí se pohybuje prevalence nadváhy a obezity nad 25 % (klasifikace dle WHO), u 11 a 13letých chlapců dokonce překračuje 35 % (**obr. 3a, 3b**). Také se zcela změnil trend, kdy jsme dříve většinou pozorovali vyšší procento dětí v kategorii nadváhy, aktuálně výrazně u obou pohlaví převládá podíl obézních jedinců. Studie sledovala i vývoj prevalence nadváhy a obezity v letech před pandemií (2015–2019). Jak ukazují **obrázky 4a** a **4b** liší se trend dle věkových kategorií. Zatímco u 5 a 7letých dětí pozorujeme spíše stagnaci ve vývoji prevalence, u dětí v pubertálním věku je již dříve zřejmý nárůst obezity, výraznější u chlapců. Období covidového lockdownu pak vedlo ke skokovému zvýšení prevalence ve všech věkových skupinách (**75**).

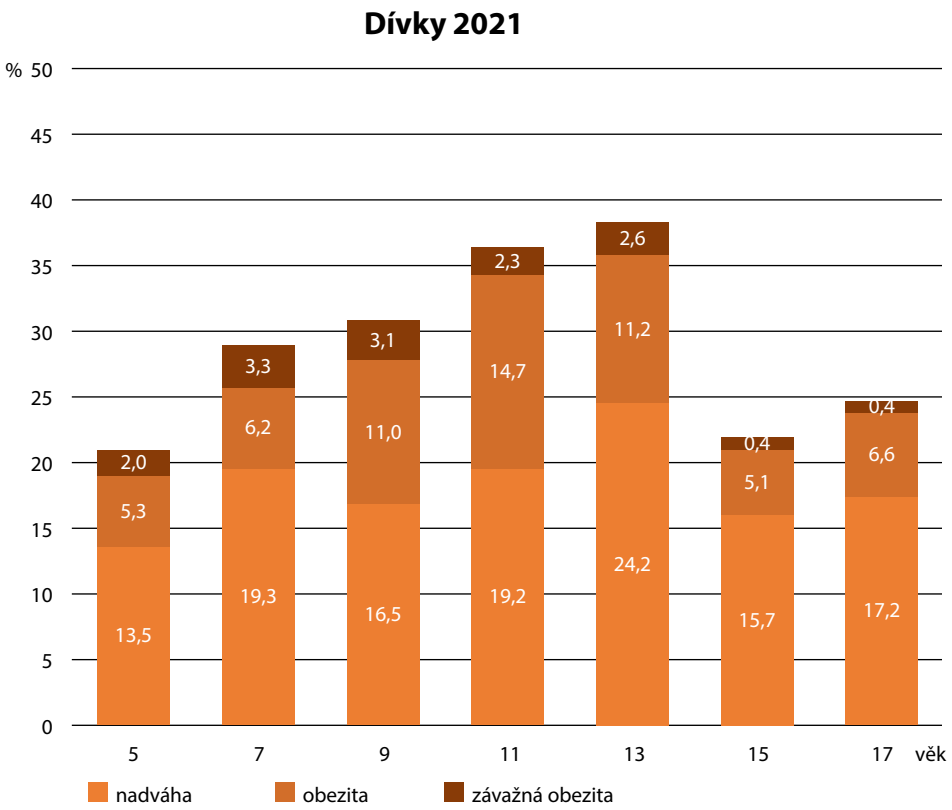
Relativní novinkou je efekt tzv. skryté neboli latentní obezity (**67**). Tento jev přímo souvisí s nedostatečnou pohybovou aktivitou, resp. rozvojem aktivní tělesné hmoty, která je nahrazována tukovou tkání. Jedná se tedy o skryté zmnožení tukové tkáně při normálních hodnotách BMI, které běžné metody skreeningového a klinického posuzování nutričního stavu dítěte neodhalí. Metabolické a kardiovaskulární důsledky jsou však stejné jako u obezity zjevné, tedy se zvýšenou hmotnostní proporcionalitou (**16, 80**). Z pohledu této skutečnosti je pak zřejmé, že údaje o prevalenci nadváhy a obezity v dětské populaci, které jsou standardně zpracovávány na podkladě kategorizace hodnot BMI, jsou značně podhodnocené. To dokládají i výsledky porovnání odhadu prevalence nadměrné hmotnosti u českých předškolních dětí na podkladě BMI a reálného procenta tělesného tuku (**67**), kde BMI uvádí o 5 až 10 % nižší hodnoty.



Obr. 3a. Prevalence nadváhy (+ 1 SD-BMI), obezity (+ 2 SD-BMI) a závažné obezity (+ 3 SD-BMI) po covidovém lockdownu v roce 2021 u českých chlapců (n = 1759).
Upraveno podle Vážná et al., 2022 (**75**).

Distribuce tělesného tuku

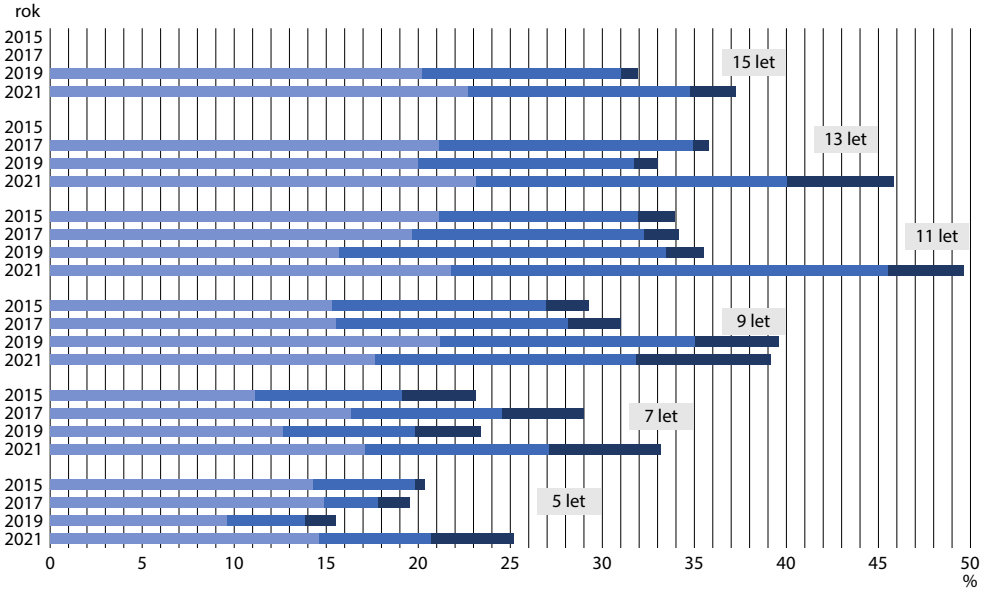
Dalším výrazným sekulárním fenoménem je změna distribuce tělesného tuku. Situace je odlišná u prepubertálních dětí a v pubertálních a adolescentních věkových skupinách. U mladších dětí převládá centrální distribuce tuku a ukládání tuku na dolních končetinách, resp. v oblasti stehna, kde nahrazuje v důsledku nízké pohybové aktivity nedostatečně rozvinutou muskulaturu. Primárně predilekční oblastí je pak břicho (**54, 66**), kde je kumulace podkožního tuku přímým korelátem tuku viscerálního a představuje tak vysoké zdravotní riziko již od předškolního věku. Sekulární změny v tloušťce vybraných kožních řas u předškolních českých dětí ukazují **obrázky 5a** a **5b**. V pubertálním věku je aktuálně predilekčním místem kumulace tuku, a to u obou pohlaví, oblast hýždí a stehna. To spolu s estrogenizačními změnami v růstu velké pánve přináší u chlapců zjevnou feminizaci jejich tělesných proporcí (viz dále).



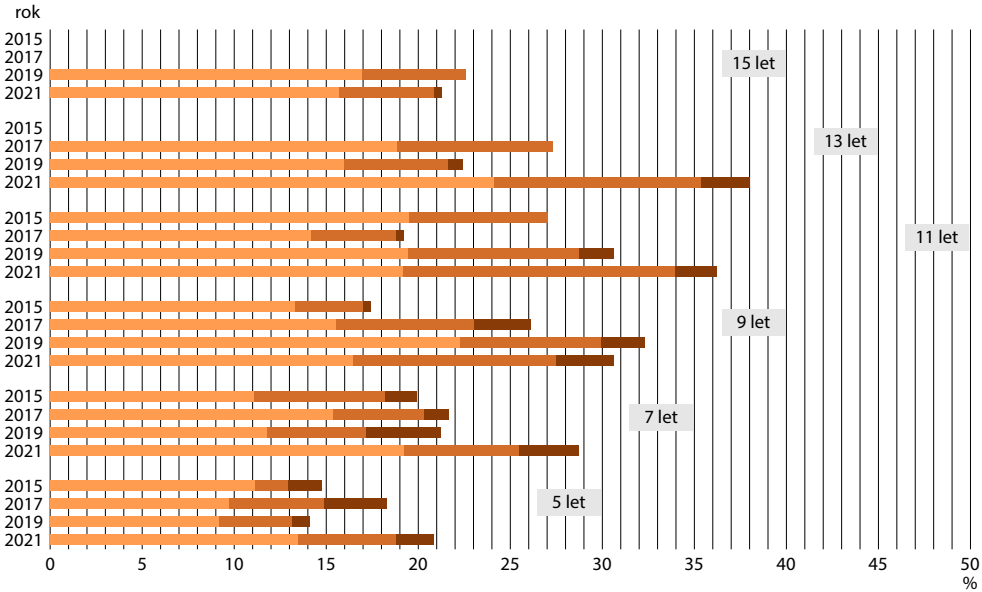
Obr. 3b. Prevalence nadváhy (+ 1 SD-BMI), obezity (+ 2 SD-BMI) a závažné obezity (+ 3 SD-BMI) po covidovém lockdownu v roce 2021 u českých dívek (n = 1758).
Upraveno podle Vážná et al., 2022 (**75**).

Obezita a puberta

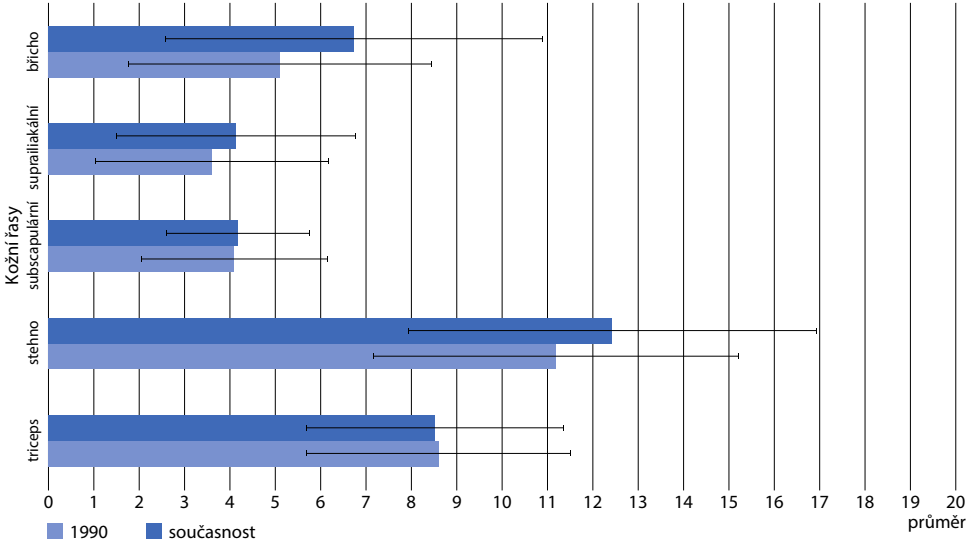
Obezita má velmi významný vliv na pubertální vývoj dítěte. Věk nástupu puberty vykazuje negativní korelaci s prepubertálními hodnotami BMI. Karlberg, 2002 (**38**) uvádí, že zvýšení hodnoty BMI od věkového průměru o jednotku (1 $kg.m^{-2}$) urychluje pubertu u obou pohlaví o 0,13 roku. Tento stav souvisí s nadměrnou produkcí leptinu, který je jedním z hlavních spouštěčů puberty, a také s významnou produkcí estrogenů tukovou tkání (**69, 70**). U dívek dochází k akceleraci růstu a pubertálního vývoje, urychluje se i kostní zrání (kostní věk) (**7, 14**). Dřívějším nástupem puberty a, v důsledku urychlení uzávěru růstových plotének, vlivem zvýšené hladiny estrogenů dochází k negativní bilanci cílové výšky ve vztahu ke genetické růstové dispozici. Zvýšené hladiny estrogenů jsou příčinou i dřívějšího dosažení pubertálního vrcholu růstové rychlosti a časnějšího nástupu



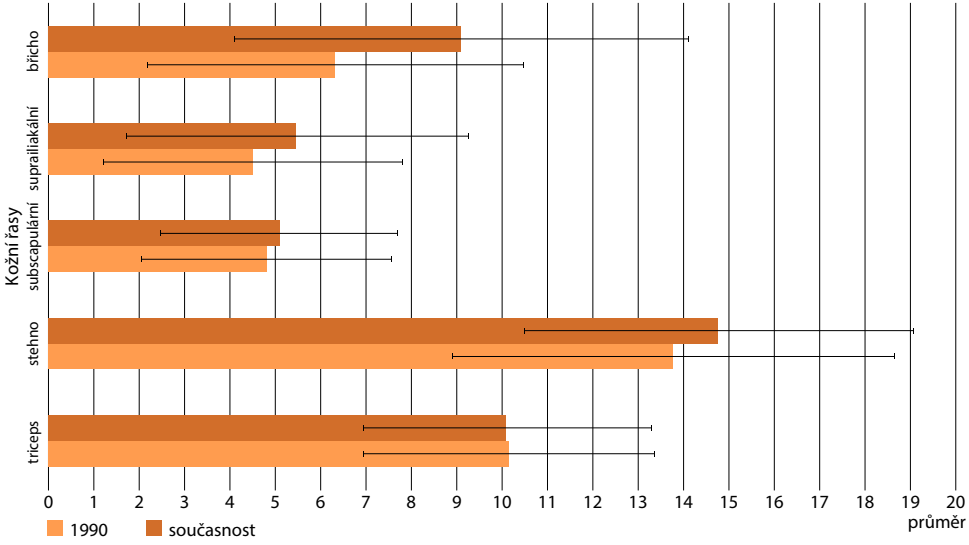
Obr. 4a. Trend vývoje prevalence nadváhy (+ 1 SD-BMI), obezity (+ 2 SD-BMI) a závažné obezity (+ 3 SD-BMI) před covidovým lockdownem u českých chlapců ve věku 5 až 17 let (n = 1759).



Obr. 4b. Trend vývoje prevalence nadváhy (+ 1 SD-BMI), obezity (+ 2 SD-BMI) a závažné obezity (+ 3 SD-BMI) před covidovým lockdownem u českých dívek ve věku 5 až 17 let (n = 1758).



Obr. 5a. Sekulární změny tloušťky kožních řas (měřeno kaliperem typu Best v milimetrech) u českých chlapců, průměrná hodnota ve věku 4–6 let. Signifikantní nárůst kožní řasy na břiše (p = 0,0001) a na stehně (p = 0,0001). Data – referenční soubor předškolních dětí z roku 1990 (4), současný soubor dětí z mateřských škol (měřeno 2016–2023, n = 414).



Obr. 5b. Sekulární změny tloušťky kožních řas (měřeno kaliperem typu Best v milimetrech) u českých dívek, průměrná hodnota ve věku 4–6 let. Signifikantní nárůst kožní řasy suprailiakální (p = 0,0001), na břiše (p = 0,0001) a na stehně (p = 0,001). Data – referenční soubor předškolních dětí z roku 1990 (4), současný soubor dětí z mateřských škol (měřeno 2016–2023, n = 397).

menarche (**26, 30, 63**). Zkrácení periody prepubertálního růstu a případný překotný průběh puberty tak může negativně ovlivnit cílovou výšku.

Pozorování vztahu tělesné hmotnosti a nástupu pubertálního spurtu, resp. věku menarche bylo publikováno již Frischem a Revellem před více jak 40 lety (**18, 19**). Tato hypotéza byla později doplněna o vztah dynamiky pubertálního vývoje u dívek a prahové hodnoty tělesného tuku (**20**). Následně se objevily studie s kritickým hodnocením této hypotézy (**23, 65, 73**). Dnešní doba se k původní hypotéze Frische a Revella vrací. Pozdější empirická pozorování i řada studií jednoznačně dřívější nástup puberty u dívek s nadměrnou hmotností potvrzují (**2, 14, 41, 42, 43, 59**).

Přesto existují názory, že sekulární akcelerace puberty u dívek není primárně podmíněná narůstající prevalencí nadváhy a obezity v dětské populaci, neboť probíhá i u hmotnostně proporčních dívek (**27**). V této studii je prezentován stagnující trend středního věku menarche, který již od 60. let 20. století zůstává neměnný ve většině států Evropy (Německo, Švédsko, Dánsko, Finsko, Holandsko). Zásadním markerem však není tělesná hmotnost, resp. hmotnostně-výšková proporcionalita dítěte, ale množství tělesného tuku. Výsledný efekt pubertální akcelerace je pak podmíněn metabolickou a hormonální aktivitou tukové tkáně (**2, 17, 25, 49, 70**). Jak je zřejmé, BMI je pouze orientačním markerem a i u jeho normálních hodnot můžeme nalézt vyšší podíl tukové tkáně v poměru k aktivní tělesné hmotě (**60**), viz výše uvedená problematika skryté (latentní) obezity (**67**). Objektivním hodnocením vztahu sekulární akcelerace puberty u dívek a nárůstu prevalence nadváhy a obezity by tak byla pouze analýza závislosti nástupu puberty a menarche ke stupni tělesné adipozity (**8, 33, 69**).

U chlapců je situace poněkud odlišná. Estrogeny z tukové tkáně mohou, stejně jako u dívek, urychlit růst a kostní zrání, objevují se i známky sekundárních pohlavních znaků. Pubertální vývoj je však veden ženským směrem, jedná se o formu periferní předčasné a časné puberty s heterosexuálním vývojem. Vlastní pubertální osa je často blokovaná, typická je absence testikulární aktivace nebo nedostatečná progrese testikulárního vývoje i růstu penisu (**7, 71**). Může se tedy naopak klinicky manifestovat obraz opožděné puberty s projevy suspektního hypogonadizmu a hypogenitalizmu. Významná je přítomnost gynekomastie již v počáteční fázi pubertálních změn (nutné odlišit od pseudogynekomastie na podkladě hromadění tukové tkáně), která signalizuje receptorovou citlivost jedince na estrogeny.

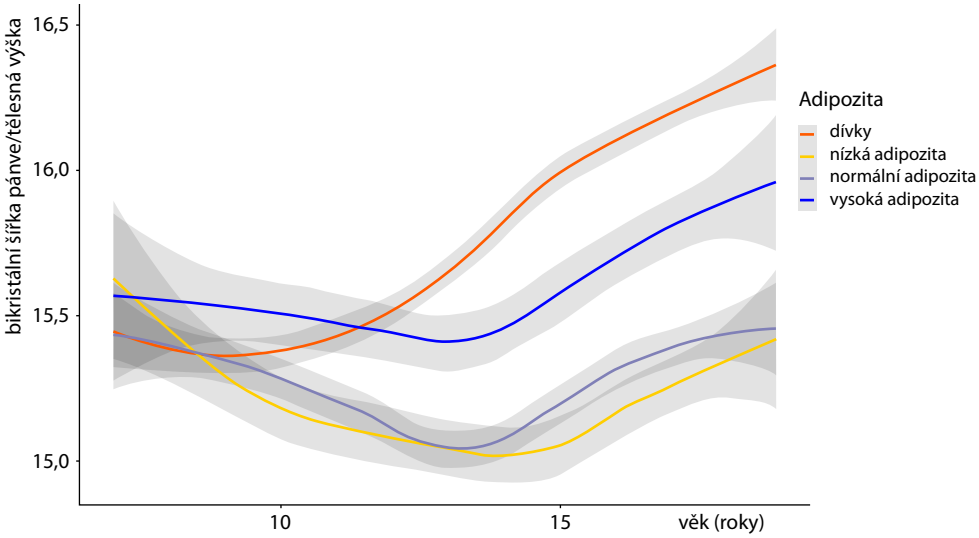
Mechanizmus adipózní estrogenizace se uplatňuje v přímé estrogenizaci organizmu periferní konverzí testosteronu na estron vlivem enzymu aromatázy z tukové tkáně (**68**). Její exprese a následná koncentrace je tkáňově specifická, s vyšší mírou v gonádách, mozku, prsní žláze a tukové tkáni (**72**). Primární funkcí tohoto enzymu je konverze androgenů (primárně testosteronu) na estrogeny (primárně estradiol). Celkový dopad na organizmus však nespočívá jen ve zvýšení hladin estrogenů. U chlapců a mužů dochází k depleci testosteronu s celou škálou navazujících komorbidit. Estrogeny vedou k akumulaci tukové tkáně a dalšímu zvýšení množství aromatázy (**9, 24**). Tento mechanizmus pozitivní zpětné vazby již byl nejen teoreticky popsán, ale i experimentálně ověřen (**1, 10**).

Uvedené změny v hormonální regulaci se odráží i ve skeletálním růstu a morfogenezi, zejména v ovlivnění mechanizmu intersexuální diference růstu velké pánve v období puberty. U člověka je

výchozím morfologickým modelem mužský (androidní) typ pánve, který je u dívek vlivem působení estrogenů v pubertě transformován na typ ženský (gynoidní) (**36**). Studie Novak et al., 2020 (**50**) pak na souboru českých mužů doložila silnou závislost mezi relativní šířkou pánve v mladé dospělosti (bikristální šířka / tělesná výška) a vyšší adipozitou v období puberty. Relativně širší pánev se rovněž odrážela v míře estrogenizace vyjádřené poměrem slinného estradiolu a testosteronu. Jak ukazuje **obrázek 6**, chlapci s vysokým podílem tělesného tuku mají pubertální profil vývoje relativní šířky pánve velmi podobný dívkám a dosahují i výrazně vyšších hodnot šířky pánve v dospělosti.

ZÁVĚR

Životní styl a stravovací návyky významně ovlivňují zdravotní stav populace. V dětském věku jsou pak přímo určujícími faktory správného růstu dítěte a fyziologického průběhu puberty. Kritický nedostatek pohybové aktivity u současných dětí se odráží v poruchách formování struktur pohybového aparátu, zejména sagitálního zakřivení páteře a podélné nožní klenby. Negativně ovlivněna je i kostní denzita a rozvoj muskulatury. Relativně novým fenoménem, zejména raného věku, je výskyt skryté (latentní) obezity, kde je nedostatečný rozvoj svalové tkáně, zejména na dolních končetinách, nahrazován do proporčního objemu daného segmentu tukem. Celkový podíl tukové tkáně dítěte je tak nadlimitní, v sumární hmotnosti, resp. SD-BMI se však neprojeví. Tuková tkáň svojí hormonální aktivitou výrazně ovlivňuje pubertální vývoj jedince. Snižuje věk nástupu puberty, mnohdy urychluje i její průběh. Tím výrazně zkracuje prepubertální růst i období pubertálního spurtu, což



Obr. 6. Ontogenetický vývoj relativní šířky pánve (bikristální šířka/ tělesná výška × 100) u českých dětí; u chlapců v rozlišení míry adipozity (nízká = 1. kvartil , střední = 2. a 3. kvartil, vysoká = 4. kvartil adipozity v daném roce života). Zdroj dat – soubor českých dětí z let 1985–1993, věk 7–18 let , n = 7348.

vede ke snížení cílové výšky dítěte vůči jeho genetické růstové dispozici. U chlapců pak hormony tukové tkáně působí na pubertální vývoj restriktivně, blokují pohlavní vyzrávání a vedou k prvkům feminizace ve formování postavy.

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MACRODACTYLY OF HAND AND COINCIDENCE WITH A MILD FORM OF POLAND SYNDROME: A REVIEW AND CASE REPORT OF A CZECH BOY

MAKRODAKTYLIE RUKY A KOINCIDENCE S MÍRNOU FORMOU POLANDOVA SYNDROMU: PŘEHLED A KAZUISTIKA ČESKÉHO CHLAPCE

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SUMMARY

Isolated macrodactyly of the hand is a rare severe congenital disease that is usually not inherited. It occurs in approximately 1/50,000–1/100,000 live births.

The clinical findings and presentation with apparent territorial soft tissue and bone overgrowth are pathognomonic of lipomatosis of nerves, which involves benign fibro-fatty infiltration.

The aims of this presentation is to summarize the current knowledge about the etiopathogenesis of hand macrodactyly, where somatic gain of function mutations of the *PIK3CA* gene, which can be recently detected in the affected tissue, play a key role in the development of this disease.

The main aim is to present the result of surgical correction of overgrown phalanges of the 3rd and 4th fingers in a boy aged 11.5 years, who was also diagnosed with a mild form of Poland syndrome. The aim of the first operation was reduction of lipofibromatous tissue, neurolysis of the n. medianus and digital nerves, release of the carpal tunnel and arrest of the growth of the affected fingers by

drilling epiphysiodesis. Histological and histochemical investigation proved nerve with lipofibromatous tissue of the palm. The timing of this operation was based on the method of anthropometric prediction of bony overgrowth of the affected fingers using comparative radiographs of both hands, data for hand growth from anthropometric research and comparison with the radiograph of the patient's father's hand. The second operation was performed at 12 years and 10 months to remove hypertrophic scars and deepen the interdigital space between the 3rd and 4th toes. The result of surgical treatment at the age of 14 years and 3 months can be assessed as relatively good in terms of cosmetic and functional aspects. However, progression of lipofibromatous hamartoma n. medianus at older age and premature osteoarthritis of the digital joints of the affected fingers cannot be excluded. Surgical treatment of hand macrodactyly should be left exclusively to those trained in congenital hand deformities. As tissue from the pathological lesion was not available at present, it was not yet possible to investigate somatic pathogenic variants in the *AKT1* and *PIK3CA* genes. No pathogenic or likely pathogenic variant was found from blood samples.

The coincidence of macrodactyly and incompletely expressed Poland syndrome in our patient deserves attention.

Keywords: macrodactyly, overgrowth, hand dysplasia, lipofibromatous hamartoma, median nerve, PI3K-AKT, somatic mosaicism, epiphysiodesis, debulking, Poland syndrome

INTRODUCTION

Isolated macrodactyly affecting the digits of the upper or lower extremity is a rare non-hereditary congenital malformation. It occurs in approximately 1/50,000–1/100,000 live births and varies according to regional and ethnical demographics (**34, 5, 18**). The fingers are abnormally large due to overgrowth of the finger skeleton and soft tissues, which involve muscle and predominantly fibro-adipose tissue. Skeletal pattering and gross morphological features of the digits are preserved (**24, 17**). Patients suffer from functional, cosmetic and psychological problems.

Enlargement of one or multiple digits, was described in the literature nearly 200 years ago. However, the etiopathogenesis of this disease has only begun to be elucidated in the last decade.

The diagnosis of macrodactyly should be reserved for patients with isolated congenital digit overgrowth affecting all tissue types. Clinical presentation and natural history of macrodactyly can vary greatly among patients. Macrodactyly in hand has a preference for the median nerve territory, mainly involving index, thumb and middle finger (**40**). Pedal macrodactyly prefers medial plantar nerve territory, the second toe is the most commonly affected (**6**). It may present at birth and combine with syndactyly, digital deviation, thenar eminence hypertrophy, palm and forearm hyperplasia. Most patients suffer from progressive overgrowth. (**5**). Tissue overgrowth can progress excessively even during adult life (**31**).

ETIOPATHOGENESIS

The cause of macrodactyly remained unknown for a long time. Somatic (postzygotic) mutations in genes affecting cell growth were considered. However, only new technologies (whole-exome sequencing) have made it possible to detect somatic mutations present in the affected tissue. After 2010, the first papers have appeared pointing to a key role of the *PIK3CA* gene in the development of this disease (**20, 27**). Recently, somatic gain of function mutations in the *PIK3CA* gene were detected in the affected tissue by other authors (**34, 18, 24, 2**). This gene encodes the alpha catalytic subunit of phosphatidylinositol-4,5-bisphosphate 3-kinase, a member of the phosphatidylinositol 3-kinase (PI3K) enzyme family, which is a critical member of the PI3K-Akt-mTOR signalling pathway mediating cell proliferation, survival and metabolism through enhancement of lipid kinase activity (**18, 34, 24**). Mutations in the *PIK3CA* gene has been also identified in other multiple overgrowth disorders, which are now, together with macrodactyly, grouped as PIK3CA-related overgrowth spectrum (PROS) disorders (**14, 15, 34, 24, 31**): congenital lipomatous overgrowth, vascular malformations, epidermal nevi and skeletal/scoliosis/spinal abnormalities (CLOVES syndrome), Klippel–Trenaunay syndrome (KTS), megalencephaly-capillary malformation (MCAP), dysplastic megalencephaly (DMEG), and capillary malformation of the lower lip, lymphatic malformation of the face and neck, and asymmetry and partial/generalized overgrowth (CLAPO syndrome). Signalling pathway PI3K-AKT-mTOR is shown schematically in **Figure 1**. Mosaic *AKT1* gene pathological variants are known to cause Proteus syndrome (**19**). In a group of 24 patients with isolated macrodactyly, Tian and colleagues (**34**) identified 4 patients with a mosaic *AKT1* p.Glu17Lys variant characteristic of Proteus syndrome. However, according to the skin presentation characteristic for this disease, these patients met the diagnostic criteria of Proteus syndrome. Other analyses identified the *PIK3CA* gene as the seed gene that causes the phenotype of isolated macrodactyly (**18, 24**).

These findings represent a significant advance in the understanding of the etiopathogenesis of macrodactyly. Nevertheless, the causes and regulatory activities that shape hyperplastic signals that lead to integrated patterning in overgrowth remain unclear (**24**).

Long before the discovery of the molecular genetic changes underlying macrodactyly, surgeons had noticed that overgrowth generally affects the territory of distribution of a single nerve (**38, 22, 6, 40, 32**). Peripheral nerves in the involved territory are usually markedly enlarged, with benign fibro-fatty infiltration (**16, 21, 7, 32, 22, 23**). This distinctive disease pattern can be visualized on plain radiographs. The case presented by Sir Robert Jones in 1898 before the London Pathological Society represents a landmark in the radiological imaging of peripheral nerve lesions (**21**). Feriz et al. (**8**) describing localised gigantism involving the lower limb used the term macrodystrophia lipomatosa (MDL). Some experts continue to consider it the most appropriate designation for the disease described (**32, 22, 23**). The highly consistent distribution of the nerve abnormality and the tissue hypertrophy indicated macrodactyly as being a nerve-mediated overgrowth (**6, 35, 24**). A potential etiology of nerve directed function underlying this disorder was proposed by Moore as early as in 1942 (**25**) and has been suggested by other authors (**13, 29, 12**). The question is how to approach these old findings and hypotheses in the light of new genetic findings. As a number of authors have demonstrated, *PIK3CA* gene mutation leads to the activation of the PI3K-AKT-mTOR

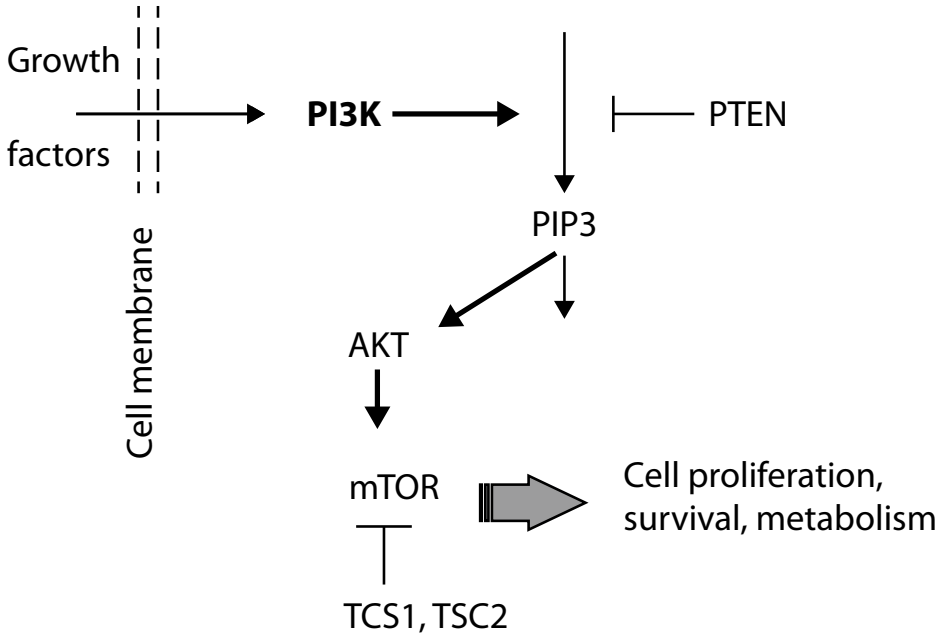


Figure 1. Schematic representation of the PI3K-AKT-mTOR signaling pathway. Adapted from Yehia & Joanne Ngeow **(41**).

PI3K – phosphatidylinositol 3-kinase

PIP2 – Phosphatidylinositol 4,5-bisphosphate

PIP3 – phosphatidylinositol (3,4,5)-trisphosphate

PTEN – Phosphatase and tensin homolog, tumor supressor gene

AKT – AKT serine-threonine protein kinase

mTOR mammalian target of rapamycin signalling pathway

TSC1, TSC2 Tuberous sclerosis 1 (hamartin), Tuberous sclerosis complex 2 (tuberin)

PIK3CA Gain of function somatic mutations cause: megalencephaly-capillary malformation syndrome, CLOVES (congenital lipomatous overgrowth, vascular malformation, epidermal naevi and skeletal/spinal anomalies), Klippel-Trenaunay syndrome, Facial infiltrating lipomatosis, fibroadipose hyperplasia (including macrodactyly). Germline mutations cause Cowden syndrome and megalencephaly-capillary malformation syndrome.

PIK3R2 germline/somatic mutations cause megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome (MPPHS)

Germline loss of function mutations of PTEN cause Cowden syndrome, Bannayan – Riley, Rucalcaba syndrome, PTEN related autism spectrum disorder, Proteus syndrome

AKT1 – somatic gain of function mutations cause Proteus syndrome (macrodactyly is frequent), germline mutations cause Cowden syndrome.

AKT3 – somatic mutations: hemimegalencephaly, germline mutations: MPPHS.

TSC1, TSC2 – loss of function mutations cause tuberous sclerosis. Macrodactyly is described as a rare manifestation in the context of tuberous sclerosis complex (boy with bilateral macrodactyly) (**30**)

signalling pathway. McNamara et al. (**24**) found high proportion of altered PIK3CA transcripts especially in nerve and adipose tissue. Activation of AKT protein has been demonstrated by immunohistochemical analysis of serine-threonine kinase (AKT) monoclonal antibody (**18)**. AKT protein expression in the adipose tissue of patients with macrodactyly was higher than that of patients with polydactyly (**18).** AKT protein, after which the signal is transmitted to the mTOR, resulting in adipocyte proliferation and the enhancement of metabolism, causing the patients' fingers/toes to develop adipose tissue hyperplasia and nerve-fiber fat infiltration, finally leading to the enlargement of the fingers or toes to form macrodactyly (**18)**.

TREATMENT

Macrodactyly is a rare disease with a very variable presentation. That is why there is still no standardized protocol for the treatment, no standardized tool to evaluate surgical outcomes and follow-up of the patients (**34,10, 31**). The treatment is a challenge even for an experienced surgeon.

There are several surgical techniques that make it possible to primarily reconstruct the affected fingers rather than amputate. Cerrato et al. (**5**) presented experience with surgical techniques that include soft tissue debulking, osteotomy for volume reduction or partial amputation, wedge osteotomy for angulation correction, epiphysiodesis, transfer of fingers from the hand or foot, and amputation of the rays. Surgical intervention is typically required to improve the size and function of the affected digits. However, when an involved digit is rapidly progressive in size, ray resection amputation may be the most appropriate treatment. (**39**).

The median nerve lipofibromatous hamartoma (LFH) treatment should be focused separately on nerve compression symptoms and macrodactyly. Carpal tunnel release is the mainstay of treatment for neuropathy (**38)**. Other authors make similar recommendations (**9, 33, 31,7**). Ezaki (**7)** offers an algorithm summary of assessment and treatment. Cavadas and Thione (**4**) documented a unique case in which a combination of ray resection, partial finger resection, and toe transfer resulted in a four-digit hand with acceptable function and cosmesis. However, despite the development of new surgical techniques, the treatment of macrodactyly remains very difficult and, especially in cases with progressive overgrowth, unsatisfactory. The hope for patients is medical targeted therapy against PI3K-AKT1-mTOR pathway based on a deeper understanding of the etiopathogenesis (**34, 24, 7, 37**).

The aim of this presentation is to summarize the known findings on the etiopathogenesis of hand macrodactyly and to show the result of surgical correction of overgrown phalanges in a boy 11.5 years old by means of carpal tunnel release, reduction of the lipofibromatous tissue, neurolysis and drilling epiphysiodesis. The timing of this surgery was based on the anthropometric prediction of bone overgrowth of the affected 3rd and 4th rays and comparison with the radiograph of the patient's father's hand.

CASE REPORT

The boy was first examined at the Centre for Defects of Locomotor Apparatus at the age of 11 years and 4 months for macrodactyly of the 3rd and 4th fingers of the right hand. This congenital anomaly of the hand, which is classified as a dysplasia according to Oberg et. al**.** (**26**), did not run in the family.

The current disease

The first signs of the disease were already observed at birth – a larger third finger of the right hand. From the age of 1 year, enlargement of the fourth finger was also noticeable. *Lymphoscintigraphy* at 7 years showed normal lymphatic system of both upper extremities from wrist to subclavian region. At 8 years of age, a *genetic examination* was performed with the following conclusion: suspected non-genetic cause of isolated limb defect. Normal male karyotype 46, XY.

Color Doppler examination of upper extremity vessels at 8.5 years showed no vascular malformation or flow changes in the right upper extremity.

Neurological examination at 9 years revealed Attention Deficit Hyperactivity Disorder (ADHD) and social immaturity. Due to ADHD, the patient is being monitored by a *paediatrician*, and no medical treatment has been instituted.

Rheumatological examination was performed at 9 years of age with the following findings: painless swelling of the 2nd, 3rd and 4th fingers of the right hand, suspected lymphedema. Short-term lymphatic drainage was without effect.

Clinical, radiological and anthropological examinations were performed at the age of 11 years and 4 months:

Anthropometric characteristics at age 11 years and 4 month
Body height: 153.6 cm (0.7 SD), weight 63 kg (2.3 SD), BMI 26.7 (2.4 SD) – obesity. Body proportions are within the normal range (sitting height 79 cm, arm span 157.6 cm), the right upper limb was 2.4 cm longer. Head circumference 55.5 cm (1.1 SD). Puberty (P2, testicular volume 6 ml) and bone age according to Tanner RUS 12.6 years were slightly accelerated. This was consistent with the growth curve. Growth was within the limits of hereditary growth potential. Hypoplasia of the left pectoralis major muscle.

Figure 2 shows the phenotype at 13 years and 1 month and 14 years and 3 months.

The boy was obese. There was mild hypoplasia of the left pectoralis major muscle and mamilla minora. Elevation of both upper limbs was unrestricted. The patient had mild orofacial stigmata (epicanthus, high palate, malocclusion, larger incisors) and ADHD symptoms.

Macrodactyly is shown in the **Figure 3a, b** and at X-ray of hands – **Figure 4**.

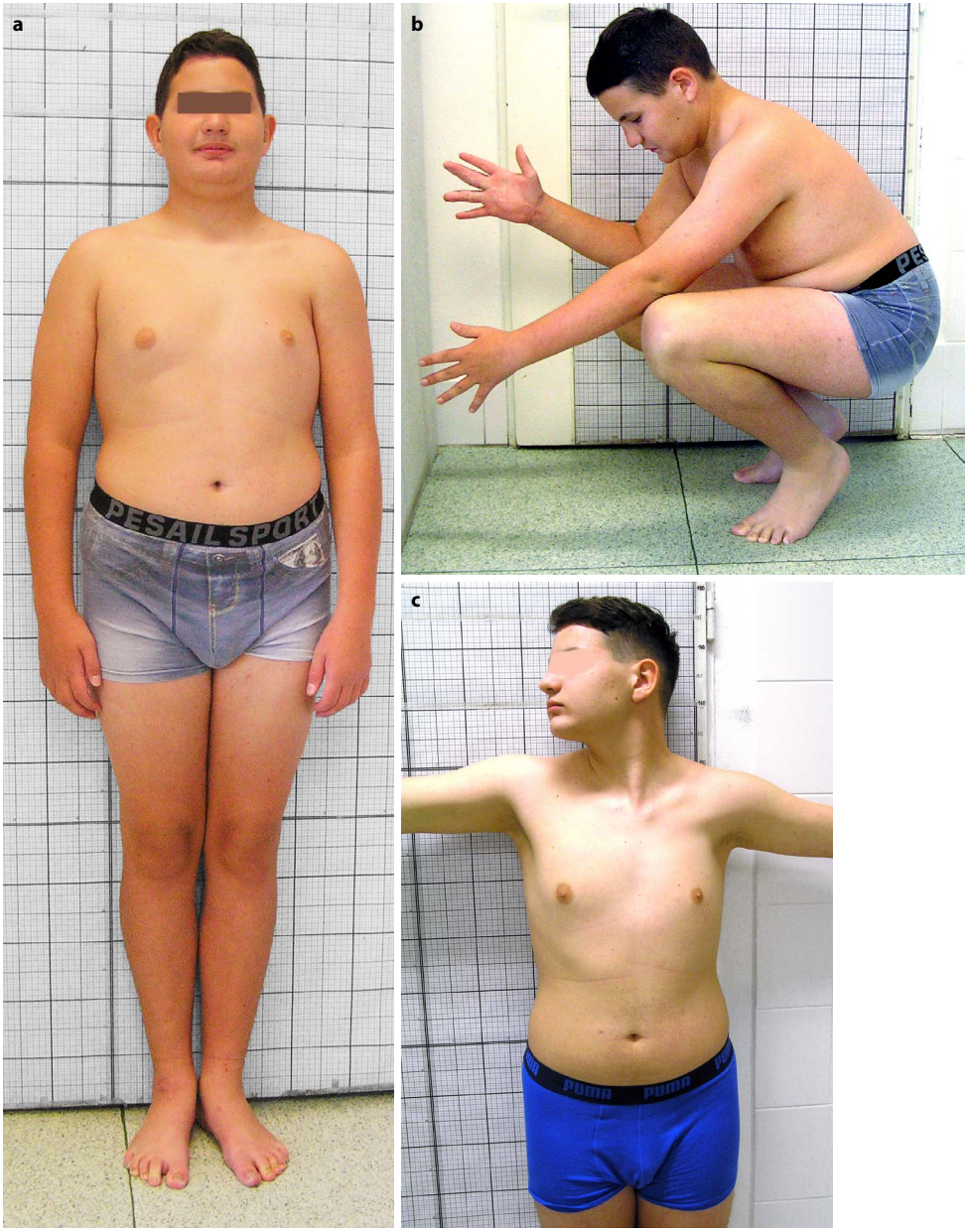


Figure 2a, b, c. Phenotype **a.** at 13 years and 1 month, **c.** at 14 years and 3 months. **a, c**. Note the hypoplasia of the left pectoralis major and mamilla minora.

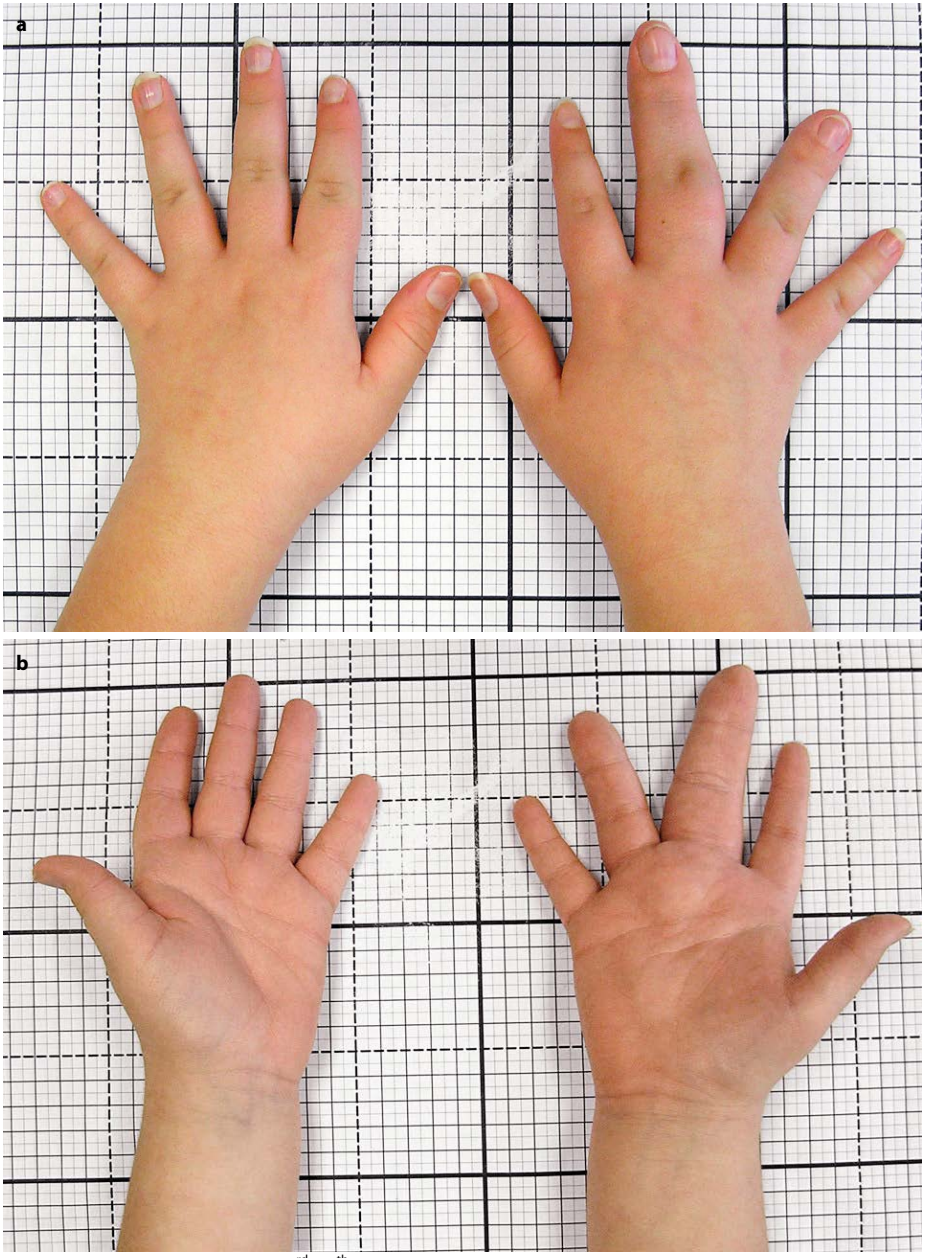


Figure 3a, b. Macrodactyly of the 3rd a 4th finger of the right hand (11 years 4 months). Note the swelling in the palm of the hand in the middle.

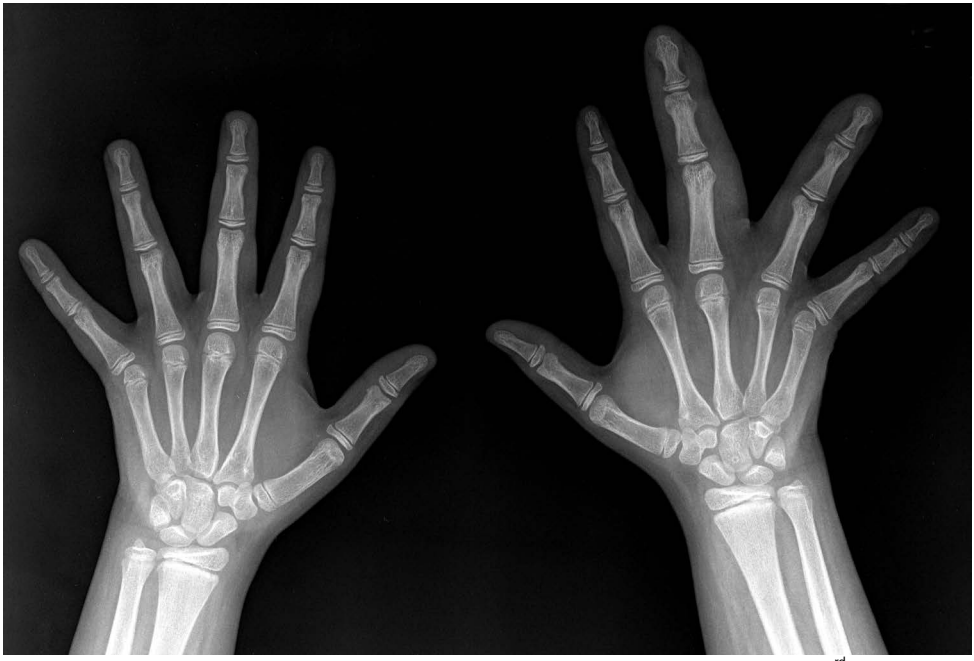


Figure 4. X-ray of hands at age of 11 years and 4 months. On the right hand all phalanges of the 3rd finger and the distal phalanx of the 4th finger are longer; radial desaxation 8° at the level of the proximal interphalangeal joint of the 3rd finger. Note the widening of the soft tissue shadow especially on the 3rd finger and commissural between the 3rd and 4th fingers.

We recommended to stop the longitudinal growth of the three phalanges of the 3rd finger and the distal phalanx of the 4th finger of the right hand by drilling epiphysiodesis.

The aim of the anthropological examination was to predict the residual growth of the 3rd and 4th finger into adulthood. Roentgenological growth charts of phalanges were not available, so we used anthropometric data on hand growth (**3**) and comparison with the hand of the patient's father.

The difference between the lengths of both hands was 8 mm. The left hand is expected to grow normally. From 11.5 years to adulthood, the hand will grow another 35–40 mm, with a slight acceleration of puberty expected to be 30–35 mm. The growth of the third finger will be approximately 15 mm. Comparison with the X-ray of the father's hand leads to the same value. The 3rd finger on the right hand will grow at least 1.2 times faster, a higher value is not excluded. We assume that the 3rd finger of the right hand will grow another 18–20 mm. Early epiphysiodesis of the growth plates on the 3rd finger could not only prevent further progression but lead to length equalization. The growth of the phalanges from the apophysis (so-called acrophysis) and into the width cannot be influenced.

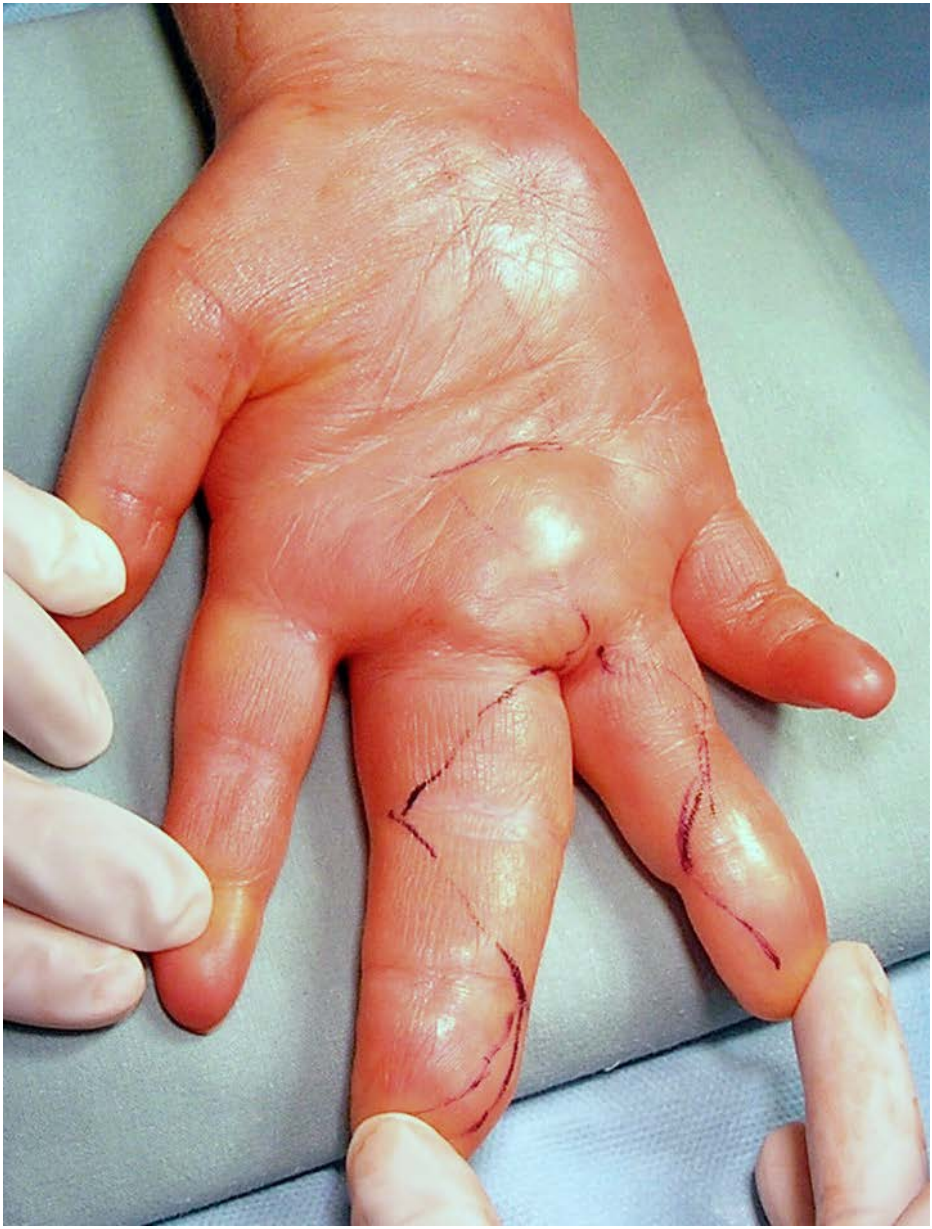


Figure 5a. First surgery at 11 years and 6 months: planning the surgical approach; **b.** neurolysis of lipofibromatous hamartoma n. medianus and digital nerves, which are very strong.

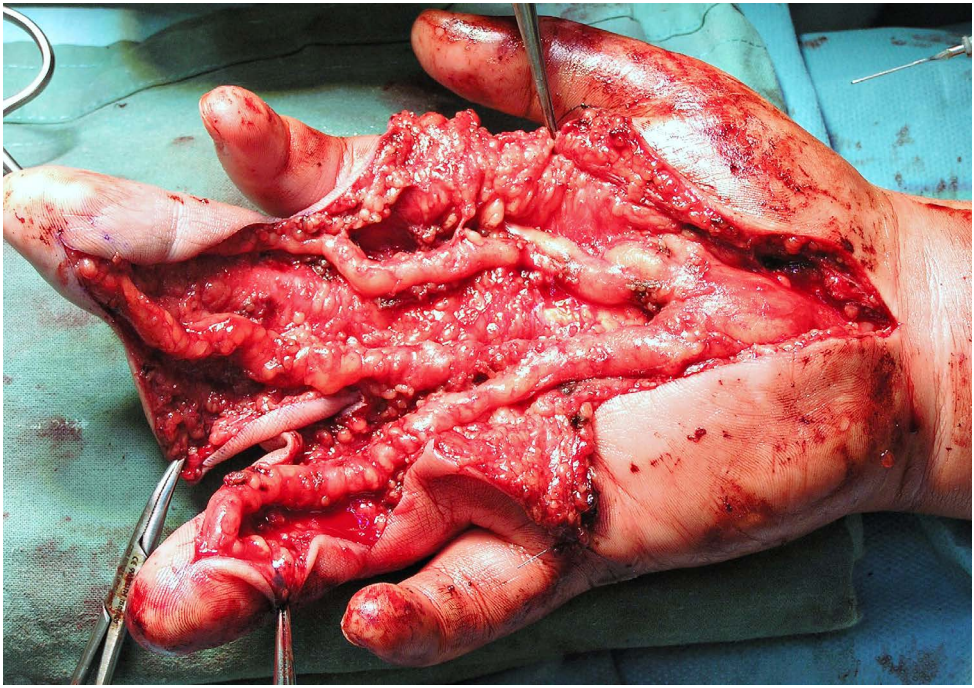


Figure 5b. First surgery at 11 years and 6 months: neurolysis of lipofibromatous hamartoma n. medianus and digital nerves, which are very strong.

Course of treatment

The first operation was performed at 11 years and 6 months: verification and neurolysis of lipofibromatous hamartoma of median nerve and digital nerves. The carpal tunnel release, reduction of the lipofibromatous tissue of the palm, 3rd and 4th fingers, drilling epiphysiodesis of the three phalanges of the 3rd finger and distal phalanx of the 4th finger were performed in one stage – see **Figure 5a, b**.

Lipofibromatous tissue of the palm was histologically and histochemically examined. **Figure 6a, b** shows a nerve with lipofibromatous tissue **– a**, and a detail of two nerves surrounded by lipofibromatous tissue – **b**.

The surgical wound on the 3rd finger healed per secundam due to necrosis of the wound margins. A short skin syndactyly of the 3rd and 4th fingers developed. A 20-degree distal interphalangeal (DIP) joint contracture of the 3rd finger was corrected with a night splint (Barinka's splint) – see **Figure 7a, b**.

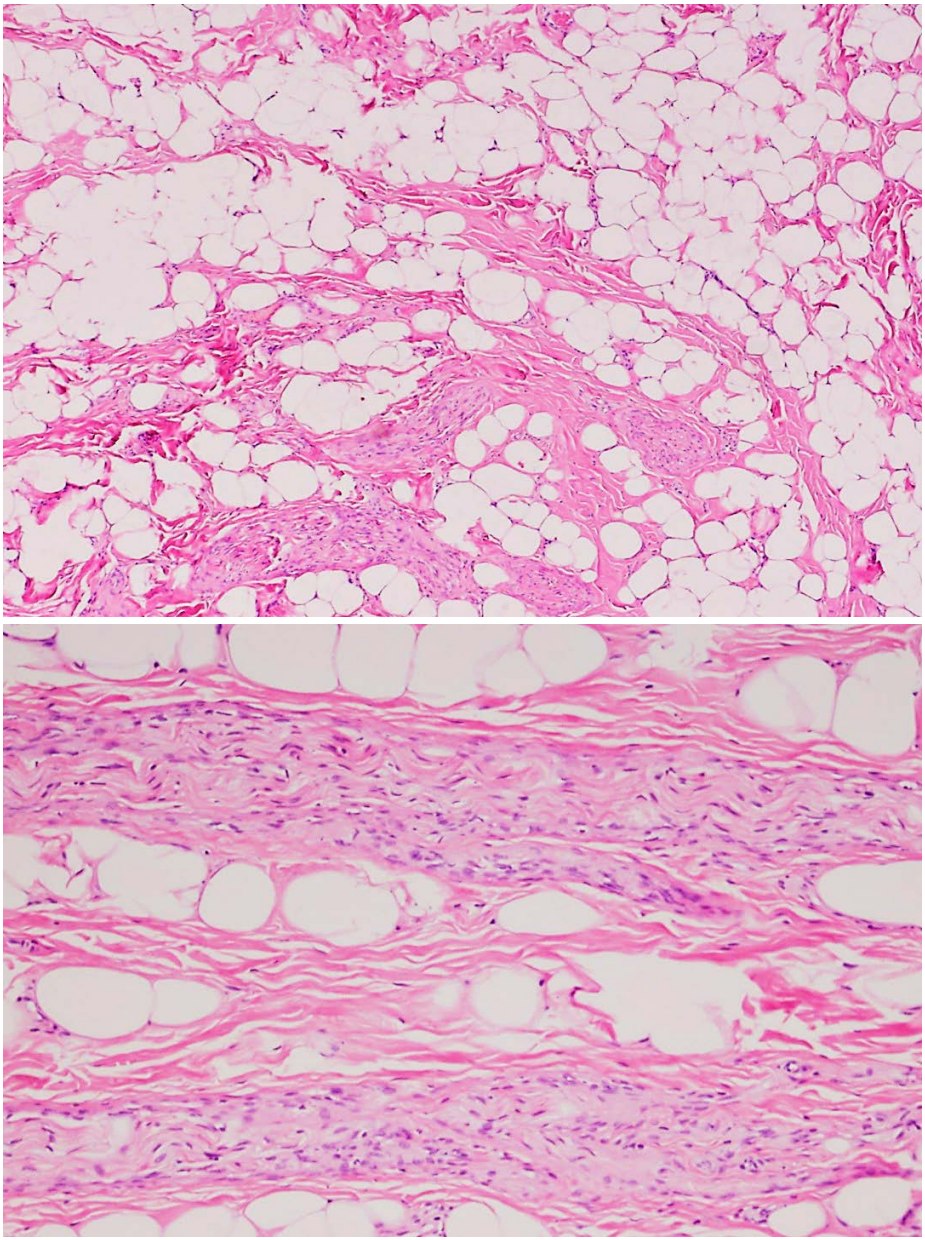


Figure 6a, b. Histological and histochemical investigation of lipofibromatous tissue of the palm: **a.** nerve with lipofibromatous tissue; **b**. detail of two nerves surrounded by lipofibromatous tissue.

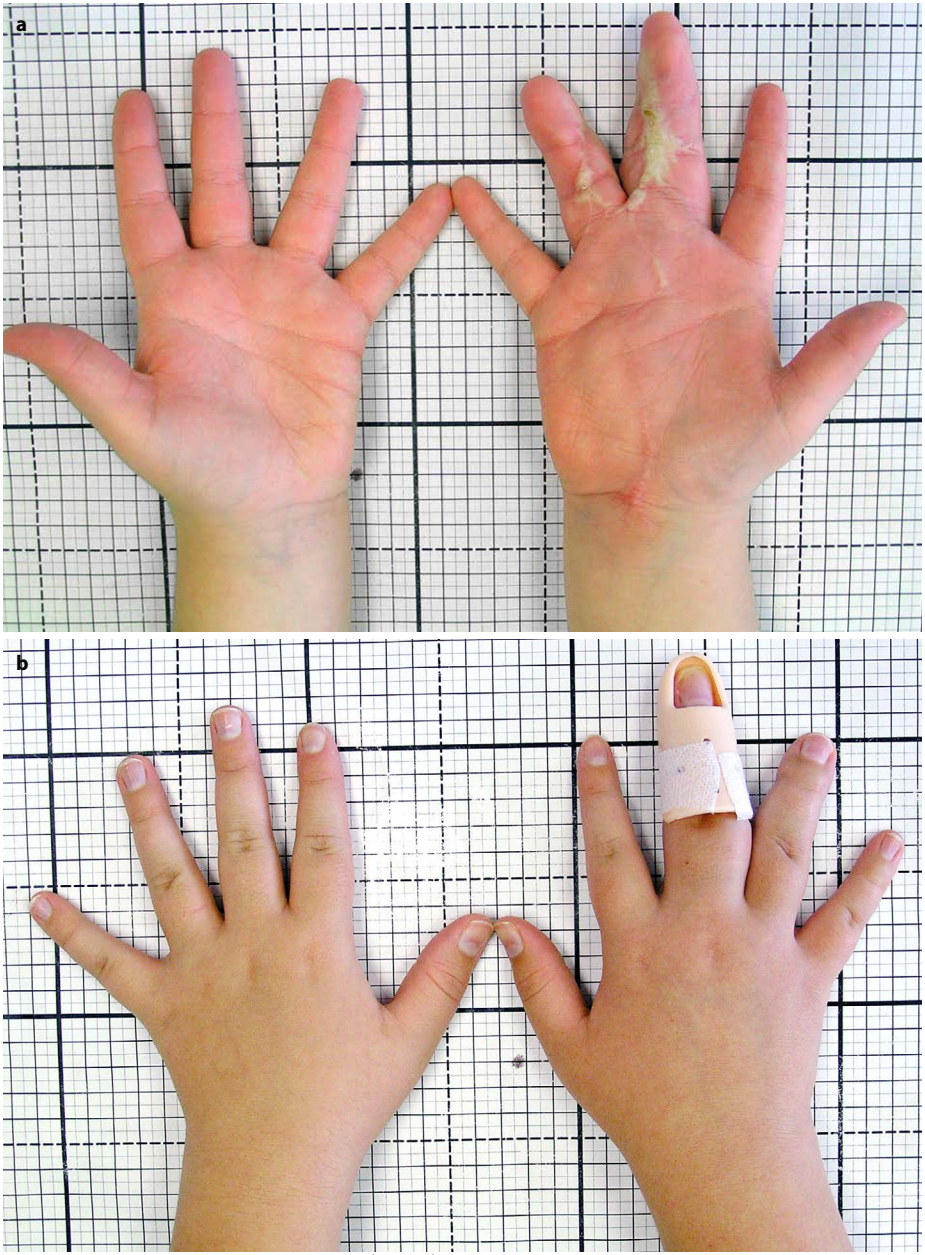


Figure 7a, b: **a.** hypertrophic scars of the 3rd and 4th fingers and short skin syndactyly; **b.** night splinting (with Barinka´s splint) due to 20-degree contracture of the distal interphalangeal joint of the 3rd finger.

The second operation was performed at 12 years and 10 months to remove the hypertrophic scar and the deep interdigital space between the 3rd and 4th fingers – see **Figure 8a**. The wound healed per primam. Passive flexion of the fingers of the hand is unrestricted and the sensitivity of the 3rd and 4th fingers is reduced. Application of a night splint to correct the DIP joint contracture and active and passive rehabilitation of the 3rd finger of the right hand was recommended.

Results are demonstrated in photographs **– Figures 8b, c, d, e**.

At the age of 14.2 years, bone age accelerated to 15.8 years. This means that the longitudinal growth of the hand is approximately complete. The length of the three phalanges of the 3rd finger is 96 mm on the right side, 94 mm on the left side and the length of the phalanges of the 4th finger is 89 mm and 91 mm respectively – **Figures 9a, b.**

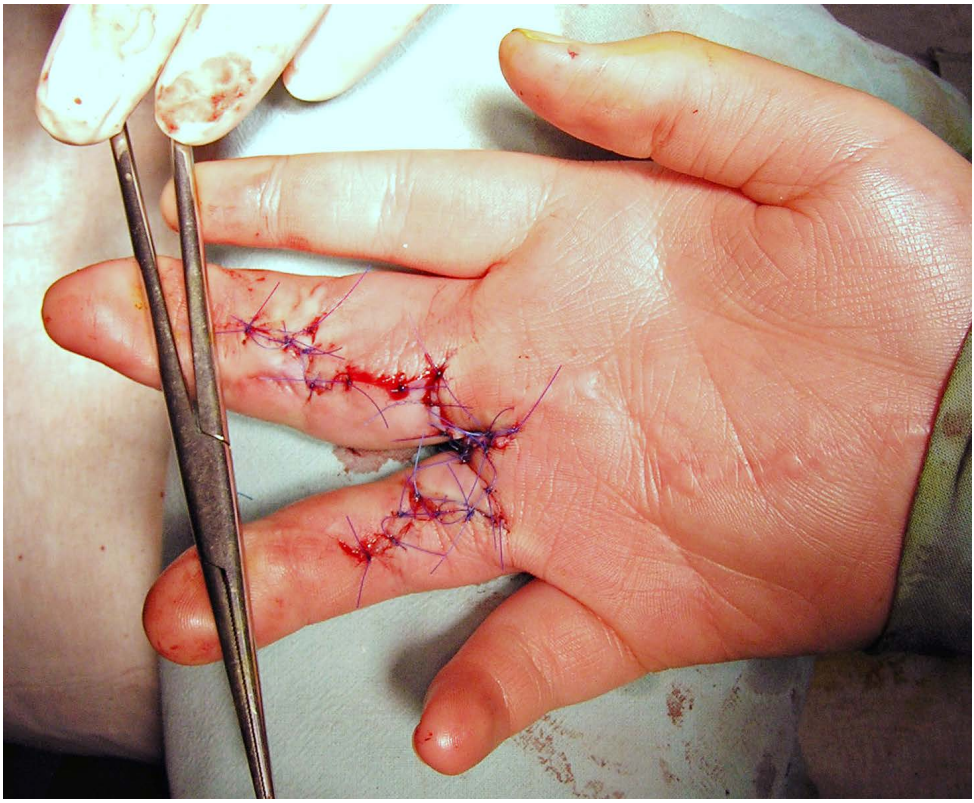
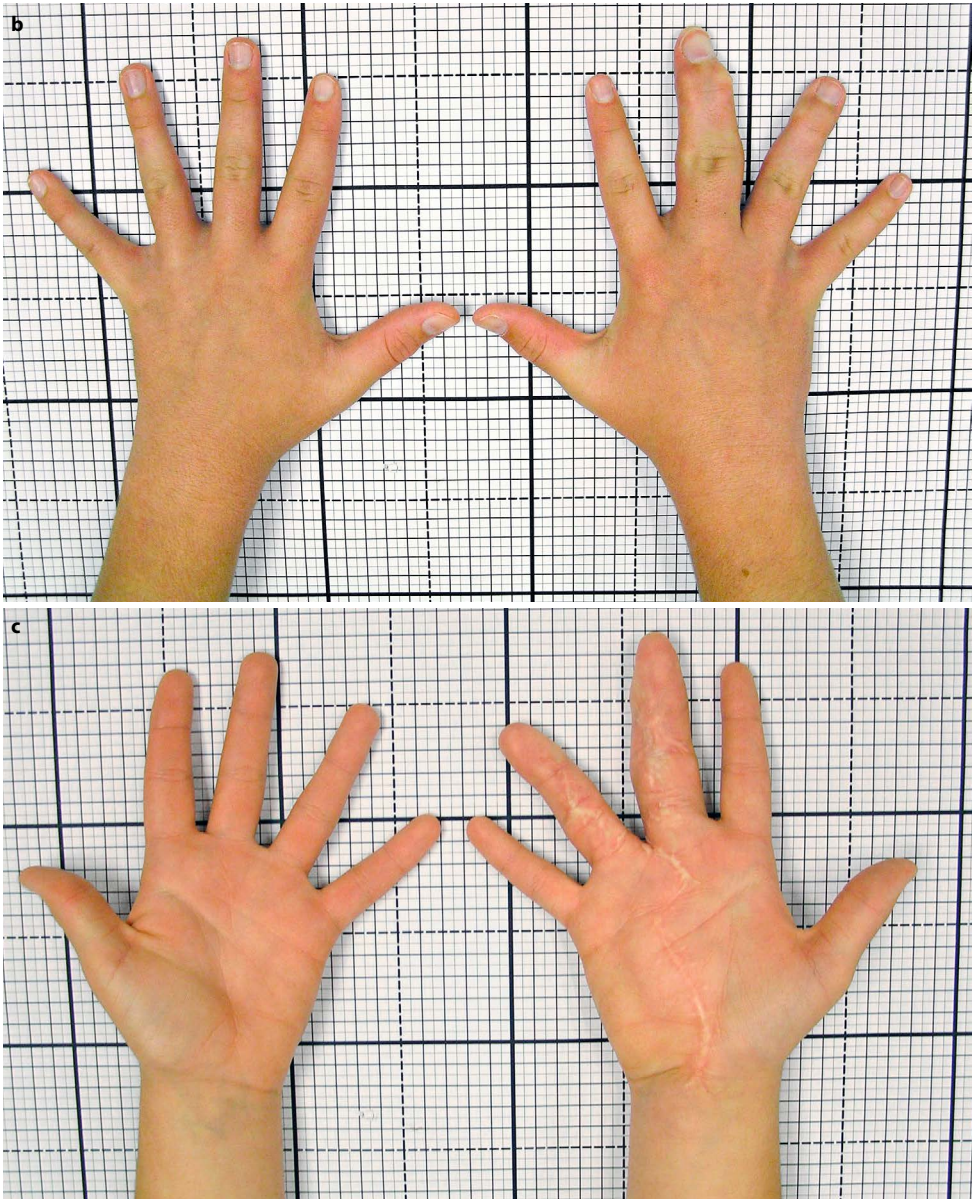


Figure 8a. Second operation at 12 years and 10 months: hypertrophic scars were removed and the interdigital space between the 3rd and 4th fingers was deepened.



Figures 8b, c. Shows the result of surgical treatment at the age of 14 years and 3 months in terms of cosmetics and function. The active flexion at the distal interphalangeal joint of the 3rd finger of the right hand is limited to 30°, while the flexion of the 3rd finger of the left hand at the same joint is 60°. Sensitivity at the distal joint of the 3rd finger is slightly reduced.

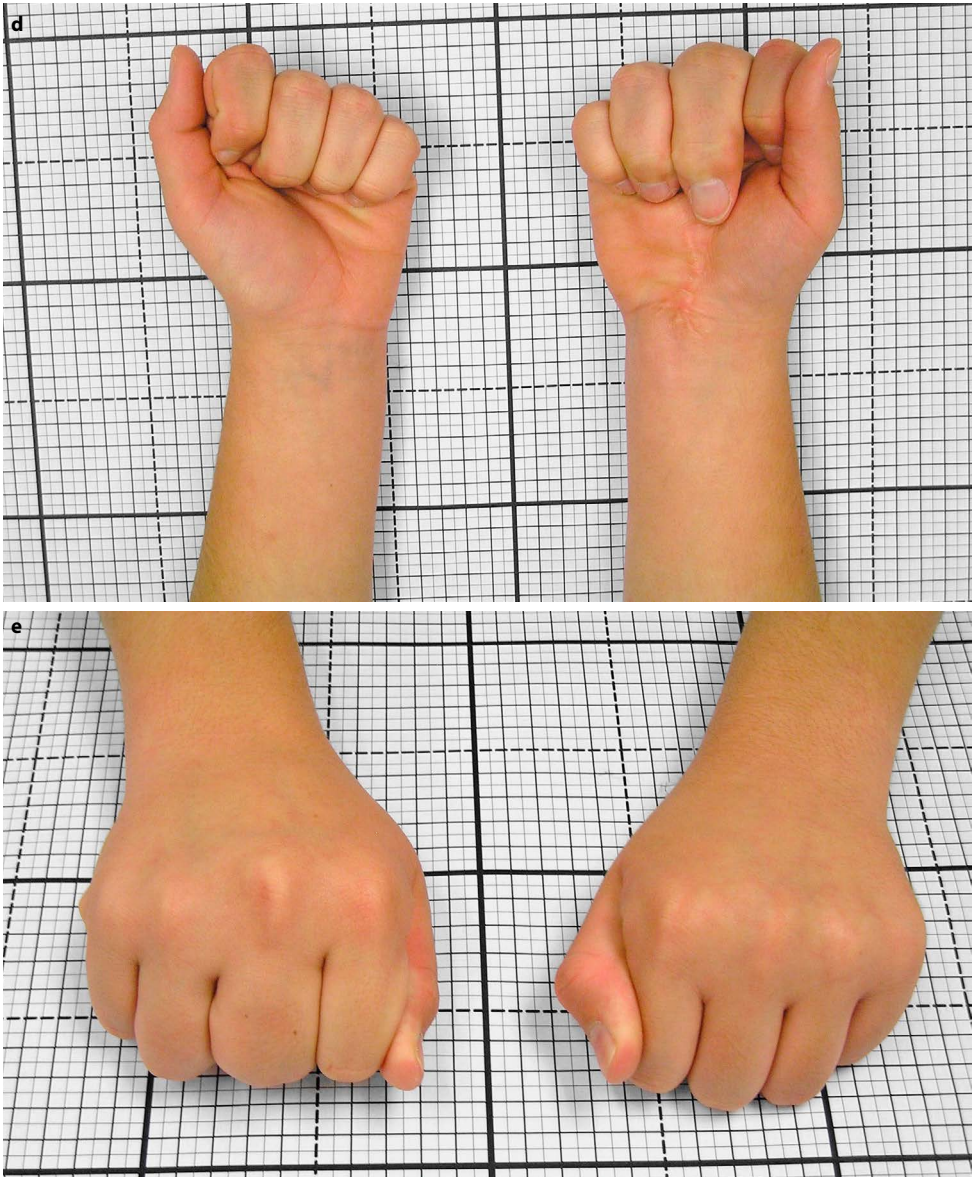


Figure 8d, e. Shows the result of surgical treatment at the age of 14 years and 3 months in terms of cosmetics and function. The active flexion at the distal interphalangeal joint of the 3rd finger of the right hand is limited to 30°, while the flexion of the 3rd finger of the left hand at the same joint is 60°. Sensitivity at the distal joint of the 3rd finger is slightly reduced.

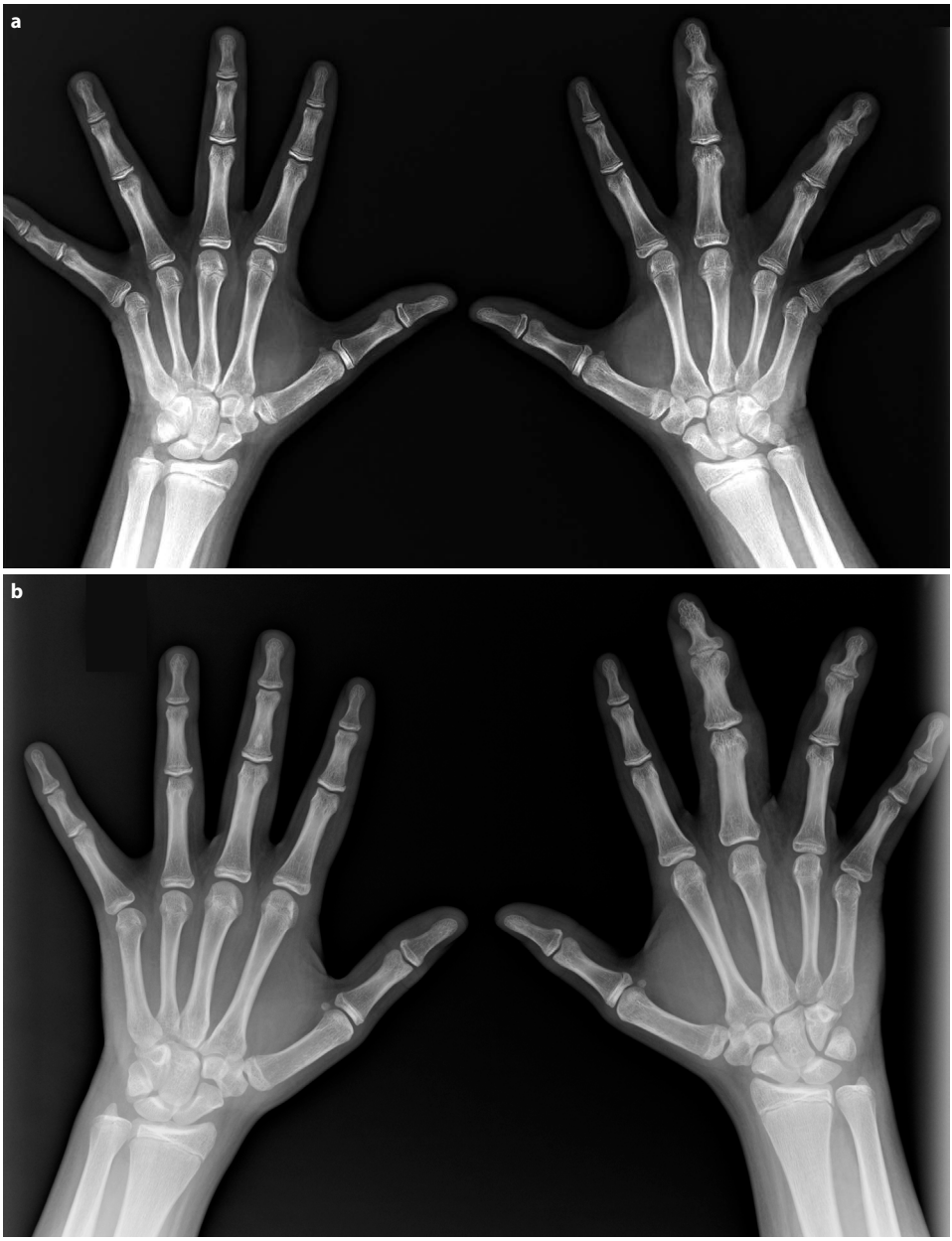


Figure 9a, b. Result of surgical treatment: X-ray **a** 13 years 1m, **b** 14 years 3 m.

Body height was 174.5 cm with prediction of 178 cm in adulthood. BMI 25.8.

Genetic examination

The patient underwent repeated genetic testing over several years. Array CGH was normal. NGS panel examination – congenital bone anomalies (1029 genes): No clearly pathogenic or likely pathogenic sequence variant was found. CNV analysis does not support the presence of deletion/duplication of whole exons of these genes. No pathogenic/probably pathogenic variant was found in the *AKT1* gene.

As tissue from the pathological lesion was not available at present, it was not yet possible to investigate somatic pathogenic variants in the *AKT1* and *PIK3CA* genes.

DISCUSSION

Macrodactyly is a rare disease classified in Nosology of genetic skeletal disorders (2023 revision) in group 31: overgrowth syndromes and segmental overgrowth (**36**). Oberg (**26**) ranked it as a dysplasia in the classification of limb defects, namely hypertrophy. The diagnosis of macrodactyly should be reserved for patients with isolated congenital digit overgrowth affecting all tissue types. Research in recent years shows that it is caused by somatic mosaicism in the *PIK3CA* gene with high proportion of altered *PIK3CA* transcripts found especially in nerve and adipose tissue (**18**). Clinical presentation and natural history of macrodactyly can vary greatly among patients (**5**). The authors present an interesting case of a boy with a relatively mild form of macrodactyly of the right hand, which was treated surgically in two stages. The result of surgical treatment at the age of 14 years and 3 months can be assessed as relatively good in terms of cosmetic and functional aspects. However, progression of lipofibromatous hamartoma of the n. medianus at older age and premature osteoarthritis of the digital joints of the affected fingers cannot be excluded (**31**).

There are a number of surgical techniques that make it possible to primarily reconstruct, not amputate, the affected fingers. Reconstruction does not result in normal fingers and requires multiple surgeries to restore function and aesthetics. More long-term outcomes and insight into the biology of the disease are needed to make more informed treatment decisions (**5**).

Macroscopic examination at the first operation (**Fig. 5b**) and histological and histochemical examinations (**Fig. 6a, b**) confirmed nerve territory-oriented macrodactyly caused by lipofibromatous hamartoma of the n. medianus, which occurs in approximately 1/3 of cases (**33, 5, 40**).

A potential etiology of nerve directed function underlying this disorder was proposed by Moore as early as in 1942 (**25**) and has been suggested by other authors (**13, 29, 12**).

Unfortunately, genetic testing of the affected tissue was not performed in our patient because it was not routinely available. Genetic testing of germinal DNA (NGS panel examination – congenital

bone anomalies, 1029 genes) shows no clearly pathogenic or likely pathogenic sequence variants. Based on our own experience and literature (**11**) we have ruled out **Proteus syndrome** (no skin and bone tumours, no lower limb length discrepancy, no foot involvement and no deep vein thrombosis or pulmonary embolism). Both clinical outcome and histological examinations are consistent with literature data on patients with somatic mosaicism in the *PIK3CA* gene.

Mutations found in patients with macrodactyly also occur in tumours. However, according to Zhao et al. (**42**), *PIK3CA*'s single pathogenic mutation cannot directly lead to tumours. Tumour develops only when it occurs together with a pathological change in another gene. Macrodactyly has biological characteristics that are not completely the same as those of tumours (**18**). It is noteworthy that so-far no malignancies have been reported in patients with macrodactyly (**7, 6, 31**).

The issues of genotype and phenotype are not yet resolved. Tian et al. (**34**) show that patients with macrodactyly deformities of the upper limbs tend to carry *PIK3CA* variants with mutations outside the helical domain, while patients with deformities in the lower limbs have *PIK3CA* variants with mutations in the helical domain (**34**). However, a significant heterogeneity in phenotypic presentations is observed even for the same variant which can cause both macrodactyly and other disease from the PROS spectrum. McNamara et al. show that genetic modifiers may also play an important role in the presentation of macrodactyly (**24**).

The presenting phenotype of the PROS disorders seems to depend on the timing of the somatic mutation (**34, 31**), the tissue localization of the mutations, and the location of the mutation in the embryo. Mutations that occur early during embryogenesis will generate many affected daughter cells, potentially of distinct differentiation routes (stroma, fat, smooth muscle, endothelium, etc.), which may result in larger and multiple body segments that are affected, such as in CLOVES syndrome. A mutation later in embryogenesis will produce lower numbers of mutated cells and yield smaller lesions, such as in macrodactyly (**31, 15**).

Currently, genetic testing is important mainly in the differential diagnosis of Proteus syndrome, which has a more severe course. However, we expect its importance to grow in the near future, especially in terms of prognosis and causal treatment. So far, medical therapy targeting mTOR or PIK3CA pathways has been used experimentally only in the most severe PROS patients (**7, 37**).

Interestingly, in our patient there is a coincidence with incompletely expressed **Poland syndrome (PS)** affecting the thoracic musculature on the left side. Currently, PS is generally considered a sporadic disorder with no clear pattern of inheritance. The syndrome is thought to be related to a failure of development of a specific artery or other interruption of blood flow during embryonic development. Although genetic and environmental factors are likely to contribute to its development, the specific genes involved have not been identified. However, there are also suggestions that PS also represents a mosaic phenotype caused by a somatic mutation occurring during development, with the severity of the phenotype depending on the time of occurrence of the mutation during embryogenesis (**11, 28, 1**).

CONCLUSION

Macrodactyly is one of the rare diseases with varying clinical presentation. Although the etiopathogenesis of the disease has been partially elucidated in the last decade, therapy remains primarily in the hands of surgeons. Surgical treatment of hand macrodactyly can be a daunting task that is often left exclusively to persons trained in congenital hand deformities.

The result of surgical treatment of hand macrodactyly in a boy at the age of 14 years and 3 months can be assessed as relatively good in terms of cosmetic and functional aspects. However, progression of lipofibromatous hamartoma of the n. medianus at older age and premature osteoarthritis of the digital joints of the affected fingers cannot be excluded.

The coincidence of macrodactyly and Poland syndrome in our patient deserves attention.

Insights into phenotypic and genetic spectrum of isolated macrodactyly may be helpful in perusing a more precise and effective management of isolated macrodactyly.

A deeper understanding of the mechanisms that lead from a somatic gene defect to lipomatous nerve involvement and overgrowth of body parts will lead to improved treatment options and prevention of progressive overgrowth.

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NOZOLOGIE GENETICKÝCH NEMOCÍ SKELETU: REVIZE 2023

NOSOLOGY OF GENETIC SKELETAL DISORDERS: 2023 REVISION

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ABSTRAKT

„Nozologie genetických poruch skeletu" prošla již 11. revizí a nyní obsahuje 771 záznamů spojených s 552 geny, které odrážejí pokroky v molekulární genetice nových nemocí díky pokroku v technologii sekvenování DNA. Nejvýznamnější změnou ve srovnání s předchozími verzemi je přijetí dyadického systému pojmenování, který systematicky spojuje fenotypovou jednotku s genem, z něhož vzniká. Považujeme to za významný krok vpřed, protože dyadické pojmenování je informativnější a méně náchylné k chybám než tradiční používání číslování podle seznamu a eponym. Navzdory přijetí dyadického pojmenování byly vyvinuty snahy o zachování pevné vazby na katalog MIM a jeho historické údaje. Stejně jako u předchozích verzí může být seznam poruch a genů v Nozologii užitečný při zvažování diferenciální diagnózy v klinice, při usměrňování bioinformatické analýzy sekvenování nové generace a poskytování základu pro nové pokroky v biologii a medicíně.

Když byla v roce 1970 sestavena a publikována první „Nozologie", jen málo z odborníků předpokládalo, že získá tak důležitou roli v oblasti genetické praxe a výzkumu a že bude motivovat k vytvoření jedenácté revize po 52 letech (tabulka 1). Přesto důvody, které podnítily vznik první „Nozologie", jsou stejné jako ty, které vedly k současné nové revizi: vyrovnání se s množstvím nových informací o rostoucím počtu a rozmanitosti skeletálních fenotypů s genetickým podkladem a snaha zajistit společný systém pojmenování pro usnadnění diagnostiky a komunikace.

Rozpoznání chromozomových aneuploidií na přechodu 50. a 60. let poskytlo biologický základ pro genetiky a zahájilo první zlatou éru klinické genetiky. Konference o vrozených vadách v letech 1969 až 1971 signalizovaly vzestup povědomí a významu klinické genetiky v průběhu šedesátých let a zahájily plodné období identifikace, vymezení a popisu nemocí. V této souvislosti bylo zřejmé, že se u „chondrodysplazie" nejedná o jedinou diagnózu, ale že existuje mnoho odlišných diagnóz; byly například rozlišeny a klinicky popsány diastrofická dysplazie, vrozená spondyloepifyzární dysplazie a takzvaná „pseudo-Morquio" dysplazie. Kromě toho biochemie umožnila rozlišit podtypy klinicky podobných poruch, přičemž nejvýznamnějším příkladem byly v té době mukopolysacharidózy. Přínos radiologických znaků a radiologů k vymezení skeletálních dysplazií si zaslouží výslovné uznání. V mnoha případech to byly právě radiologické znaky a jejich vývoj v závislosti na čase („čtvrtý rozměr" zdůrazňovaný Andresem Giedionem), které umožnily nejen rozlišit mezi nemocemi, které měly vnější podobnost, ale také rozpoznat „radiologický podpis genu" u fenotypově odlišných poruch (např. achondrogeneze typu 2 a spondyloepifyzární dysplazie congenita) a vytvořit tak první genové rodiny (Spranger, 1985) (a viz níže).

V roce 1970 byl vypracován první prototyp „Nozologie" (Nomenklatura konstitučních (vnitřních) onemocnění kostí, 1971; [International nomenclature of constitutional bone diseases. Constitutional bone diseases without known pathogenesis], 1971; [International nomenclature of constitutional diseases of bone], 1970; McKusick & Scott, 1971). V té době však byla práce nazývána „Nomenklatura", nikoliv nozologie; cílem bylo, aby všichni odborníci používali stejný název pro stejnou nemoc.

V 80. letech 20. století se v nozologii začala uplatňovat molekulární kritéria, nejprve u osteogenesis imperfecta s objevem genetických variant v kolagenu 1. Koncept „rodin kostních dysplazií", který vznikl z různých patogenních variant v jediném genu, byl navržen v 80. letech (Spranger, 1985) a potvrzen v devadesátých letech, s nemocemi spojenými s COL2A1 a FGFR3 jako významnými příklady. Od té doby se Nozologie pohybuje na hraně mezi definováním nemocí buď na základě klinických a radiologických znaků nebo na základě odpovědných genů (Beighton et al., 1992; Bonafe et al., 2015; Hall, 2002; International nomenclature and classification of the osteochondrodysplasias (1997). International working group on constitutional diseases of bone, 1998; International nomenclature of constitutional diseases of bone, 1979; International nomenclature of constitutional diseases of bone. Revision, May 1983, 1983; Lachman, 1998; Mortier et al., 2019; Superti-Furga & Unger, 2007; Warman et al., 2011).

Nozologie byla tradičně uspořádána do skupin nemocí – zpočátku na základě radiologických kritérií, poté podle kritérií biochemických (metabolických dráh) a následně stále více podle funkčních a molekulárních. Uspořádání do skupin bylo zachováno i v současné revizi, protože pomáhá při vyhledávání nemocí relevantních pro nálezy u konkrétního pacienta. Na druhou stranu, příroda má větší komplexnost, než lze zachytit v Nozologii, a náš pokus o klasifikaci je tak nutně jak arbitrární, tak zjednodušený, protože mnoho poruch může být klasifikováno do více než jedné skupiny. Proto jsme se rozhodli vypustit termín „klasifikace" z názvu; jedná se pouze o „Nozologii".

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
Group 1	**1. FGFR3 chondrodysplasia group**				
NOS 01–0010	Thanatophoric dysplasia type 1	AD	*FGFR3*	187600	Includes previous "platyspondylyic dysplasia type San Diego"
NOS 01–0020	Thanatophoric dysplasia (type 2), FGFR3-related	AD	*FGFR3*	187601	Radiographic differences between types 1 and 2 are correlated to specific *FGFR3* variants
NOS 01–0030	Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), FGFR3-related	AD	*FGFR3*	616482	
NOS 01–0040	Achondroplasia, FGFR3-related	AD	*FGFR3*	100800	
NOS 01–0050	Hypochondroplasia, FGFR3-related	AD	*FGFR3*	146000	
	See also group 33 for craniosynostosis syndromes linked to FGFR3 variants, as well as CATSHL in group 30 and LADD syndrome in group 40 for other *FGFR3*-related phenotypes; rare *FGFR3* missense variants have been reported in idiopathic short stature but a causal link is not yet established and their significance remains unclear				
Group 2	**Type 2 collagen disorders**				
NOS 02-0010	Achondrogenesis, COL2A1-related (formerly type 2, type Langer-Saldino)	AD	*COL2A1*	200610	Achondrogenesis type 2 and hypochondrogenesis form one phenotypic continuum
NOS 02-0020	Hypochondrogenesis, COL2A1-related	AD	*COL2A1*	200610	Achondrogenesis type 2 and hypochondrogenesis form one phenotypic continuum
NOS 02-0030	Platyspondylic dysplasia, type Torrance, COL2A1-related	AD	*COL2A1*	151210	Often variants in the C-propeptide of collagen 2

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 02-0040	Spondyloepiphyseal dysplasia congenita (SEDC), COL2A1-related	AD, AR*	*COL2A1*	183900, 604864	Includes mild SED with premature onset arthrosis, also known as osteoarthrosis with mild chondrodysplasia; includes Namaqualand type hip dysplasia. Mild SED cases may resemble MED (see note). AR*: very rare SED cases with biallelic *COL2A1* variants have been reported
NOS 02-0050	Spondyloepimetaphyseal dysplasia, COL2A1-related	AD	*COL2A1*	184250, 184253, 184255, 616583	Also known as "SED with marked metaphyseal changes". Includes SEMD type Strudwick, SMD type Algerian, SED type Stanescu, dysspondyloenchondromatosis, and some cases of SMD "corner fracture" type
NOS 02-0060	Kniest dysplasia, COL2A1-related	AD	*COL2A1*	156550	
NOS 02-0070	Spondyloperipheral dysplasia, COL2A1-related	AD	*COL2A1*	271700	Like Torrance dysplasia, often variants in the C-propeptide of collagen 2
NOS 02-0080	SED with metatarsal shortening, COL2A1-related	AD	*COL2A1*	609162	Often associated with the p.R275C variant; formerly "Czech dysplasia"
NOS 02-0090	Stickler syndrome, COL2A1-related	AD	*COL2A1*	108300	Monoallelic loss-of-function variants; see also *COL11A1, COL11A2, COL9A1, COL9A2, COL9A3*
NOS 02-0100	Dysplasia of the proximal femoral epiphyses, COL2A1-related	AD	*COL2A1*	150600, 608805	Heterogeneous condition, not all cases are due to COL2A1 variants (usually p.G393S; p.G717S; p. G1170S). The condition called "Meyer dysplasia of the hip" is not associated with *COL2A1* variants
	See also the pseudoachondroplasia-multiple epiphyseal dysplasia group for recessively inherited variants of Stickler syndrome as well as for overlapping phenotypes with normal stature and premature onset arthrosis; as well as spondylometaphyseal dysplasia Sutcliffe (or "corner fractures" type), *FN1*-related				
Group 3	**Type 11 collagen disorders**				
NOS 03-0010	Stickler syndrome, COL11A1-related	AD, MOS	*COL11A1*	604841	Can also result from somatic mosaicism for a *COL11A1* variant
NOS 03-0020	Marshall syndrome, COL11A1-related	AD	*COL11A1*	154780	One report with homozygous p.G901E variant in two affected sibs (PMID 22499343)
NOS 03-0030	Stickler syndrome, COL11A2-related (non-ocular type)	AD	*COL11A2*	184840	
NOS 03-0040	Fibrochondrogenesis, COL11A1-related	AR, AD	*COL11A1*	228520	
NOS 03-0050	Fibrochondrogenesis, COL11A2-related	AR, AD	*COL11A2*	614524	
NOS 03-0060	Otospondylomegaepiphyseal dysplasia (OSMED), recessive type, COL11A2-related	AR	*COL11A2*	215150	
NOS 03-0070	Otospondylomegaepiphyseal dysplasia (OSMED), dominant type, COL11A2-related	AD	*COL11A2*	184840	Formerly Weissenbacher-Zweymüller syndrome and Stickler syndrome type 3
	See also Stickler syndrome type 1 in collagen 2 group (Group 2) as well as recessive forms of Stickler syndrome in the pseudoachondroplasia-multiple epiphyseal dysplasia group (Group 9) Sulfation disorders				
Group 4	**Sulfation disorders**				
NOS 04-0010	Achondrogenesis, SLC26A2-related (formerly achondrogenesis type 1B, or type Fraccaro)	AR	*SLC26A2*	600972	Formerly known as achondrogenesis, type Fraccaro

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 04-0020	Atelosteogenesis, SLC26A2-related (formerly atelosteogenesis type 2)	AR	*SLC26A2*	256050	Includes former entities de la Chapelle dysplasia, McAlister dysplasia, and neonatal osseous dysplasia
NOS 04-0030	Diastrophic dysplasia, SLC26A2-related	AR	*SLC26A2*	222600	
NOS 04-0040	Multiple epiphyseal dysplasia, SLC26A2-related (autosomal recessive type, rMED)	AR	*SLC26A2*	226900	See also multiple epiphyseal dysplasias and pseudoachondroplasia group (group 9)
NOS 04-0050	Spondylo-epi-metaphyseal dysplasia, PAPSS2-related	AR	*PAPSS2*	612847	Formerly "SEMD Pakistani type"; includes the former "recessive brachyolmia, recessive type" as well as the older entities "Toledo brachyolmia" and "Hobaek brachyolmia"
NOS 04-0060	Chondrodysplasia with congenital joint dislocations, IMPAD1-related	AR	*IMPAD1*	614078	Some features similar to Catel-Manzke syndrome, TGDS-related, as well as to Desbuquois syndrome, CANT1-related
NOS 04-0070	Chondrodysplasia with congenital joint dislocations, CHST3-related	AR	*CHST3*	143095	Includes recessive Larsen syndrome, humero-spinal dysostosis, and SED type Omani
NOS 04-0080	Chondrodysplasia with hypomyelinating leucodystrophy, SLC35B2-related	AR	*SLC35B2*	See 610788	
NOS 04-0090	Ehlers-Danlos syndrome, musculocontractural type, CHST14-related	AR	*CHST14*	601776	Includes adducted thumb-clubfoot syndrome
NOS 04-0100	Ehlers-Danlos syndrome, musculocontractural type, DSE-related	AR	*DSE*	615539	
NOS 04-0110	Osteochondrodysplasia, brachydactyly, and overlapping malformed digits (OCBMD), CHST11-related	AR	*CHST11*	618167	
NOS 04-0120	Developmental delay with corpus callosum, skeletal, and renal abnormalities, HS2ST1-related	AR	*HS2ST1*	619194	
	See also filamin disorders (Group 6) and dysplasias with multiple joint dislocations (Group 5) for other conditions with dislocations, as well as brachydactyly, CHSY1-related, for phalangeal changes reminiscent of the sulfation disorders.				
Group 5	**Dysplasias with multiple joint dislocations**				
NOS 05-0010	Baratela-Scott syndrome, XYLT1-related	AR	*XYLT1*	615777	May have intellectual disability; formerly Desbuquois dysplasia type 2
NOS 05-0020	Desbuquois dysplasia (with accessory ossification center in digit 2), CANT1-related	AR	*CANT1*	251450	
NOS 05-0030	Desbuquois dysplasia (with short metacarpals and elongated phalanges, Kim type), CANT1-related	AR	*CANT1*	251450	
NOS 05-0040	SEMD with joint laxity (Hall type or leptodactylic type), KIF22-related	AD	*KIF22*	603546	
NOS 05-0050	SEMD with joint laxity, EXOC6B-related	AR	*EXOC6B*	618395	Phenotype resembles SEMD-JL leptodactylic or type Hall (preceding line)
NOS 05-0060	SEMD with joint laxity (Beighton type), B3GALT6-related (Ehlers-Danlos syndrome, spondylodysplastic type 2, EDSSPD2)	AR	*B3GALT6*	271640	Includes MIM 609465–Al-Gazali syndrome as neonatal form

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 05-0070	Ehlers-Danlos syndrome, spondylodysplastic type 1 (EDSSPD1), B4GALT7-related	AR	*B4GALT7*	130070	Formerly known as "EDS, progeroid form"; includes Larsen syndrome, La Reunion type; see also B3GALT6 deficiency above
NOS 05-0080	Multiple joint dislocations, short stature, craniofacial dysmorphisms, and skeletal dysplasia, with or without heart defects, B3GAT3-related	AR	*B3GAT3*	245600	The phenotype is very variable and has been reported also as "Larsen-like" or as "pseudodiastrophic dysplasia". Intellectual disability and severe osteopenia with fractures have been observed. The OMIM entry includes older descriptions that are probably unrelated.
NOS 05-0090	Skeletal dysplasia with joint laxity and advanced bone age (SDJLABA), CSGALNACT1-related	AR	*CSGALNACT1*	618870	
NOS 05-0100	Skeletal dysplasia with joint dislocations and amelogenesis imperfecta, SLC10A7-related	AR	*SLC10A7*	618363	
	Note: remarkably, this group contains several disorders of glycosaminoglycan synthesis. In spite of this group being named after a clinical feature (dysplasias with joint dislocations), the phenotypes in this group are related to those of the preceding Group 4 (sulfation disorders) and of the following Group 6 (filamin disorders) justifying its placement here. See also: Temtamy type brachydactyly, *CHSY1*-related, as well as SEMD with microcephaly, retinal dystrophy and hearing loss, *PISD*-related (Liberfarb syndrome), for other conditions with congenital dislocations, as well as EDSSPD3, *SLC39A13*-related, in the SEMD group.				
Group 6	**Filamins and related disorders**				
NOS 06-0010	Frontometaphyseal dysplasia, FLNA-related	XL	*FLNA*	305620	*FLNA* gene also associated with MIM 300049, MIM 300321, MIM 314400, MIM 300048, MIM 300049 (see) and conditions below in this group
NOS 06-0020	Frontometaphyseal dysplasia, MAP3K7-related	AD	*MAP3K7*	617137	
NOS 06-0030	Frontometaphyseal dysplasia, TAB2-related	AD	*TAB2*		No MIM entry yet; *TAB2* gene also associated with MIM 614980–congenital heart defects, nonsyndromic, 2
NOS 06-0040	Cardiospondylocarpofacial syndrome, MAP3K7-related	AD	*MAP3K7*	157800	
NOS 06-0050	Melnick-Needles syndrome, FLNA-related	XL	*FLNA*	309350	Includes osteodysplasty
NOS 06-0060	Otopalatodigital syndrome type 1 (OPD1), FLNA-related	XL	*FLNA*	311300	
NOS 06-0070	Otopalatodigital syndrome type 2 (OPD2), FLNA-related	XL	*FLNA*	304120	
NOS 06-0080	Terminal osseous dysplasia (TOD), FLNA-related	XL	*FLNA*	300244	Includes digitocutaneous dysplasia
NOS 06-0090	Larsen syndrome, FLNB-related	AD	*FLNB*	150250	
NOS 06-0100	Atelosteogenesis type 1, FLNB-related	AD	*FLNB*	108720, 112310	Includes Boomerang dysplasia, Piepkorn dysplasia, and spondylohumerofemoral (giant cell) dysplasia
NOS 06-0110	Atelosteogenesis type 3, FLNB-related	AD	*FLNB*	108721	
NOS 06-0120	Spondylocarpotarsal synostosis syndrome, FLNB-related	AR	*FLNB*	272460	
NOS 06-0130	Spondylocarpotarsal synostosis syndrome, RFLNA-related	AR	*RFLNA*		Entity proven, no MIM entry yet

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 06-0140	Spondyocarpotarsal synostosis syndrome with contractures and pterygia, MYH3-related	AD, AR	*MYH3*	178110, 618469	frequently biallelic loss of function variants; monoallelic missense variants in the *MYH3* gene associated with MIM 193700-Arthrogryposis 2A, and MIM 618436-Arthrogryposis 2B3
NOS 06-0150	Frank-ter Haar syndrome, SH3PXD2B-related	AR	*SH3PXD2B*	249420	Includes previous Borrone dermatocardioskeletal syndrome
	See also chondrodysplasia with congenital joint dislocations, CHST3-related ("recessive Larsen syndrome") and the group of dysplasias with multiple dislocations, above (Group 5)				
Group 7	**Proteoglycan core proteins disorders**				
NOS 07-0010	Dyssegmental dysplasia, HSPG2-related	AR	*HSPG2*	224410, 224400	Variable severity; Includes both former Silverman Handmaker and Rolland-Desbuquois types
NOS 07-0020	Myotonic chondrodystrophy, HSPG2-related (Schwartz- Jampel syndrome)	AR	*HSPG2*	255800	Variable severity; includes previous Burton dysplasia
NOS 07-0030	Spondylo-epiphyseal dysplasia, ACAN-related (dominant, Kimberley type)	AD	*ACAN*	608361	
NOS 07-0040	Spondylo-epi-metaphyseal dysplasia, ACAN-related (recessive, aggrecan type)	AR	*ACAN*	612813	
NOS 07-0050	Short stature with advanced bone age, ACAN-related	AD	ACAN	165800	Sometimes with osteochondritis dissecans; other cases short stature with no skeletal features and normal bone age
NOS 07-0060	SEMD, BGN-related (Camera type)	XL	BGN	300106	The *BGN* gene is also associated with a connective tissue-arterial aneurysms disorder (Meester-Loeys syndrome, MIM300989)
Group 8	**TRPV4 disorders**				
NOS 08-0010	Metatropic dysplasia, TRPV4-related	AD, MOS	*TRPV4*	156530	Includes so-called "hyperplastic", lethal, and non-lethal forms. Can also result from somatic mosaicism for a *TRPV4* variant.
NOS 08-0020	Spondyloepimetaphyseal dysplasia, TRPV4-related (Maroteaux type)	AD	*TRPV4*	184095	Previously known as "pseudo-Morquio syndrome type 2". Includes the obsolete MIM 168400-parastremmatic dwarfism entry, a phenotypic variant.
NOS 08-0030	Spondyloepiphyseal dysplasia, Kozlowski type	AD	*TRPV4*	184252	
NOS 08-0040	Brachyolmia, TRPV4-related	AD	*TRPV4*	113500	
NOS 08-0050	Familial digital arthropathy with brachydactyly, TRPV4-related	AD	*TRPV4*	606835	
	Missense variants in the *TRPV4* gene can be responsible for different types of peripheral neuropathies (see under MIM 605427). The *TRPV4* skeletal phenotypes can sometimes be associated with neuropathy.				
Group 9	**Pseudoachondroplasia and the multiple epiphyseal dysplasias**				
NOS 09-0010	Pseudoachondroplasia, COMP-related	AD	*COMP*	177170	
NOS 09-0020	Multiple epiphyseal dysplasia, COMP-related	AD	*COMP*	132400	
NOS 09-0030	Multiple epiphyseal dysplasia, MATN3-related	AD	*MATN3*	607078	
NOS 09-0040	Multiple epiphyseal dysplasia, CANT1-related	AR	*CANT1*	617719	

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 09-0050	Multiple epiphyseal dysplasia, COL9A1-related	AD	*COL9A1*	614135	
NOS 09-0060	Multiple epiphyseal dysplasia, COL9A2-related	AD	*COL9A2*	600204	
NOS 09-0070	Multiple epiphyseal dysplasia, COL9A3-related	AD	*COL9A3*	600969	
NOS 09-0080	Stickler syndrome, recessive type, COL9A1-related	AR	*COL9A1*	614134	See also Groups 2 and 3
NOS 09-0090	Stickler syndrome, recessive type, COL9A2-related	AR	*COL9A2*	614284	
NOS 09-0100	Stickler syndrome, recessive type, COL9A3-related	AR	*COL9A3*	120270	
NOS 09-0110	Multiple epiphyseal dysplasia with microcephaly and nystagmus (Lowry-Wood syndrome), RNU4ATAC-related	AR	*RNU4ATAC*	226960	See also Microcephalic osteodysplastic primordial dwarfism, *RNU4ATAC*-related, as well as Roifman syndrome, *RNU4ATAC*-related, both in the primordial dwarfism group (Group 21), for conditions with different severity from the *RNU4ATAC* gene
	See also multiple epiphyseal dysplasia, recessive type, SLC26A2-related, as well as ASPED. Some *COL2A1* variants can make a MED-like phenotype. Some MED or MED-like phenotypes remain genetically unclear.				
Group 10	**Skeletal disorders caused by abnormalities of cilia or ciliary signaling**				
NOS 10-0010	Short rib-polydactyly syndrome (SRPS), DYNC2H1-related	AR	*DYNC2H1*	613091, 263520	There is significant clinical and radiological overlap between SRP1/3 and ATD. Some forms of both remain unlinked to the known genes. This gene can also be responsible for chondroectodermal dysplasia (Ellis-van Creveld), see below.
NOS 10-0020	Short rib-polydactyly syndrome (SRPS), IFT80-related	AR	*IFT80*	611263	
NOS 10-0030	Short rib-polydactyly syndrome (SRPS), IFT81-related	AR	*IFT81*	617895	
NOS 10-0040	Short rib-polydactyly syndrome (SRPS), WDR34-related	AR	*WDR34*	615633	
NOS 10-0050	Short rib-polydactyly syndrome (SRPS), WDR60-related	AR	*WDR60*	615503	
NOS 10-0060	Short rib-polydactyly syndrome (SRPS), DYNC2LI1 related	AR	*DYNC2LI1*	617088	
NOS 10-0070	Short rib-polydactyly syndrome (SRPS), NEK1-related	AR	*NEK1*	263520	Possibly also digenic inheritance combining *NEK1* with *DYNC2H1* variants
NOS 10-0080	Short rib-polydactyly syndrome (SRPS), IFT122-related	AR	*IFT122*	269860	
NOS 10-0090	Short rib-polydactyly syndrome (SRPS), WDR19-related	AR	*WDR19*	614091	*WDR19* is associated with MIM 614091, 614376, 614378, 615633 as well as with nephronopthisis (MIM 614377), Senior-Loken syndrome (MIM 616307) and Mainzer- Saldino syndrome (see below)
NOS 10-0100	Short rib-polydactyly syndrome (SRPS), INTU-related	AR	*INTU*	617925	
NOS 10-0110	Short rib-polydactyly syndrome (SRPS), TRAF3IP1-related	AR	*TRAF3IP1*	See 607380	*TRAF3IP1* also known as *IFT154*
NOS 10-0120	Endocrine-cerebro-osteo dysplasia (ECO), CILK1-related	AR	*CILK1*	612651	

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 10-0130	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), DYNC2H1-related	AR	*DYNC2H1*	613091	
NOS 10-0140	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), DYNC2LI1-related	AR	*DYNC2LI1*	See 617088	
NOS 10-0150	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), WDR34-related	AR	*WDR34*	See 615633	
NOS 10-0160	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), TCTEX1D2-related	AR	*TCTEX1D2*	617405	
NOS 10-0170	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), WDR60-related	AR	*WDR60*	See 615503	
NOS 10-0180	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), WDR19-related	AR	*WDR19*	614376	*WDR19* is associated with MIM 614091, 614376, 614378, 615633 as well as with nephronopthisis (MIM 614377), Senior-Loken syndrome (MIM 616307) and Mainzer Saldino syndrome (see below)
NOS 10-0190	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), IFT140-related	AR	*IFT140*	266920	
NOS 10-0200	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), TTC21B-related	AR	*TTC21B*	613819	Gene also known for nephronophthisis (MIM 613820)
NOS 10-0210	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), IFT122-related	AR	*IFT122*	See 269860	Subsumed under SRPS (MIM 269860)
NOS 10-0220	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), WDR35-related	AR	*WDR35*	614091	
NOS 10-0230	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), IFT43-related	AR	*IFT43*	617866	
NOS 10-0240	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), IFT80-related	AR	*IFT80*	611623	
NOS 10-0250	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), IFT172-related	AR	*IFT172*	615630	
NOS 10-0260	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), IFT81-related	AR	*IFT81*	617895	
NOS 10-0270	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), IFT52-related	AR	*IFT52*	617102	
NOS 10-0280	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), CFAP410-related	AR	*CFAP410*	602271	
NOS 10-0290	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), CEP120-related	AR	*CEP120*	616300	Described in severe cases resembling SRPS; the *CEP120* gene is also associated with Joubert syndrome (MIM 617761)

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 10-0300	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), KIAA0586-related	AR	*KIAA0586*	616546	Gene also associated with Joubert syndrome (MIM 616490)
NOS 10-0310	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), GRK2-related	AR	*GRK2*	See 109635	
NOS 10-0320	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), TRAF3IP1-related	AR	*TRAF3IP1*	See 607380	*TRAF3IP1* also known as *IFT154*
NOS 10-0330	Short-rib thoracic dysplasia (formerly asphyxiating thoracic dysplasia – Jeune syndrome), KIAA0753-related	AR	*KIAA0753*	619479	*KIAA0753* variants also associated with orofaciodigital syndrome (MIM 617127) and with Joubert syndrome (MIM 619476)
NOS 10-0340	Axial spondylometaphyseal dysplasia, CFAP410-related	AR	*CFAP410*	602271	
NOS 10-0350	Axial spondylometaphyseal dysplasia, NEK1-related	AR	*NEK1*	See 252100	
NOS 10-0360	Chondroectodermal dysplasia (Ellis-van Creveld), EVC1-related	AR	*EVC1*	225500	See also Weyers acrofacial (acrodental) dysostosis (MIM 193530)
NOS 10-0370	Chondroectodermal dysplasia (Ellis-van Creveld), EVC2-related	AR	*EVC2*		
NOS 10-0380	Chondroectodermal dysplasia (Ellis-van Creveld), WDR35-related AR	WDR35			
NOS 10-0390	Chondroectodermal dysplasia (Ellis-van Creveld), DYNC2LI1-related	AR	*DYNC2LI1*	See 617088	
NOS 10-0400	Chondroectodermal dysplasia (Ellis-van Creveld), GLI1-related	AR	*GLI1*	See 165220	
NOS 10-0410	Chondroectodermal dysplasia (Ellis-van Creveld), SMO-related	AR	*SMO*		A single case with compound heterozygosity missense variants reported
NOS 10-0420	Orofaciodigital syndrome type 4 (Mohr-Majewski), TCTN3-related	AR	*TCTN3*	258860	
NOS 10-0430	Orofaciodigital syndrome type 2 (Mohr syndrome), NEK1-related	AR	*NEK1*	252100	
NOS 10-0440	Cranioectodermal dysplasia (Levin-Sensenbrenner), IFT122-related	AR	*IFT122*	218330	
NOS 10-0450	Cranioectodermal dysplasia (Levin-Sensenbrenner), WDR35-related	AR	*WDR35*	613610	
NOS 10-0460	Cranioectodermal dysplasia (Levin-Sensenbrenner), WDR19-related	AR	*WDR19*	614378	*WDR19* is associated with MIM 614091, 614376, 614378, 615633 as well as with nephronopthisis (MIM 614377), Senior-Loken syndrome (MIM 616307) and Mainzer-Saldino syndrome (see below)
NOS 10-0470	Cranioectodermal dysplasia (Levin-Sensenbrenner), IFT40-related	AR	*IFT40*	see 614620	see short rib thoracic dysplasia, *IFT140*-associated, above
NOS 10-0480	Cranioectodermal dysplasia (Levin-Sensenbrenner), IFT43-related	AR	*IFT43*	614009	
NOS 10-0490	Joubert syndrome with short-rib thoracic dysplasia, CSPP1-related	AR	*CSPP1*	615636	In OMIM as "Joubert syndrome type 21"; not all cases have thoracic dysplasia
NOS 10-0500	Atrial defects-polydactyly-multiple congenital malformation syndrome, PRKACA-related	AD	*PRKACA*	619142	OMIM created the name of "Cardioacrofacial syndrome 1".

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 10-0510	Atrial defects-polydactyly-multiple congenital malformation syndrome, PRKACB-related	AD, MOS	*PRKACB*	619143	OMIM created the name of "Cardioacrofacial syndrome 2"; one published patient later reclassified as "Ellis-van Creveld syndrome".
NOS 10-0520	Mainzer-Saldino syndrome, IFT140-related	AR	*IFT140*	266920	*IFT140* also associated with isolated retinitis pigmentosa (MIM 617781)
NOS 10-0530	Mainzer-Saldino syndrome, IFT172-related	AR	*IFT172*		*IFT172* also associated with Bardet-Biedl syndrome (MIM 619471) and isolated retinitis pigmentosa (616394)
NOS 10-0540	Mainzer-Saldino syndrome, WDR19-related	AR	*WDR19*	See 614376	*WDR19* is also associated with MIM 614091, 614376, 614378, 615633 as well as with nephronopthisis (MIM 614377), and Senior-Loken syndrome (MIM 616307)
NOS 10-0550	Meckel syndrome, MKS1-related	AR	*MKS1*	249000	
NOS 10-0560	Meckel syndrome, TMEM216-related	AR	*TMEM216*	603194	
NOS 10-0570	Meckel syndrome, TMEM67-related	AR	*TMEM67*	607361	
NOS 10-0580	Meckel syndrome, CEP290-related	AR	*CEP290*	611134	
NOS 10-0590	Meckel syndrome, RPGRIP1L-related	AR	*RPGRIP1L*	611561	
NOS 10-0600	Meckel syndrome, CC2D2A-related	AR	*CC2D2A*	612284	
NOS 10-0610	Thoracolaryngopelvic dysplasia (Barnes)	SP		187760	Dominant transmission reported, but diagnostic criteria not stringent. The existence pf this entity is disputed.
	Given the common genetic basis of several entries in this group and the absence (so far) of clear genotype-phenotype correlations, the distinction between chondroectodermal dysplasia, asphyxiating thoracic dystrophy (see below for name change), short rib-polydactyly syndromes and related conditions is historical and restricted to the clinical phenotypes. We have followed MIM and used the term "short-rib thoracic dysplasia" instead of "asphyxiating thoracic dysplasia", to avoid the negative connotation and inaccuracy of "asphyxiating". See also paternal UPD14 and Cerebro-costo-mandibular syndrome (rib gap syndrome), *SNRPB*-related, both in Group 36. The Bardet-Biedl syndrome with its large phenotypic spectrum has not been included in spite of minor skeletal involvement, as the predominant clinical features are non-skeletal.				
Group 11	**Metaphyseal dysplasias**				
NOS 11-0010	Metaphyseal dysplasia Schmid (MCS), COL10A1-related	AD	*COL10A1*	156500	Pathogenic variants are typically located in the C-terminal domain of the protein.
NOS 11-0020	Cartilage-hair hypoplasia (CHH; metaphyseal dysplasia, McKusick type), RMRP-related	AR	*RMRP*	250250	The phenotype of CHH is variable and includes MIM 607095-anauxetic dysplasia as well as MIM 250460-metaphyseal dysplasia without hypotrichosis
NOS 11-0030	Metaphyseal dysplasia with short stature (CHH-like), POP1-related	AR	*POP1*	617396	The clinical spectrum is variable. The denomination of "anauxetic dysplasia 2" in MIM is confusing as anauxetic dysplasia is a variant of Cartilage-Hair Hypoplasia
NOS 11-0040	Metaphyseal dysplasia with short stature (CHH-like), NEPRO-related	AR	*NEPRO*	618853	Facial features and hypotrichosis reminiscent of Cartilage-Hair Hypoplasia
NOS 11-0050	Metaphyseal dysplasia with pancreatic insufficiency and cyclic neutropenia (Shwachman-Bodian-Diamond syndrome), SBDS-related	AR	*SBDS*	260400	See also severe spondylodysplastic dysplasia, Sedaghatian-like

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 11-0060	Metaphyseal dysplasia with pancreatic insufficiency and cyclic neutropenia (SBDS type 2), EFL1-related	AR	*EFL1*	617941	
NOS 11-0070	Metaphyseal dysplasia with pancreatic insufficiency and cyclic neutropenia, DNAJC21-related	AR	*DNAJC21*	617052	Known in OMIM as Bone Marrow Failure Syndrome 3; BMFS3
NOS 11-0080	Shwachman-Diamond like syndrome, SRP54-related	AD	*SRP54*	618752	Known in OMIM as Neutropenia, severe congenital, 8
NOS 11-0090	Metaphyseal dysplasia Spahr, MMP13-related	AR	*MMP13*	250400	Recessive, biallelic variants
NOS 11-0100	Metaphyseal anadysplasia, MMP13-related	AD	*MMP13*	602111	Dominant, monoallelic type; includes SEMD Missouri type
NOS 11-0110	Metaphyseal anadysplasia, MMP9-related	AR	*MMP9*	613073	
NOS 11-0120	Metaphyseal dysplasia with maxillary hypoplasia, RUNX2-related	AD	*RUNX2*	156510	Frequently associated with intragenic duplication of exons 3 to 5 or 3 to 6. See also Cleidocranial dysplasia, RUNX2-related (below; MIM 119600), as well as non- syndromic midline craniosynostosis, RUNX2-related, below
	See Rhizomelic spondylo-metaphyseal dysplasia with remissi on, LBR-related (Group 13), for another anadysplasia-like disorder				
Group 12	**Spondylometaphyseal dysplasias (SMD)**				
NOS 12-0010	Spondyloenchondrodysplasia with immune dysregulation (SPENCD), ACP5-related	AR	*ACP5*	607944	
NOS 12-0020	Odontochondrodysplasia (ODCD), TRIP11-related	AR	*TRIP11*	184260	See also Achondrogenesis, TRIP11-related (formerly type 1A)
NOS 12-0030	Spondylometaphyseal dysplasia Sutcliffe (or "corner fractures" type), FN1-related	AD	*FN1*	184255	Some cases are linked to *COL2A1* but not the original family
NOS 12-0040	Spondylometaphyseal dysplasia with cone-rod dystrophy, PCYT1A-related	AR	*PCYT1A*	608940	
NOS 12-0050	Spondylometaphyseal dysplasia with corneal dystrophy, PLCB3-related	AR	*PLCB3*	618961	
NOS 12-0060	Chondrodysplasia-pseudohermaphroditism syndrome, HHAT-related	AR	*HHAT*	600092	Also known as Nivelon-Nivelon-Mabille syndrome (sic)
	See also SMD Kozlowski, *TRPV4*-related, Severe spondylometaphyseal dysplasia (Sedaghatian type), *GPX4*-related, as well as Axial spondylometaphyseal dysplasia, *CFAP410*-related and Axial spondylometaphyseal dysplasia, *NEK1*-related. In addition, there are many reports of sporadic patients with unclassified SMD variants.				
Group 13	**Spondyloepi(meta)physeal dysplasias (SE(M)D)**				
NOS 13-0010	SED tarda, X-linked (SED-XL), TRAPPC2-related	XL	*TRAPPC2*	313400	
NOS 13-0020	SED with diabetes mellitus (Wolcott-Rallison syndrome), EIF2AK3-related	AR	*EIF2AK3*	226980	
NOS 13-0030	Dyggve-Melchior-Clausen dysplasia, DYM-related	AR	*DYM*	223800	
NOS 13-0040	Smith-McCort dysplasia, DYM-related	AR	*DYM*	607326	
NOS 13-0050	Smith-McCort dysplasia, RAB33B-related	AR	*RAB33B*	615222	
NOS 13-0060	SEMD, BNIP1-related	AR	*BNIP1*	see 603291	
NOS 13-0070	SEMD, MATN3-related	AR	*MATN3*	608728	See also *MATN3*-related MED in Group 9

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 13-0080	SEMD, DDRGK1-related (Shohat type)	AR	*DDRGK1*	602557	
NOS 13-0090	SEMD with leucodystrophy, AIFM1-related	XL	*AIFM1*	300232	
NOS 13-0100	SEMD, RSPRY1-related	AR	*RSPRY1*	616723	
NOS 13-0110	SEMD, TMEM165-related	AR	*TMEM165*	614727	Congenital disorder of glycosylation type IIk
NOS 13-0120	SEMD with microcephaly, retinal dystrophy and hearing loss, PISD-related (Liberfarb syndrome)	AR	*PISD*	618889	Phenotypically variable; in some affected individuals hearing and vision may be unaffected
NOS 13-0130	SEMD, UFSP2-related	AD	*UFSP2*	142669, 617974	Includes Familial hip dysplasia (Beukes)
NOS 13-0140	SEMD, short limb–abnormal calcification type, DDR2-related	AR	*DDR2*	271665	See also other dysplasias with stippling
NOS 13-0150	Immuno-osseous dysplasia, SMARCAL1-related (Schimke type)	AR	*SMARCAL1*	242900	Nephrotic syndrome is an important manifestation; see also EXTL3 deficiency, below
NOS 13-0160	SEMD with immune deficiency and intellectual disability, EXTL3-related	AR	*EXTL3*	617425	Also known as "Immunoskeletal dysplasia with developmental abnormalities"; includes Omenn syndrome with chondrodysplasia; see also *SMARCAL1*, above
NOS 13-0170	SEMD with immune deficiency, PGM3-related	AR	*PGM3*	615816	Known in OMIM as "immunodeficiency 23"
NOS 13-0180	SEMD with intellectual disability, NANS-related	AR	*NANS*	610442	
NOS 13-0190	SEMD with severe short stature, RPL13-related	AD	*RPL13*	618728	
NOS 13-0200	SEMD with elevated lysosomal enzymes, MBTPS1-related	AR	*MBTPS1*	618392	only two unrelated individuals known so far; in OMIM as "Kondo-Fu type"; possible role of lysosomal dysfunction in pathogenesis is unclear
NOS 13-0210	Short stature, skeletal dysplasia, liver failure, optic nerve atrophy and Pelger-Huet anomaly, NBAS-related	AR	*NBAS*	616483	Combination of clinical features is variable; also known as infantile liver failure syndrome type 2
NOS 13-0220	Short stature, skeletal dysplasia and liver failure, RINT1-related	AR	*RINT1*	618641	Combination of clinical features is variable; also known as infantile liver failure syndrome type 3
NOS 13-0230	Spondylodysplastic Ehlers-Danlos syndrome (SDEDSS type 3), SLC39A13-related	AR	*SLC39A13*	612350	*SLC39A13*/ZIP13 zinc transporter
NOS 13-0240	Spondylar and nasal alterations with striated metaphyses (SPONASTRIME dysplasia), TONSL-related	AR	*TONSL*	271510	Possibly genetically heterogeneous
NOS 13-0250	Spondyloepiphyseal dysplasia, sensorineural hearing loss, impaired intellectual development, and Leber congenital amaurosis (SHILCA) syndrome, NMNAT1-related	AR	*NMNAT1*	619260	Nonsyndromic Leber congenital amaurosis (LCA9; MIM 608553) is also caused by biallelic *NMNAT1* variants
NOS 13-0260	Platyspondyly (brachyolmia) with amelogenesis imperfecta, LTBP3-related	AR	*LTBP3*	601216	
NOS 13-0270	Cerebral, ocular, dental, auricular, and skeletal anomalies (CODAS syndrome), LONP1-related	AR	*LONP1*	600373	Mitochondrial chaperonopathy

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 13-0280	Epiphyseal and vertebral dysplasia, microtia, flat nose plus associated malformation (EVEN-PLUS syndrome), HSPA9-related	AR	*HSPA9*	616854	Mitochondrial chaperonopathy
NOS 13-0290	Cataracts, growth hormone deficiency, sensory neuropathy, sensorineural hearing loss, and skeletal dysplasia (CAGSSS syndrome), IARS2-related	AR	*IARS2*	616007	
NOS 13-0300	Steel syndrome, COL27A1-related	AR	*COL27A1*	615155	
NOS 13-0310	Rhizomelic spondylo-metaphyseal dysplasia with remission, LBR-related	AR	*LBR*	618019	
NOS 13-0320	Rhizomelic spondylo-epi-metaphyseal dysplasia, GNPNAT1-related	AR	*GNPNAT1*	619598	
	See also: Opsismodysplasia, *INPPL1*-related; Mucopolysaccharidosis type 4, *GALNS*-related (type 4A; Morquio disease), as well as Progressive pseudorheumatoid dysplasia (PPRD), *WISP3*-related. See also the non-genetic SEMD phenocopy, "Chondrodysplasia and growth failure following early hematopoietic stem cell transplantation", ***https://doi.org/10.1002/ajmg.a. 62021, PMID: 33398909.				
Group 14	**Severe spondylodysplastic dysplasias**				
NOS 14-0010	Achondrogenesis, TRIP11-related (formerly type 1A)	AR	*TRIP11*	200600	
NOS 14-0020	Schneckenbecken dysplasia, SLC35D1-related	AR	*SLC35D1*	269250	
NOS 14-0030	Severe spondylometaphyseal dysplasia (Sedaghatian type), GPX4-related	AR	*GPX4*	250220	
NOS 14-0040	Severe spondylometaphyseal dysplasia (SMD Sedaghatian-like), SBDS-related	AR	*SBDS*	260400	
NOS 14-0050	Opsismodysplasia, INPPL1-related	AR	*INPPL1*	258480	Includes lethal and milder cases
NOS 14-0060	Spondylometaphyseal dysplasia, PAM16-related	AR	*PAM16*	613320	
NOS 14-0070	Carbohydrate deficient glycoprotein syndrome, ALG9-related (ALG9-CDG; Gillessen-Kaesbach-Nishimura syndrome)	AR	*ALG9*	263210, 60877	
	See also Thanatophoric dysplasia, FGFR3-related; achondrogenesis and Torrance dysplasia, *COL2A1*-related; Fibrochondrogenesis, *COL11A1*-related; Achondrogenesis, *SLC26A2*-related; and Metatropic Dysplasia, *TRPV4*-related				
Group 15	**Mesomelic and rhizo-mesomelic dysplasias**				
NOS 15-0010	Dyschondrosteosis (Leri-Weill), SHOX-related	Pseudo-AD	*SHOX*	127300	Includes Reinhardt-Pfeiffer dysplasia, MIM 191400. Clinical continuum with Idiopathic short stature (MIM 300582)
NOS 15-0020	Mesomelic dysplasia (Langer type), SHOX-related	Pseudo-AR	*SHOX*	249700	
NOS 15-0030	Omodysplasia, recessive type, GPC6-related	AR	*GPC6*	258315	
NOS 15-0040	Omodysplasia, dominant type, FZD2-related	AD	*FZD2*	164745	
NOS 15-0050	Robinow syndrome, WNT5A-related	AD	*WNT5A*	180700	
NOS 15-0060	Robinow syndrome, DVL1-related	AD	*DVL1*	616331	
NOS 15-0070	Robinow syndrome, DVL3-related	AD	*DVL3*	616894	
NOS 15-0080	Robinow syndrome, FZD2-related	AD	*FZD2*		

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 15-0090	Robinow syndrome, recessive type, ROR2-related	AR	*ROR2*	268310	Includes previous COVESDEM (costo-vertebral segmentation defect with mesomelia); see also brachydactyly type B
NOS 15-0100	Robinow syndrome, recessive type, NXN-related	AR	*NXN*		
NOS 15-0110	Mesomelic dysplasia, HOXD-related (Kim or Korean type, Kantaputra type, Fryns type)	AD	*HOXD*	156232	Duplications at HOXD gene cluster locus; phenotypes is variable also within families
NOS 15-0120	Mesomelic dysplasia, Nievergelt type	AD	*163400*		
NOS 15-0130	Mesomelic dysplasia, Kozlowski-Reardon type	AR	*249710*		
NOS 15-0140	Mesomelic dysplasia with acral synostoses (Verloes- David-Pfeiffer type)	AD	*SULF1*, *SLCO5A1*	600383	Microdeletion syndrome involving two adjacent genes
NOS 15-0150	Mesomelic dysplasia (Savarirayan type), ID4-related	AD	*ID4*	605274	Microdeletions on 6p22.3
NOS 15-0160	Mesomelic dysplasia with digital anomalies and intellectual disability (KINSSHIP syndrome), AFF3-related	AD	*AFF3*	619297	In spite of the acronym, this condition is quite different from both Nievergelt and Savarirayan mesomelic dysplasias
NOS 15-0170	Oculo-skeletal syndrome with rhizomelic shortening, MAB21L2-related	AD	*MAB21L2*	615877	In OMIM as "Microphthalmia/Coloboma and skeletal dysplasia syndrome". Skeletal involvement not in all individuals. Two brothers with biallelic variants (AR?) had ocular but no skeletal involvement.
	See also Tibial hemimelia-polysyndactyly-triphalangeal thumb, *ZRS*-related, also consider: mesomelic dysplasia, Camera type (MIM#611886), the status of which remains unconfirmed				
Group 16	**Acromesomelic dysplasias**				
NOS 16-0010	Acromesomelic dysplasia (type Maroteaux), NPR2-related	AR	*NPR2*	602875	
NOS 16-0020	Acromesomelic dysplasia, PRKG2-related	AR	*PRKG2*	619636, 619638	Condition associated with biallelic loss of function variants. Three brothers form one family were found to have a spondylo-metaphyseal dysplasia phenotype (in OMIM as "619638 – Spondylometaphyseal dysplasia, Pagnamenta type". Needs to be confirmed)
NOS 16-0030	Grebe dysplasia, GDF5-related	AR	*GDF5*	200700	Includes acromesomelic dysplasia Hunter-Thompson type and acromesomelic dysplasia with genital anomalies; see also see other GDF5-related disorders
NOS 16-0040	Grebe dysplasia, BMPR1B-related	AR	*BMPR1B*	609441	
NOS 16-0050	Fibular hypoplasia and complex brachydactyly (Du Pan), GDF5-related	AR	*GDF5*	228900	See also other GDF5-related disorders
NOS 16-0060	Fibular hypoplasia and complex brachydactyly (Du Pan), BMPR1B-related	AR	*BMPR1B*	See 603248	
NOS 16-0070	Acromesomelic dysplasia, Osebold-Remondini type	AD		112910	
Group 17	**Acromesomelic dysplasias**				
NOS 17-0010	Acrocapitofemoral dysplasia, IHH-related	AR	*IHH*	607778	See other conditions associated with the *IHH* gene in this table
NOS 17-0020	Geleophysic dysplasia, ADAMTSL2-related	AR	*ADAMTSL2*	231050	

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 17-0030	Geleophysic dysplasia, FBN1-related	AD	*FBN1*	614185	
NOS 17-0040	Geleophysic dysplasia, LTBP3-related	AD	*LTBP3*	617809	
NOS 17-0050	Acromicric dysplasia, FBN1-related	AD	*FBN1*	102370	Includes acrolaryngeal dysplasia, previously known as Fantasy Island dysplasia or Tattoo dysplasia, and Moore-Federman syndrome
NOS 17-0060	Acromicric dysplasia, LTBP3-related	AD	*LTBP3*	See 617809	
NOS 17-0070	Weill-Marchesani syndrome, dominant, FBN1-related	AD	*FBN1*	608328	
NOS 17-0080	Weill-Marchesani syndrome, ADAMTS10-related	AR	*ADAMTS10*	277600	
NOS 17-0090	Weill-Marchesani syndrome, ADAMTS17-related	AR	*ADAMTS17*	613195	
NOS 17-0100	Weill-Marchesani syndrome, LTBP2-related	AR	*LTBP2*	614819	
NOS 17-0110	Myhre dysplasia, SMAD4-related	AD	*SMAD4*	139210	
NOS 17-0120	Acrodysostosis, PDE4D-related	AD	*PDE4D*	614613	Includes acroscyphodysplasia (see PMID 30006632)
NOS 17-0130	Acrodysostosis, PRKAR1A-related	AD	*PRKAR1A*	101800	
NOS 17-0140	Angel-shaped phalango-epiphyseal dysplasia (ASPED)	AD		105835	Possibly related or allelic to brachydactyly type C
NOS 17-0150	Albright hereditary osteodystrophy, GNAS-related	AD	*GNAS*	103580	Overlaps with progressive osseous heteroplasia
NOS 17-0160	Leri Pleonosteosis, linked to 8q22.1	AD	*8q22.1*	151200	Duplication at 8q22.1 encompassing GDF6 and SDC2
NOS 17-0170	SED with brachydactyly, MIR140-related	AD	*MIR140*	618618	Brachydactyly with cone-shaped epiphyses
	See also Cartilage-Hair Hypoplasia, RMRP-related, and the brachdydactyly groups, below (Groups 18 and 19)				
Group 18	**Brachydactylies (isolated)**				
NOS 18-0010	Brachydactyly type A1, IHH-related	AD	*IHH*	112500	
NOS 18-0020	Brachydactyly type A2, BMPR1B-related	AD	*BMPR1B*	112600	
NOS 18-0030	Brachydactyly type A2, BMP2-related	AD	*BMP2*	112600	Duplication of BMP2 enhancer
NOS 18-0040	Brachydactyly type A2, GDF5-related	AD	GDF5	112600	See also Grebe dysplasia, GDF5-related; Fibular hypoplasia and complex brachydactyly (Du Pan), GDF5-related; Brachydactyly type C, GDF5-related; and Multiple synostoses syndrome, GDF5-related
NOS 18-0050	Brachydactyly type B1, ROR2-related	AD	*ROR2*	113000	See also Robinow syndrome/COVESDEM
NOS 18-0060	Brachydactyly type B2, NOG-related	AD	*NOG*	611377	
NOS 18-0070	Brachydactyly type C, GDF5-related	AD	*GDF5*	113100	See other GDF5-related disorders
NOS 18-0080	Brachydactyly type D, HOXD13-related	AD	*HOXD13*	113200	Brachydactyly type D is often a component of Brachydactyly type E
NOS 18-0090	Brachydactyly type E, HOXD13-related	AD	*HOXD13*	113300	

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 18-0100	Brachydactyly with anonychia (Cooks syndrome), KCNJ2-related	AD	*KCNJ2*	106995	Duplications of *SOX9/KCNJ2* regulatory region
NOS 18-0110	Preaxial brachydactyly, PAX3 type, linked to 2q35-36	AD	*2q35-36*		Deletions leading to disruption of TADs and abnormal expression of *PAX3*
	See also brachdactyly, PTHLH-related (below)				
Group 19	**Brachydactylies as part of syndromes**				
NOS 19-0010	Trichorhinophalangeal dysplasia types 1/3	AD	*TRPS1*	190350, 190351	TRPS1 and 3 are a phenotypic spectrum
NOS 19-0020	Langer-Giedion syndrome (Trichorhinophalangeal dysplasia type 2)	AD	*TRPS1, EXT1*	150230	Microdeletion syndrome; see also multiple cartilaginous exostoses
NOS 19-0030	Catel-Manzke syndrome, TGDS-related	AR	*TGDS*	616145	
NOS 19-0040	Deafness, onychodystrophy, osteodystrophy, retardation and seizures (DOORS) syndrome	AR	*TBC1D24*	220500	"Osteodystrophy" and "retardation" are misnomers
NOS 19-0050	Brachydactyly–intellectual disability syndrome, HDAC4-related	AD	*HDAC4*	600430	The existence of this entity is questionable. *HDAC4* variants alone may not be sufficient to produce either brachydactyly or intellectual disability. Some patients have microdeletions involving contiguous genes (2q37 deletion syndrome). *HDAC4* variants have been associated with a developmental disorder (see MIM 619797)
NOS 19-0060	Hyperphosphatasia with intellectual disability, brachytelephalangy, and distinct face, PIGV-related	AR	*PIGV*	239300	Several other related defects of GPI synthesis known, most cases not known for skeletal changes; see for example, MIM 610293 for a summary
NOS 19-0070	Brachydactyly-short stature-hypertension syndrome, PDE3A-related (Bilginturan syndrome)	AD	*PDE3A*	112410	
NOS 19-0080	Brachydactyly, obesity and intellectual disability syndrome, PRMT7-related	AR	*PRMT7*	617157	Phenotype reminiscent of Albright Hereditary Ostedystrophy (AHO), GNAS-related (see above) but recessive. In OMIM as "617157–Short stature, brachydactyly, intellectual developmental disability, and seizures"
NOS 19-0090	Microcephaly-oculo-digito-esophageal-duodenal syndrome, MYCN-related (Feingold syndrome)	AD	*MYCN*	164280	
NOS 19-0100	Hand-foot-genital syndrome, HOXA13-related	AD	*HOXA13*	140000	Includes Guttmacher syndrome
NOS 19-0110	Rubinstein-Taybi syndrome, CREBBP-related	AD	*CREBBP*	180849	
NOS 19-0120	Rubinstein-Taybi syndrome, EP300-related	AD	*EP300*	613684	
NOS 19-0130	Brachydactyly, Temtamy type, CHSY1-related	AR	*CHSY1*	605282	
NOS 19-0140	Hyperphalangism, characteristic facies, hallux valgus and bronchomalacia (Chitayat syndrome), ERF-related	AD	*ERF*	617180	Typically a monoallelic Y89C substitution
NOS 19-0150	Hypoacusis with facial an digital anomalies (Keipert syndrome), GPC4-related	XL	*GPC4*	301026	Brachytelephalangy is the most consistent skeletal signs

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 19-0160	Christian type brachydactyly	AD		112450	
NOS 19-0170	Coffin-Siris syndrome, ARID1A-related	AD	*ARID1A*	614607	
NOS 19-0180	Coffin-Siris syndrome, ARIB1B-related	AD	*ARID1B*	135900	Variants in various components of the SWI/SNF complex have been reported in patients with a diagnosis of Coffin-Siris syndrome
NOS 19-0190	Coffin-Siris syndrome, SMARCB1-related	AD	*SMARCB1*	614608	
NOS 19-0200	Coffin-Siris syndrome, SMARCA4-related	AD	*SMARCA4*	614609	
NOS 19-0210	Coffin-Siris syndrome, SMARCE1-related	AD	*SMARCE1*	616938	
NOS 19-0220	Cardiomyopathy and brachydactyly, LMNA-related (Heart-hand syndrome type IV)	AD	*LMNA*	610140	in OMIM as "Heart-Hand syndrome, Slovenian type"
	See also CDP, X-linked recessive, ARSE-related (brachytelephalangic type; CDPX1)				
Group 20	**Bent bones dysplasia group**				
NOS 20-0010	Campomelic dysplasia (CD), SOX9-related	AD	*SOX9*	114290	Includes acampomelic campomelic dysplasia (ACD), mild campomelic dysplasia (MIM 602196); so-called Ischio- pubic--patellar dysplasia, as well as some cases of isolated Pierre-Robin sequence
NOS 20-0020	Stüve-Wiedemann syndrome, LIFR-related	AR	*LIFR*	601559	Includes former neonatal Schwartz-Jampel syndrome or SJS type 2
NOS 20-0030	Stüve-Wiedemann syndrome, IL6ST-related	AR	*IL6ST*	619751	
NOS 20-0040	Kyphomelic dysplasia with facial dysmorphism, KIF5B-related	AD	*KIF5B*	211350	The name "kyphomelic dysplasia" has been applied to heterogeneous conditions
NOS 20-0050	Bent bone dysplasia, FGFR2-related	AD	*FGFR2*	614592	
NOS 20-0060	Bent bone dysplasia, LAMA5-related	AR	*LAMA5*		Biallelic LAMA5 variants are associated with congenital or infantile nephrotic syndrome (MIM)
	Bent bones is an unspecific finding, particularly in a prenatal setting, that can be observed in numerous other conditions, such as those with bone fragility; thus see the OI-bone fragility group (group 26) as well as Hypophosphatasia, *ALPL*-related.				
Group 21	**Primordial dwarfism and slender bones group**				
NOS 21-0010	3-M syndrome, CUL7-related	AR	*CUL7*	273750	Includes dolichospondylic dysplasia and Yakut short stature syndrome
NOS 21-0020	3-M syndrome, OBSL1-related	AR	*OBSL1*	612921	
NOS 21-0030	3-M syndrome, CCDC8-related	AR	*CCDC8*	614205	
NOS 21-0040	Sanjad-Sakati syndrome, recessive, TBCE-related	AR	*TBCE*	241410	In OMIM as "Kenny-Caffey type 1" but does not correspond to the disorder described by Kenny and Caffey which is the dominant form
NOS 21-0050	Kenny-Caffey syndrome, dominant, FAM111A-related	AD	*FAM111A*	127000	
NOS 21-0060	Osteocraniostenosis, FAM111A-related	AD	*FAM111A*	602361	

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 21-0070	Hallermann-Streiff syndrome			234100	Usually sporadic; some cases have phenotypic overlap with osteocraniostenosis, *FAM111A*-related
NOS 21-0080	Microcephalic osteodysplastic primordial dwarfism, RNU4ATAC-related	AR	*RNU4ATAC*	210710	Was MOPD 1/3; usually homozygous variants; includes Taybi-Linder cephaloskeletal dysplasia
NOS 21-0090	Roifman syndrome, RNU4ATAC-related	AR	*RNU4ATAC*	616651	See other RNU4ATAC-related condition in this table
NOS 21-0100	Microcephalic osteodysplastic primordial dwarfism, PCNT-related	AR	*PCNT*	210720	Was MOPD2, Majewski type
NOS 21-0110	Microcephalic osteodysplastic primordial dwarfism, ATR-related	AR	*ATR*	210600	In MIM as Seckel syndrome 1
NOS 21-0120	Microcephalic osteodysplastic primordial dwarfism, RBBP8-related	AR	*RBBP8*	606744	In MIM as Seckel syndrome 2. The RBBP8 gene is also associated with Jawad syndrome (microcephaly with intellectual disability and digital anomalies; MIM 251255)
NOS 21-0130	Microcephalic osteodysplastic primordial dwarfism, CEP152-related	AR	*CEP152*	613823	In MIM as Seckel syndrome 5. The CEP152 gene also causes primary microcephaly (MIM 614852)
NOS 21-0140	Microcephalic osteodysplastic primordial dwarfism, DNA2-related	AR	*DNA2*	615807	In MIM as Seckel syndrome 8. The DNA2 gene is also associated with autosomal dominant progressive external ophthalmoplegia with mitochondrial DNA deletions (MIM 615156)
NOS 21-0150	Microcephalic osteodysplastic primordial dwarfism, TRAIP-related	AR	*TRAIP*	616777	In MIM as Seckel syndrome 9
NOS 21-0160	Microcephalic osteodysplastic primordial dwarfism, NSMCE2-related	AR	*NSMCE2*	617253	In MIM as Seckel syndrome 10
NOS 21-0170	Microcephalic osteodysplastic primordial dwarfism, CENPE-related	AR	*CENPE*	see 616051	In MIM as autosomal recessive primary microcephaly
NOS 21-0180	Microcephalic osteodysplastic primordial dwarfism, CRIPT-related	AR	*CRIPT*	615789	In MIM as short stature with microcephaly and distinctive facies
NOS 21-0190	Microcephalic osteodysplastic primordial dwarfism, XRCC4-related	AR	*XRCC4*	616541	In MIM as short stature, microcephaly and endocrine dysfunction
NOS 21-0200	Microcephalic osteodysplastic primordial dwarfism, or microcephaly-short stature-micromelia-limb abnormalities, DONSON-related	AR	*DONSON*	251230, 617604	Milder affected patients may fall into the Meier-Gorlin syndrome spectrum
NOS 21-0210	IMAGE syndrome (intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia, and genital anomalies)	AD	*CDKN1C*	614732	Gene also known to cause Beckwith-Wiedemann syndrome (MIM 130650). IMAGE-associated variants are clustered in the PCNA-binding region and are maternally transmitted (gene is imprinted with preferential maternal expression)
NOS 21-0220	IMAGE syndrome/FILS syndrome, POLE-related	AR	*POLE*	618336, 615139	The phenotype is variable and may include immune deficiency (OMIM 615139)
NOS 21-0230	Saul-Wilson syndrome, COG4-related	AD	*COG4*	618150	
NOS 21-0240	Short stature, facial dysmorphism, skeletal and dental anomalies syndrome, SCUBE3-related	AR	*SCUBE3*	619184	in OMIM as "short stature, facial dysmorphism, and skeletal anomalies with or without cardiac anomalies 2"
NOS 21-0250	Ear-patella-primordial short stature syndrome (Meier-Gorlin), ORC4-related	AR	*ORC1*	224690	

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 21-0260	Ear-patella-primordial short stature syndrome (Meier-Gorlin), ORC4-related	AR	*ORC4*	613800	
NOS 21-0270	Ear-patella-primordial short stature syndrome (Meier-Gorlin), ORC6-related	AR	*ORC6*	613803	
NOS 21-0280	Ear-patella-primordial short stature syndrome (Meier-Gorlin), CDT1-related	AR	*CDT1*	605525	
NOS 21-0290	Ear-patella-primordial short stature syndrome (Meier-Gorlin), CDC6-related	AR	*CDC6*	613805	A single case reported so far
NOS 21-0300	Ear-patella-primordial short stature syndrome (Meier-Gorlin), CDC45-related	AR	*CDC45*	603465	
NOS 21-0310	Ear-patella-primordial short stature syndrome (Meier-Gorlin), MCM3-related	AR	*MCM3*	See 602693	
NOS 21-0320	Ear-patella-primordial short stature syndrome (Meier-Gorlin), MCM5-related	AR	*MCM5*	602696	
NOS 21-0330	Ear-patella-primordial short stature syndrome (Meier-Gorlin), MCM7-related	AR	*MCM7*	See 600592	
NOS 21-0340	Ear-patella-primordial short stature syndrome (Meier-Gorlin), GMNN-related	AD	*GMNN*	613804	
NOS 21-0350	Ear-patella-primordial short stature syndrome (Meier-Gorlin) with craniosynostosis, GINS2-related	AD	*GINS2*	See 610609	A single case reported so far
Group 22	**Lysosomal storage diseases with skeletal involvement**				
NOS 22-0010	Mucopolysaccharidosis type 1, IDUA-related	AR	*IDUA*	607014, 607015, 607016	Was type 1H-Hurler syndrome, type 1S-Scheie syndrome
NOS 22-0020	Mucopolysaccharidosis type 2, IDS-related	XL	*IDS*	309900	Known as Hunter syndrome
NOS 22-0030	Mucopolysaccharidosis type 3, SGSH-related (type 3A)	AR	*SGSH*	252900	Known as Sanfilippo A syndrome
NOS 22-0040	Mucopolysaccharidosis type 3, NAGLU-related (type 3B)	AR	*NAGLU*	252920	Known as Sanfilippo B syndrome
NOS 22-0050	Mucopolysaccharidosis type 3, HSGNAT-related (type 3C)	AR	*HSGNAT*	252930	Known as Sanfilippo C syndrome
NOS 22-0060	Mucopolysaccharidosis type 3, GNS-related (type 3D)	AR	*GNS*	252940	Known as Sanfilippo D syndrome
NOS 22-0070	Mucopolysaccharidosis type 4, GALNS-related (type 4A)	AR	*GALNS*	253000	Known as Morquio A syndrome
NOS 22-0080	Mucopolysaccharidosis type 4, GLB1-related (type 4B)	AR	*GLB1*	253010	Known as Morquio B syndrome
NOS 22-0090	Mucopolysaccharidosis type 6, ARSB-related	AR	*ARSB*	253200	Known as Maroteaux-Lamy syndrome
NOS 22-0100	Mucopolysaccharidosis type 7, GUSB-related	AR	*GUSB*	253220	Known as Sly syndrome
NOS 22-0110	Mucopolysaccharidosis type 10, ARSK-related	AR	*ARSK*	610011	
NOS 22-0120	Mucopolysaccharidosis-plus syndrome, VPS33A-related	AR	*VPS33A*	617303	
NOS 22-0130	Fucosidosis, FUCA-related	AR	*FUCA*	230000	

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 22-0140	alpha-Mannosidosis, MAN2B1-related	AR	*MAN2B1*	248500	
NOS 22-0150	beta-Mannosidosis, MANBA-related	AR	*MANBA*	248510	
NOS 22-0160	Aspartylglucosaminuria, AGA-related	AR	*AGA*	208400	
NOS 22-0170	Gangliosidosis GM1, GLB1-related	AR	*GLB1*	230500	Several forms, see also mucopolysaccharidosis type 4B (Morquio B) above
NOS 22-0180	Sialidosis, NEU1-related	AR	*NEU1*	256550	Several forms of different severity
NOS 22-0190	Galactosialidosis, PPGB-related	AR	*PPGB*	256540	Several forms of different severity
NOS 22-0200	Sialic acid storage disease (SIASD), SLC17A5-related	AR	*SLC17A5*	269920	
NOS 22-0210	Multiple sulfatase deficiency, SUMF-related	AR	*SUMF1*	272200	
NOS 22-0220	Mucolipidosis II (I-cell disease), GNPTAB-related	AR	*GNPTAB*	252500	The old entity of Pacman dysplasia is the prenatal manifestation of mucolipidosis II with hyperparathyroidism
NOS 22-0230	Mucolipidosis III (Pseudo-Hurler polydystrophy), GNPTAB-related	AR	*GNPTAB*	252600	
NOS 22-0240	Mucolipidosis III (Pseudo-Hurler polydystrophy), GNPTG-related	AR	*GNPTG*	252605	In general somewhat milder phenotype than the GNPTAB-related form
NOS 22-0250	Mucolipidosis, GCAF-related	AR	*CGAF*	619345	The gene was previously known as TMEM251 and encodes for a "GNTAP cleavage and activity factor" (see GNTAP, above)
NOS 22-0260	Gaucher disease, GBA-related	AR	*GBA*	230800	Long-standing Gaucher disease can have bone changes that are different from the "dysostosis multiplex" pattern seen in other lysosomal diseases in this group
	See also familial arthritis with hyaluronidase deficiency ("mucopolysaccharidosis type 9"), *HYAL1*-related; SEMD with elevated lysosomal enzymes, *MBTPS1*-related, above; as well as Farber disease, *ASAH1*-related, below.				
Group 23	**Chondrodysplasia punctata (CDP) group**				
NOS 23-0010	CDP, X-linked recessive, ARSE-related (brachytelephalangic type; CDPX1)	XL	*ARSE*	302950	
NOS 23-0020	CDP, X-linked dominant, EBP-related (Conradi-Hünermann type; CDPX2)	XL	*EBP*	302960	
NOS 23-0030	Congenital hemidysplasia, ichthyosis, limb defects (CHILD) syndrome, NSDHL-related	XL	*NSDHL*	308050	
NOS 23-0040	Keutel syndrome, MGP-related	AR	*MGP*	245150	
NOS 23-0050	Greenberg dysplasia, LBR-related	AR	*LBR*	215140	Includes hydrops-ectopic calcification--moth-eaten appearance dysplasia (HEM) and dappled diaphyseal dysplasia; possibly includes also the ultrarare entity designed as Astley-Kendall dysplasia. See also the non- lethal condition associated with *LBR*, above
NOS 23-0060	Rhizomelic CDP, PEX7-related	AR	*PEX7*	215100	
NOS 23-0070	Rhizomelic CDP, DHPAT-related	AR	*DHPAT*	222765	
NOS 23-0080	Rhizomelic CDP, AGP5-related	AR	*AGPS*	600121	

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 23-0090	Rhizomelic CDP, FAR1-related	AR	*FAR1*	616154	MIM calls this entity "peroxisomal fatty acyl-CoA reductase 1 disorder"; skeletal phenotype milder than other rCDP forms. The *FAR1* gene is also associated with cataracts, spastic paraparesis, and speech delay (MIM 619338, AD)
NOS 23-0100	Rhizomelic CDP, PEX5-related	AR	*PEX5*	616716	
NOS 23-0110	CDP tibial-metacarpal type			118651	Some cases possibly caused by maternal auto-immune disease
	Note: stippling can occur in several syndromes such as Zellweger cerebro-hepato-renal syndrome (see OMIM for the many genetic types), Smith-Lemli-Opitz (MIM 270400), in Mucolipidosis II (I-cell disease), *GNPTAB*-related, mild forms of Raine dysplasia, *FAM20C*-related, and others. See also SEMD short limb-abnormal calcification type, *DDR2*-related. Stippling in the fetus is also observed as a consequence of maternal auto-immune disease, sometimes presenting as "CDP tibial-metacarpal type".				
Group 24	**Osteopetrosis and related osteoclast disorders**				
NOS 24-0010	Osteopetrosis, neonatal or infantile form, TCIRG1-related	AR	*TCIRG1*	259700	
NOS 24-0020	Osteopetrosis, neonatal or infantile form, CLCN7-related	AR	*CLCN7*	611490	
NOS 24-0030	Osteopetrosis, neonatal or infantile form, SNX10-related	AR	*SNX10*	615085	-
NOS 24-0040	Osteopetrosis, infantile form, with nervous system involvement, OSTM1-related	AR	*OSTM1*	259720	Includes former osteopetrosis with infantile neuraxonal dysplasia (MIM 600329)
NOS 24-0050	Osteopetrosis, infantile form, osteoclast--poor with immunoglobulin deficiency, TNFRSF11A-related	AR	*TNFRSF11A*	612301	See also below in this group, dysosteosclerosis, TNFRSF11A-related, as well as MIM 602080-familial expansile osteolysis
NOS 24-0060	Osteopetrosis, intermediate form, TCIRG1-related	AR	*TCIRG1*	259700	
NOS 24-0070	Osteopetrosis, intermediate form, TNFSF11-related	AR	*TNFSF11*	259710	
NOS 24-0080	Osteopetrosis, intermediate form, PLEKHM-related	AR	*PLEKHM1*	611497	
NOS 24-0090	Osteopetrosis, intermediate form, CLCN7-related	AR	*CLCN7*	259710	
NOS 24-0100	Osteopetrosis, late-onset, dominant form, CLCN7-related	AD	*CLCN7*	166600	
NOS 24-0110	Osteopetrosis with renal tubular acidosis, CA2-related	AR	*CA2*	259730	
NOS 24-0120	Osteopetrosis with ectodermal dysplasia and immune defect (OLEDAID), IKBKG-related	XL	*IKBKG*	300301	
NOS 24-0130	Osteopetrosis, moderate form, SLC4A2-related	AR	*SLC4A2*	See 109280	A single adult patient reported, phenotype may evolve
NOS 24-0140	Osteopetrosis, moderate form with defective leucocyte adhesion, FERMT3-related	AR	*FERMT3*	612840	In OMIM as Leucocyte Adhesion Deficiency 3 (LAD3) – MIM 612840
NOS 24-0150	Osteopetrosis, moderate form with defective leucocyte adhesion, RASGRP2-related	AR	*RASGRP2*	615888	OMIM only includes bleeding disorder, platelet type, 18 (MIM 615888) for this gene
NOS 24-0160	Osteosclerotic metaphyseal dysplasia, LRKK1-related	AR	*LRRK1*	615198	The name may be misleading as the condition is best described as a form of osteopetrosis

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 24-0170	Pyknodysostosis, CTSK-related	AR	*CTSK*	265800	In some individuals, the features of pyknodyostosis are absent and the disorder mimics osteopetrosis
NOS 24-0180	Dysosteosclerosis, SLC29A3-related	AR	*SLC29A3*	224300	
NOS 24-0190	Dysosteosclerosis, TNFRSF11A-related	AR	*TNFRSF11A*	224300	This entity probably forms a spectrum with Osteopetrosis, intermediate form, TNFSF11-related (above)
NOS 24-0200	Dysosteosclerosis with degenerative encephalopathy and brain malformation, CSF1R-related	AR	*CSF1R*	618476	In OMIM as "Brain abnormalities, neurodegeneration and dysosteosclerosis (BANDDOS)"; gene also associated with MIM 221820–leukoencephalopathy with spheroids.
	Note: osteomesopyknosis (MIM 166450) may represent a form of osteopetrosis. In a pattern similar to the ciliary disorders, the phenotypes from individual loci are variable and may overlap with those of other loci.				
Group 25	**Osteosclerotic disorders**				
NOS 25-0010	Desmosterolosis, DHCR4-related	AR	*DHCR24*	602398	See also other sterol-metabolism related conditions
NOS 25-0020	Raine dysplasia, FAM20C-related	AR	*FAM20C*	259775	Variable severity, many cases are perinatal severe, some cases show survival to adulthood; then often combined with FGF23 elevation and hypophosphatemic rickets
NOS 25-0030	Caffey disease, COL1A1-related	AD	*COL1A1*	114000	Rare specific variants in *COL1A1*. See also osteogenesis imperfecta related to collagen 1 genes.
NOS 25-0040	Caffey dysplasia (severe variants with prenatal onset)	AR?		114000	
NOS 25-0050	Dysplastic cortical hyperostosis, Kozlowski-Tsuruta type				A few sporadic cases known, phenotype consistent, molecular basis unknown
NOS 25-0060	Dysplastic cortical hyperostosis, Al-Gazali type			601356	Only a few cases known. Im OMIM as "Lethal short-limb skeletal dysplasia, Al Gazali type". Not to be confused with "Al-Gazali syndrome", a rare variant of *B3GALT6* disorders (see above)
NOS 25-0070	Osteopoikilosis, LEMD3-related	AD	*LEMD3*	166700	Includes Buschke-Ollendorff syndrome (same OMIM entry)
NOS 25-0080	Melorheostosis with osteopoikilosis, LEMD3-related	AD	*LEMD3*	166700	Includes mixed sclerosing bone dysplasia
NOS 25-0090	Melorheostosis, MAP2K1-related	SP	*MAP2K1*	155950	Possibly locus heterogeneity
NOS 25-0100	Osteopathia striata with cranial sclerosis (OSCS), AMER1related	XL	*AMER1*	300373	
NOS 25-0110	Pyle disease, SFRP4-related	AR	*SFRP4*	265900	The name "metaphyseal dysplasia, Pyle type" is misleading (no growth plate dysplasia) and should be avoided
NOS 25-0120	Craniometaphyseal dysplasia, ANKH-related	AD	*ANKH*	123000	Dominant type
NOS 25-0130	Craniometaphyseal dysplasia, GJA1-related	AR	*GJA1*	218400	Recessive type
NOS 25-0140	Diaphyseal dysplasia Camurati-Engelmann, TGFB1-related	AD	*TGFB1*	131300	Gain-of-function variants
NOS 25-0150	Hyperostosis-Hyperphosphatemia syndrome, GALNT3-related	AR	*GALNT3*	211900	Formerly hyperphosphatemic tumoral calcinosis type 1

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 25-0160	Hyperostosis-Hyperphosphatemia syndrome, FGF23-related	AR	*FGF23*	617993	Formerly hyperphosphatemic tumoral calcinosis type 2
NOS 25-0170	Hyperostosis-Hyperphosphatemia syndrome, KL-relathed	AR	*KL*	617994	Formerly hyperphosphatemic tumoral calcinosis type 3
NOS 25-0180	Cerebellar hypoplasia-endosteal sclerosis, POLR3B-related	AR	*POLR3B*	213002	
NOS 25-0190	Hematodiaphyseal dysplasia Ghosal, TBXAS1-related	AR	*TBXAS1*	231095	
NOS 25-0200	Hypertrophic osteoarthropathy, HPGD-related	AR	*HPGD*	259100	Includes cranio-osteoarthropathy, some cases of recessive pachydermoperiostosis, as well as recessively inherited isolated digital clubbing (MIM 119900)
NOS 25-0210	Hypertrophic osteoarthropathy, SLCO2A1-related	AD, AR	*SLCO2A1*	614441	
NOS 25-0220	Oculodentoosseous dysplasia (ODOD), GJA1-related, dominant, mild type	AD	*GJA1*	164200	
NOS 25-0230	Oculodentoosseous dysplasia (ODOD) GJA1-related, recessive, severe type	AR	*GJA1*	257850	Possibly homozygous form of mild ODOD
NOS 25-0240	Osteoectasia with hyperphosphatasia (juvenile Paget disease), OPG-related	AR	*OPG*	239000	
NOS 25-0250	Osteosclerosis, LRP5-related	AD	*LRP5*	144750, 607634	Includes previous AD osteopetrosis type 1 (OPTA1)
NOS 25-0260	Sclerosteosis, SOST-related	AR	*SOST*	269500	See also sclerosteosis, SOST-related, below
NOS 25-0270	Sclerosteosis, LRP4-related	AR	*LRP4*	614305	
NOS 25-0280	Endosteal hyperostosis, van Buchem type, SOST-related	AR	*SOST*	239100	Specific 52 kb deletion downstream of SOST
NOS 25-0290	Endosteal hyperostosis, Worth type	AD	*LRP5*	144750	
NOS 25-0300	Craniodiaphyseal dysplasia, SOST-related	AD	*SOST*	122860	Presumed dominant negative variant
NOS 25-0310	Craniodiaphyseal dysplasia, SP7-related	AR	*SP7*	See 606633	One family reported; SP7 variants also associated with Osteogenesis imperfecta (MIM 613849), see below
NOS 25-0320	Trichodentoosseous dysplasia, DLX3-related	AD	*DLX3*	190320	
NOS 25-0330	Diaphyseal medullary stenosis with malignant fibrous histiocytoma, MTAP-related	AD	*MTAP*	112250	Also known as Hardcastle disease
NOS 25-0340	Craniotubular dysplasia, TMEM53-related	AR	*TMEM53*	619727	
NOS 25-0350	Craniometadiaphyseal dysplasia, Wormian bone type	AR		269300	
NOS 25-0360	Lenz-Majewski hyperostotic dysplasia, PTDSS1-related	AD	*PTDSS1*	151050	
NOS 25-0370	Osteochondrodysplasia with hypertrichosis (Cantu syndrome), ABCC9-related	AD	*ABCC9*	239850	
NOS 25-0380	Familial Paget disease of bone, SQSTM1-related	AD	*SQSTM1*	167250	
NOS 25-0390	Inclusion body myopathy, Paget disease of bone and frontotemporal dementia	AD	*VCP*	167320	Monoallelic variants in the VCP gene are also associated with MIM 616687-Charcot-Marie-Tooth disease 2Y, and with MIM 613954-Frontotemporal dementia and/ or amyotrophic lateral sclerosis 6.

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 25-0400	Endosteal hyperostosis, oligodontia, short stature, facial dysmorphism and intellectual disability, POLR3GL-related	AR	*POLR3GL*	619234	Phenotypic elements will need to be evaluated more precisely; one patient reported as Wiedemann- Rautenstrauch-syndrome-like
NOS 25-0410	Metaphyseal dysplasia, Braun-Tinschert type	AD		605946	
NOS 25-0420	Trichothiodystrophy with axial osteosclerosis	AR			A subset of patients with trichothiodystrophy have marked osteosclerosis but have not been molecularly characterized so far
	See also the chondrodysplasia punctata group (group 23); as well as familial expansile osteolysis, *TNFRSF11A*-related (below); and trichothiodystrophy with central osteosclerosis (PMID 15148554)				
Group 26	**Osteogenesis imperfecta and bone fragility group**				
NOS 26-0010	Osteogenesis imperfecta, non-deforming (Sillence type 1), COL1A1-related	AD	*COL1A1*	166200	Usually with persistently blue sclerae, can have signs of connective tissue weakness (in MIM as OI type I)
NOS 26-0020	Osteogenesis imperfecta, non-deforming (Sillence type 1), COL1A2-related	AD	*COL1A2*	166200	Usually with persistently blue sclerae, can have signs of connective tissue weakness (in MIM as OI type I)
NOS 26-0030	Osteogenesis imperfecta, severe perinatal form (Sillence type 2) COL1A1-related	AD	*COL1A1*	166210	Formerly "perinatal lethal"; in OMIM as OI type II
NOS 26-0040	Osteogenesis imperfecta, severe perinatal form (Sillence type 2), COL1A2-related	AD	*COL1A2*	166210	Formerly "perinatal lethal"; in OMIM as OI type II
NOS 26-0050	Osteogenesis imperfecta, severe perinatal form (Sillence type 2), CRTAP-related	AR	*CRTAP*	610682	Formerly "perinatal lethal"; in OMIM as OI type VII
NOS 26-0060	Osteogenesis imperfecta, severe perinatal form (Sillence type 2), P3H1-related	AR	*P3H1*	610915	Formerly "perinatal lethal"; in OMIM as OI type VIII
NOS 26-0070	Osteogenesis imperfecta, severe perinatal form (Sillence type 2), PPIB-related	AR	*PPIB*	259440	Formerly "perinatal lethal"; in OMIM as OI type IX
NOS 26-0080	Osteogenesis imperfecta, progressively deforming (Sillence type 3), COL1A1-related	AD	*COL1A1*	259420	In OMIM as OI type III
NOS 26-0090	Osteogenesis imperfecta, progressively deforming (Sillence type 3), COL1A2-related	AD	*COL1A2*	259420	In OMIM as OI type III
NOS 26-0100	Osteogenesis imperfecta, progressively deforming (Sillence type 3), IFITM5-related	AD	*IFITM5*	610967	In OMIM OI type III; phenotype is distinct but in some instances can minimize OI type III
NOS 26-0110	Osteogenesis imperfecta, progressively deforming (Sillence type 3), SERPINF1-related	AR	*SERPINF1*	613982	In OMIM as OI type VI
NOS 26-0120	Osteogenesis imperfecta, progressively deforming (Sillence type 3), CRTAP-related	AR	*CRTAP*	610682	In OMIM OI type VII
NOS 26-0130	Osteogenesis imperfecta, progressively deforming (Sillence type 3), P3H1-related	AR	*P3H1*	610915	In OMIM OI type VIII
NOS 26-0140	Osteogenesis imperfecta, progressively deforming (Sillence type 3), PPIB-related	AR	*PPIB*	see 259440	In OMIM OI type IX
NOS 26-0150	Osteogenesis imperfecta, progressively deforming (Sillence type 3), SERPINH1-related	AR	*SERPINH1*	613848	In OMIM OI type X
NOS 26-0160	Osteogenesis imperfecta, progressively deforming (Sillence type 3), FKBP10-related	AR	*FKBP10*	610968	In OMIM OI type XI

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 26-0170	Osteogenesis imperfecta, progressively deforming (Sillence type 3), TMEM38B-related	AR	*TMEM38B*	615066	In OMIM OI type XIV
NOS 26-0180	Osteogenesis imperfecta, progressively deforming (Sillence type 3), BMP1-related	AR	*BMP1*	614856	In OMIM OI type XIII
NOS 26-0190	Osteogenesis imperfecta, progressively deforming (Sillence type 3), WNT1-related	AR	*WNT1*	615220	In OMIM as OI type XV. Biallelic variants; monoallelic variants may result in AD osteoporosis.
NOS 26-0200	Osteogenesis imperfecta, progressively deforming (Sillence type 3), CREB3L1-related	AR	*CREB3L1*	616229	In OMIM as OI type XVI. Has severe joint laxity and scoliosis, Ehlers-Danlos-like
NOS 26-0210	Osteogenesis imperfecta, progressively deforming (Sillence type 3), SPARC-related	AR	*SPARC*	616507	In OMIM as OI type XVII
NOS 26-0220	Osteogenesis imperfecta, progressively deforming (Sillence type 3), TENT5A-related	AR	*TENT5A*	617952	In OMIM as OI type XVIII
NOS 26-0230	Osteogenesis imperfecta, progressively deforming (Sillence type 3), MBTPS2-related	XLR	*MBTPS2*	301014	In OMIM as OI type XIX
NOS 26-0240	Osteogenesis imperfecta, progressively deforming (Sillence type 3), MESD-related	AR	*MESD*	618644	In OMIM as OI type XX
NOS 26-0250	Osteogenesis imperfecta, progressively deforming (Sillence type 3) with neurodevelopmental features, KDELR2-related	AR	*KDELR2*	619131	In OMIM as OI type XXI. Frequency of neurodevelopmental delay not clear yet.
NOS 26-0260	Osteogenesis imperfecta, progressively deforming (Sillence type 3), CCD134-related	AR	*CCD134*	619795	In OMIM as OI typeXXII
NOS 26-0270	Osteogenesis imperfecta, moderate form (Sillence type 4), COL1A1-related	AD	*COL1A1*	166220	In OMIM as OI type IV
NOS 26-0280	Osteogenesis imperfecta, moderate form (Sillence type 4), COL1A2-related	AD	*COL1A2*	166220	In OMIM as OI type IV
NOS 26-0290	Osteogenesis imperfecta, moderate form (Sillence type 4), WNT1-related	AR	*WNT1*	see 166220	In OMIM as OI type XV
NOS 26-0300	Osteogenesis imperfecta, moderate form (Sillence type 4), IFITM5-related	AD	*IFITM5*	166220	in OMIM OI type IV
NOS 26-0310	Osteogenesis imperfecta, moderate form (Sillence type 4), CRTAP-related	AR	*CRTAP*	see 610682	In OMIM as OI type VII
NOS 26-0320	Osteogenesis imperfecta, moderate form (Sillence type 4), PPIB-related	AD	*PPIB*	see 259440	In OMIM as OI type IX
NOS 26-0330	Osteogenesis imperfecta, moderate form (Sillence type 4), FKBP10-related	AR	*FKBP10*	see 610968	In OMIM as OI type XI
NOS 26-0340	Osteogenesis imperfecta, moderate form (Sillence type 4), SP7-related	AR	*SP7*	613849	In OMIM as OI type XII
NOS 26-0350	Osteogenesis imperfecta with calcification of interosseous membranes and/or hypertrophic callus (OI type 5), IFITM5-related	AD	*IFITM5*	610967	When calcification of intraosseous membranes or hypertrophic callus are not observed, may mimic progressively deforming or moderate OI (Sillence types 3 and 4)
NOS 26-0360	Osteogenesis imperfecta with craniosynostosis (Cole- Carpenter syndrome), P4HB-related	AD	*P4HB*	112240	Craniosynostosis is not well documented in this condition in spite of the name.

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 26-0370	Osteogenesis imperfecta with craniosynostosis (Cole- Carpenter syndrome), SEC24D-related	AR	*SEC24D*	616294	Was Cole-Carpenter syndrome 2. Possibly misnomer, as most patients do not have craniosynostosis but rather large fontanels.
NOS 26-0380	Osteoporosis – X-linked form, PLS3-related	XL	*PLS3*	300910	
NOS 26-0390	Osteoporosis–X-linked form, MBPTS2-related	XL	*MBTPS2*	301014	In OMIM as OI type XIX; gene also associated with MIM 300918, MIM308205, MIM 308800
NOS 26-0400	Osteoporosis–dominant form, WNT1-related	AD	*WNT1*	615220	OMIM OI type XV
NOS 26-0410	Osteoporosis – AD form, LRP5-related	AD	*LRP5*	166710, 601884	Monoallelic variants; biallelic variants result in MIM 259770 osteoporosis--pseudoglioma (see below); this gene is also associated with hyperostotic forms (see below) as well as with MIM 601813–exudative vitreoretinopathy, as well as MIM 617875–polycystic liver disease
NOS 26-0420	Osteoporosis–AD form, ARHGAP25-related	AD	*ARHGAP25*	see 610587	
NOS 26-0430	Bruck syndrome type 1 (BS1), FKBP10-related	AR	*FKBP10*	259450	See autosomal recessive OI, above; intrafamilial variability between OI type 3, arthrogryposis and Bruck syndrome 1 is documented
NOS 26-0440	Bruck syndrome type 2 (BS2), PLOD2-related	AR	*PLOD2*	609220	
NOS 26-0450	Osteoporosis-pseudoglioma syndrome, LRP5-related	AR	*LRP5*	259770	When eye involvement is absent, may mimic progressively deforming or moderate OI (Sillence types 3 and 4)
NOS 26-0460	Bone fragility with calvarial "doughnut" lesions, SGSM2-related	AD	*SGMS2*	126550	Overlap with a spondylo-metaphyseal dysplasia phenotype
NOS 26-0470	Spondylo-ocular dysplasia, XYLT2-related	AR	*XYLT2*	605822	
NOS 26-0480	Gnathodiaphyseal dysplasia, ANO5-related	AD	*ANO5*	166260	Gene also associated with OMIM 613319-Miyoshi muscular dystrophy 3, and OMIM 611307-recessive limb-girdle muscular dystrophy 12
NOS 26-0490	Osteoporosis with developmental delay and microcephaly, COPB2-related	AD	*COPB2*	619884	Clinically variable, microcephaly in some cases only
NOS 26-0500	Geroderma osteodysplasticum, GORAB-related	AR	*GORAB*	231070	
NOS 26-0510	Cutis laxa, PYCR1-related	AR	*PYCR1*	612940	Autosomal recessive form, type 2B (ARCL2B). Skeletal features overlapping with progeroid EDS and geroderma osteodysplasticum
NOS 26-0520	Cutis laxa, ATP6V0A2-related	AR	*ATP6V0A2*	278250, 219200	Autosomal recessive form, type 2A (ARCL2A); wrinkly skin syndrome. Skeletal features overlapping with progeroid EDS and geroderma osteodysplasticum
NOS 26-0530	Wiedemann-Rautenstrauch syndrome, POLR3A-related	AR	*POLR3A*	264090	Gene also associated with MIM 607694-Leukodystrophy, hypomyelinating, with or without oligodontia and/or hypogonadotropic hypogonadism

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 26-0540	Singleton-Merten dysplasia, IFIH-related	AD	*IFIH1*	182250	Gene also associated with MIM 615846-Aicardi-Goutieres syndrome 7, and OMIM 619773-Immunodeficiency 95
NOS 26-0550	Singleton-Merten dysplasia, DDX58-related	AD	*DDX58*	616298	
	Note: some of the recently discovered OI variants are still limited to very small numbers of patients; thus, the association with OI "Sillence type 3" is tentative and may be too restrictive as other phenotypes might emerge in the future. See also: Short stature, skeletal dysplasia, liver failure, optic nerve atrophy and Pelger-Huet anomaly, NBAS-related, above (Group 13); as well as all the Loeys-Dietz syndrome variants and the Snyder-Robinson syndrome, *SMS*-related (Group 31).				
Group 27	**Disorders of bone mineralisation**				
NOS 27-0010	Hypophosphatasia, ALPL-related, recessive (biallelic) forms	AR	*ALPL*	241500	Includes perinatal, infantile and juvenile forms
NOS 27-0020	Hypophosphatasia, ALPL-related, dominant (monoallelic) forms	AD	*ALPL*	146300	Includes juvenile and adult forms as well as odontohypophosphatasia
NOS 27-0030	Hypophosphatemic rickets, PHEX-related	XL	*PHEX*	307800	X-linked, most common genetic form of hypophosphatemic rickets
NOS 27-0040	Hypophosphatemic rickets, FGF23-related	AD	*FGF23*	193100	Autosomal dominant
NOS 27-0050	Hypophosphatemic rickets, DMP1-related	AR	*DMP1*	241520	Autosomal recessive (ARHR1)
NOS 27-0060	Hypophosphatemic rickets, ENPP1-related	AR	*ENPP1*	613312	Autosomal recessive (ARHR2)
NOS 27-0070	Hypophosphatemic rickets, SGK3-related	AD	*SGK3*	see 607591	Autosomal dominant
NOS 27-0080	Hypophosphatemic rickets with hypercalciuria, CLCN5-related	XL	*CLCN5*	300554	X-linked; part of Dent's disease complex (progressive proximal renal tubulopathy with hypercalciuria, low molecular weight proteinuria, and nephrocalcinosis; MIM 300009)
NOS 27-0090	Hypophosphatemic rickets with hypercalciuria, SLC34A3-related	AR	*SLC34A3*	241530	Autosomal recessive (HHRH)
NOS 27-0100	Vitamin D-dependent rickets, CYP27B1-related	AR	*CYP27B1*	264700	Formerly type 1A
NOS 27-0110	Vitamin D-dependent rickets, CYP2R1-related	AR	*CYP2R1*	600081	Formerly type 1B
NOS 27-0120	Vitamin D-dependent rickets, VDR-related	AR	*VDR*	277440	Formerly type 2A
NOS 27-0130	Vitamin D-dependent rickets, CYP3A4-related	AD	*CYP3A4*	619073	Formerly type 3; specific monoallelic variants that increase enzyme activity leading to rapid degradation of active vitamin D
NOS 27-0140	Vitamin D-dependent rickets, HNRNPC-related	AD?	*HNRNPC*	see 164020	Formerly type 2B; molecular basis (supposed HNRNPC dominant negative) from a single patient
NOS 27-0150	Familial hyperparathyroidism, CDC73-related	AD	*CDC73*	145000, 145001	With or without jaw tumors
NOS 27-0160	Familial hyperparathyroidism linked to chromosome 2	AD	*2p14-p13.3*	610071	Linkage studies; no gene identified
NOS 27-0170	Familial hyperparathyroidism, GCM2-related	AD	*GCM2*	617343	Variants in this gene also cause familial isolated hypoparathyroidism (MIM 618883)

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 27-0180	Neonatal hyperparathyroidism, CASR-related	AR, AD	*CASR*	239200	"Severe" form (but see below, transient form also CASR-related). Variants in the CASR gene can also result in autosomal dominant hypocalcemia (MIM 601198)
NOS 27-0190	Neonatal hyperparathyroidism, TRPV6-related	AR	*TRPV6*	618188	Transient form
NOS 27-0200	Familial hypocalciuric hypercalcemia with transient neonatal hyperparathyroidism, CASR-related	AD	*CASR*	145980	Other forms of familial hypocalciuric hypercalcemia do not show significant skeletal phenotypes
NOS 27-0210	Calcium pyrophosphate deposition disease (familial chondrocalcinosis), ANKH-related	AD	*ANKH*	118600	Loss-of-function variants (see also craniometaphyseal dysplasia, dominant type)
NOS 27-0220	Calcium pyrophosphate deposition disease (familial chondrocalcinosis), TNFRSF11B-related	AD	*TNFRSF11B*	see 602643	Apparently monoallelic gain-of-function variants
NOS 27-0230	Cutaneous skeletal hypophosphatemia syndrome	MOS	*HRAS*		Somatic mosaicism for activating variants in HRAS with elevated FGF23 levels
NOS 27-0240	Cutaneous skeletal hypophosphatemia syndrome	MOS	*NRAS*		Somatic mosaicism for activating variants in NRAS with elevated FGF23 levels
	Note: Hyperparathyroidism due to parathyroid adenoma occurs in a number of genetic disorders, for example, in Multiple Endocrine Neoplasias (see MIM for variants). See also Group 28, below, as well as Raine dysplasia, *FAM20C*-related				
Group 28	**Skeletal disorders of the parathyroid hormone signaling cascade**				
NOS 28-0010	Metaphyseal dysplasia, Jansen type, PTHR1-related	AD	*PTHR1*	156400	Caused by activating variants
NOS 28-0020	Metaphyseal dysplasia, Csukasi-Krakow type, SIK3-related	AR	*SIK3*	618162	disruption of mTOR signaling downstream of the PTH receptor
NOS 28-0030	Blomstrand dysplasia, PTHR1-related	AR	*PTHR1*	215045	Caused by recessive (biallelic) loss-of--function variants
NOS 28-0040	Eiken dysplasia, PTHR1-related	AR	*PTHR1*	600002	Caused by recessive (biallelic) hypomorphic variants
NOS 28-0050	Brachydactyly, PTHLH-related (brachdactyly type E2)	AD	*PTHLH*	613382	Haploinsufficiency; with or without short stature
NOS 28-0060	Osteolysis, PTHLH-related	AD	*PTHLH*		Duplications of *PTHLH* causing acro--osteolysis; see also Groups 30 and 18
	Note: see also Acrodysostosis, *PDE4D*-related and *PRKAR1A*-related, above; and Albright hereditary osteodystrophy, GNAS-related. Monoallelic loss-of-function variants in *PTHR1* lead to primary failure of tooth eruption (MIM 125350)				
Group 29	**Osteolysis group**				
NOS 29-0010	Familial expansile osteolysis, TNFRSF11A-related	AD	*TNFRSF11A*	174810, 602080	Includes early-onset familial Paget disease of bone. See other *TNFRSF11A*-related phenoytpes in Group 24
NOS 29-0020	Mandibuloacral dysplasia, LMNA-related	AR	*LMNA*	248370	See also Progeria (in this group), *LMNA*-related cardiomyopathy and brachydactyly (Group 19) as well as many other conditions in MIM related to *LMNA*
NOS 29-0030	Mandibuloacral dysplasia, ZMPSTE24-related	AR	*ZMPSTE24*	608612	
NOS 29-0040	Mandiculoacral dysplasia, MTX2-related	AR	*MTX2*	619127	
NOS 29-0050	Progeria, Hutchinson-Gilford type, LMNA-related	AD	*LMNA*	176670	
NOS 29-0060	Multicentric osteolysis, nodulosis and arthropathy (MONA), MMP2-related	AR	*MMP2*	259600	Includes Winchester-Torg syndrome and nodulosis-arthropathy-osteolysis syndrome

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 29-0070	Multicentric osteolysis, nodulosis and arthropathy (MONA), MMP14-related	AR	*MMP14*	277950	A biallelic homozygous *MMP14* variant seen in the original Winchester syndrome family
NOS 29-0080	Hajdu-Cheney syndrome, NOTCH2-related	AD	*NOTCH2*	102500	Includes the Serpentine fibula-polycystic kidney syndrome (SFPKS)
NOS 29-0090	Multicentric carpal-tarsal osteolysis with and without nephropathy, MAFB-related	AD	*MAFB*	166300	
NOS 29-0100	Penttinen syndrome, PDGFRB-related	AD	*PDGFRB*	601812	See also MIM 601812-Kosaki overgrowth syndrome
NOS 29-0110	Nestor Guillermo progeria syndrome, BANF1-related	AR	*BANF1*	603811	
NOS 29-0120	Farber disease, ASAH1-related	AR	*ASAH1*		The chronic, adult form of Farber disease can present as osteolysis
	Note: several neurologic conditions may cause acroosteolysis. See also Osteolysis, *PTHLH*-related (above), Pyknodysostosis, *CTSK*-related; cleidocranial dysplasia, *RUNX2*-related; Keutel syndrome, *MGP*-related; Singleton-Merten dysplasia, *IFIH*-related; and Singleton-Merten dysplasia, *DDX58*-related				
Group 30	**Disorganized development of skeletal components group**				
NOS 30-0010	Multiple cartilaginous exostoses, EXT1-related (MCE; or multiple osteochondromas, MO)	AD	*EXT1*	133700	
NOS 30-0020	Multiple cartilaginous exostoses, EXT2-related (MCE; or multiple osteochondromas, MO)	AD	*EXT2*	133701	
NOS 30-0030	Cherubism, SH3BP2-related	AD	*SH3BP2*	118400	
NOS 30-0040	Fibrous dysplasia, polyostotic form (McCune-Albright syndrome), GNAS-related	MOS	*GNAS*	174800	Somatic mosaicism for gain-of-function variants; includes Mazabraud syndrome with intramuscular myxomas
NOS 30-0050	Progressive osseous heteroplasia (POH), GNAS-related	AD	*GNAS*	166350	Germline loss-of-function of paternal allele
NOS 30-0060	Metachondromatosis, PTPN11-related	AD	*PTPN11*	156250	Loss-of-function variants (in contrast to Noonan syndrome) with loss of heterozygosity in lesional tissue
NOS 30-0070	Osteoglophonic dysplasia, FGFR1-related	AD	*FGFR1*	166250	Craniosynostosis is also an important feature (Group 34)
NOS 30-0080	Fibrodysplasia ossificans progressiva (FOP), ACVR1-related	AD	*ACVR1*	135100	Most cases sporadic but dominant transmission documented
NOS 30-0090	Neurofibromatosis type 1, NF1-related	AD	*NF1*	162200	
NOS 30-0100	Cherubism with gingival fibromatosis (Ramon syndrome)	AR		266270	Some similarities to primary intraosseous vascular malformation, ELMO2-related (see below)
NOS 30-0110	Dysplasia epiphysealis hemimelica (Trevor)	SP		127800	Some familial cases reported ("familial Trevor disease") but probably represent a different condition
NOS 30-0120	Lipomembraneous osteodystrophy with leukoencephalopathy, TREM2-related (Nasu-Hakola)	AR	*TREM2*	618193	Also known as presenile dementia with bone cysts
NOS 30-0130	Lipomembraneous osteodystrophy with leukoencephalopathy, TYROBP-related (Nasu-Hakola)	AR	*TYROBP*	221770	Also known as presenile dementia with bone cysts
NOS 30-0140	Enchondromatosis, IDH1-related (Ollier disease)	MOS	*IDH1*	166000	Somatic mosaicism for specific *IDH1* variants. See also MIM 147700 and 137800

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 30-0150	Enchondromatosis, IDH2-related (Ollier disease)	MOS	*IDH2*	166000	Somatic mosaicism for *IDH2* variants; significantly rarer than IDH1 variants. See also MIM 147650 and 613657, D-2-hydroxyglutaric aciduria 2
NOS 30-0160	Enchondromatosis with hemangiomas, IDH1-related (Maffucci disease)	MOS	*IDH1*	614569	Somatic mosaicism for specific IDH1 variants. See also MIM 147700 and 137800
NOS 30-0170	Enchondromatosis with hemangiomas, IDH2-related (Maffucci disease)	MOS	*IDH2*	614569	Somatic mosaicism for IDH2 variants; significantly rarer than IDH1 variants. See also MIM 147650 and 613657, D-2-hydroxyglutaric aciduria 2
NOS 30-0180	Metaphyseal chondromatosis with D-2-hydroxyglutaric aciduria, IDH1-related	MOS	*IDH1*	614875	Includes so-called cheirospondyloenchondromatosis. Somatic mosaicism for *IDH1* variants. Possibly also *IDH2* variants but not yet well documented
NOS 30-0190	Primary intraosseous vascular malformation, ELMO2-related	AR	*ELMO2*	606893	
NOS 30-0200	Osteofibrous dysplasia, MET-related	AD, SP	*MET*	607278	Possibly corresponding to the former "Campanacci dysplasia"
NOS 30-0210	Genochondromatosis	AD		137360	"Geno" from Greek "knee", but upper limbs also affected. Probably includes the condition known as Vaandrager-Peña syndrome
NOS 30-0220	Gorham-Stout disease and familial diffuse angiomatosis of bone	SP (MOS?), AD		see 123880	Severe Gorham-Stout disease is mostly sporadic. Somatic *KRAS* variants have been found in rare cases. In contrast, milder cases may be familial ("familial diffuse cystic angiomatosis of bone"; see OMIM 123880).
	Note: *PTEN*-related disorders are not included because the overgrowth is restricted to macrocephaly. See also: Proteus syndrome, *AKT1*-related; Spondyloenchondrodysplasia with immune dysregulation (SPENCD), *ACP5*-related; Spondyloepimetaphyseal dysplasia, *COL2A1*-related ("SED with marked metaphyseal changes", including dysspondyloenchondromatosis); Cutaneous skeletal hypophosphatemia syndrome, *HRAS*-related and NRAS-related. Some patients with *SOX6* variants have osteochondromas.				
Group 31	**Overgrowth (tall stature) syndromes and segmental overgrowth**				
NOS 31-0010	Marfan syndrome, FBN1-related	AD	*FBN1*	154700	See also as differential diagnosis: homocystinuria and marfanoid habitus with ID (Lujan Fryns syndrome): *MED12; ZDHHC9; UPF3B*
NOS 31-0020	Congenital contractural arachnodactyly (Beals-Hecht syndrome), FBN2-related	AD	*FBN2*	121050	
NOS 31-0030	Loeys-Dietz syndrome, TGFBR1-related	AD	*TGFBR1*	609192	Osteopenia with propensity to fractures may be observed in all variants of the Loeys-Dietz syndrome
NOS 31-0040	Loeys-Dietz syndrome, TGFBR2-related	AD	*TGFBR2*	610168	
NOS 31-0050	Loeys-Dietz syndrome, TGFB2-related	AD	*TGFB2*	614816	
NOS 31-0060	Loeys-Dietz syndrome, TGFB3-related	AD	*TGFB3*	615582	
NOS 31-0070	Loeys-Dietz syndrome, SMAD2-related	AD	*SMAD2*	619656	
NOS 31-0080	Loeys-Dietz syndrome, SMAD3-related	AD	*SMAD3*	613795	
NOS 31-0090	Weaver syndrome, EZH2-related	AD	*EZH2*	277590	Some cases reported with *NSD1*, *EED*, and *SUZ12* variants
NOS 31-0100	Cohen-Gibson (Weaver-like) syndrome, EED-related	AD	*EED*	617561	

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 31-0110	Imagawa-Matsumoto (Weaver like) syndrome, SUZ12-related	AD	*SUZ12*	606245	
NOS 31-0120	Sotos syndrome, NSD1-related	AD	*NSD1*	117550	
NOS 31-0130	Sotos syndrome, APC2-related	AR	*APC2*	617169	
NOS 31-0140	Malan (Sotos-like) syndrome, NFIX-related	AD	*NFIX*	614753	
NOS 31-0150	Luscan-Lumish syndrome, SETD2-related	AD	*SETD2*	616831	
NOS 31-0160	Tatton-Brown-Rahman syndrome, DNMT3A-related	AD	*DNMT3A*	615879	
NOS 31-0170	Marshall-Smith syndrome, NFIX-related	AD	*NFIX*	602535	See also Malan syndrome. The localization of the monoallelic variants determine the Malan vs. Marshall Smith phenotype
NOS 31-0180	Beckwith-Wiedemann syndrome	AD	*11p15.5 region*	130650	Variant or deletion of imprinted genes within the chromosome 11p15.5 region
NOS 31-0190	Simpson-Golabi-Behmel syndrome, GPC3-related	XL	*GPC3*	312870	
NOS 31-0200	Proteus syndrome, AKT1-related	MOS	*AKT1*	176920	
NOS 31-0210	Hypoinsulinemic hypoglycemia with hemihypertrophy (HIHGHH), AKT2-related	AD	*AKT2*		Gene also associated with OMIM 125853 diabetes mellitus type II
NOS 31-0220	Congenital ipomatous overgrowth, vascular Malformations, epidermal Nevi, spinal/skeletal anomalies/scoliosis (CLOVES) syndrome, PIK3CA-related	MOS	*PIK3CA*	612918	Also named PIK3CA-related overgrowth syndrome (PROS); somatic variants; see MIM 171834
NOS 31-0230	Fibroadipose hyperplasia, PIK3CA-related	MOS	*PIK3CA*	See 171834	See MIM 171834 for the many conditions associated with somatic *PIK3CA* variants
NOS 31-0240	Snyder-Robinson syndrome (intellectual disability, tall stature, osteoporosis and fractures), SMS-related	XLR	*SMS*	309583	
NOS 31-0250	Overgrowth syndrome with 2q37 translocations	SP	*NPPC*	see 600296	Overgrowth probably caused by overexpression of *NPPC*
NOS 31-0260	Tall stature with long halluces, NPR2-related	AD	*NPR2*	615923	Monoallelic gain-of-function variants in *NPR2*; in OMIM as epiphyseal chondrodysplasia, Miura type
NOS 31-0270	Tall stature with long halluces, NPR3-related	AR	*NPR3*	619543	Biallelic loss-of-function variants in *NPR3*; in OMIM as Boudin-Mortier syndrome
NOS 31-0280	Moreno-Nishimura-Schmidt syndrome	SP		608811	
NOS 31-0290	Camptodactyly, tall stature and hearing loss syndrome (CATSHL), FGFR3-related	AD, AR	FGFR3	610474	Original family with monoallelic (dominant negative?) variant; a second family with biallelic variants (see Group 1)
NOS 31-0300	Kosaki overgrowth syndrome, PDGFRB-related	AR	PDGFRB	616592	See also MIM 601812-Pentinnen syndrome
NOS 31-0310	Segmental odontomaxillary dysplasia, ACTB-related	MOS	ACTB	see 102630	See PMID 32585735; see also MIM 243310-Baraitser-Winter syndrome
	See also: Shprintzen-Goldberg syndrome, SKI-related, in the craniosynostosis group. Note: this group does not include disorders that cause overgrowth secondary to vascular malformations, such as Klippel-Trenaunay syndrome, at least until a genetic (somatic) origin will have been demonstrated.				
Group 32	**Genetic inflammatory or rheumatoid-like osteoarthropathies**				
NOS 32-0010	Progressive pseudorheumatoid dysplasia (PPRD), WISP3-related	AR	*WISP3*	208230	Also known as SED with progressive arthropathy

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 32-0020	Chronic infantile neurologic cutaneous articular syndrome (CINCA), CIAS1-related (neonatal onset multisystem inflammatory disease (NOMID))	AD	*CIAS1*	607115	
NOS 32-0030	Sterile multifocal osteomyelitis, periostitis, and pustulosis (CINCA/NOMID-like), IL1RN-related	AR	*IL1RN*	See 147679	
NOS 32-0040	Chronic recurrent multifocal osteomyelitis with congenital dyserythropoietic anemia (CRMO with CDA; Majeed syndrome), LPIN2-related	AR	*LPIN2*	609628	
NOS 32-0050	Familial juvenile arthritis with hyaluronidase deficiency, HYAL1-related	AR	*HYAL1*	601492	Also known as mucopolysaccharidosis type 9, although clinically no storage
NOS 32-0060	Hyaline Fibromatosis Syndrome, ANTXR2-related	AR	*ANTXR2*	236490, 228600	Previously known as infantile systemic hyalinosis, juvenile hyaline fibromatosis, and puretic syndrome
	Farber disease, *ASAH1*-related (osteolysis group 29, an d MIM 228000) shows phenotypic overlap with the conditions in this group.				
Group 33	**Cleidocranial dysplasia and related disorders**				
NOS 33-0010	Cleidocranial dysplasia, RUNX2-related	AD	*RUNX2*	119600	See also MIM 156510-metaphyseal dysplasia with maxillary hypoplasia, as well as non-syndromic midline craniosynostosis, RUNX2-related, below
NOS 33-0020	Cleidocranial-like dysplasia, CBFB-related	AD	*CBFB*	See 121360	See also MIM 601626, familial leukemia
NOS 33-0030	CDAGS syndrome (craniosynostosis, delayed fontanel closure, parietal foramina, imperforate anus, genital anomalies, skin eruption), RNU12-related	AR	*RNU12*	603116	
NOS 33-0040	Yunis-Varon dysplasia, FIG4-related	AR	*FIG4*	216340	Gene also causes OMIM 612577 amyotrophic lateral sclerosis 11, and OMIM 611228 CMT disease 4J
NOS 33-0050	Yunis-Varon dysplasia, VAC14-related	AR	*VAC14*		Only one case of VAC14-related Yunis-Varon reported so far, so association needs to be confirmed. Gene also associated with OMIM 617054 Striatonigral degeneration, childhood-onset (several patients reported)
NOS 33-0060	Parietal foramina, MSX2-related	AD	*MSX2*	168500	
NOS 33-0070	Parietal foramina, ALX4-related	AD	*ALX4*	609597	See also frontonasal dysplasia type 1
NOS 33-0080	Parietal foramina with cleidocranial dysplasia, MSX2-related	AD	*MSX2*	168550	*MSX2* variants also cause craniosynostosis Boston type
	See also: pyknodysostosis, *CTSK*-related; cutis laxa, *ATP6V0A2*-related; mandibuloacral dysplasia, *LMNA*-related; progeria, Hutchinson-Gilford type, *LMNA*-related; and Hajdu-Cheney syndrome, *NOTCH2*-related, for similar clavicular defects or osteolysis. See also Crane-Heise syndrome (MIM 218090), the nosologic status of which remains unclear.				
Group 34	**Syndromes featuring craniosynostosis**				
NOS 34-0010	Pfeiffer syndrome, FGFR1-related	AD	*FGFR1*	101600	Most have *FGFR1* p.P252R variant; Includes Jackson-Weiss syndrome (MIM 123150)
NOS 34-0020	Pfeiffer syndrome, FGFR2-related	AD	*FGFR2*	101600	
NOS 34-0030	Apert syndrome, FGFR2-related	AD	*FGFR2*	101200	

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 34-0040	Craniosynostosis with cutis gyrata (Beare-Stevenson), FGFR2-related	AD	*FGFR2*	123790	Notably p.S372Y or p.Y375C variants
NOS 34-0050	Crouzon syndrome, FGFR2-related	AD	*FGFR2*	123500	
NOS 34-0060	Crouzon-like craniosynostosis with acanthosis nigricans, FGFR3-related	AD	*FGFR3*	612247	Defined by specific *FGFR3* .A391E variant; also known as Crouzonodermoskeletal syndrome
NOS 34-0070	Craniosynostosis, Muenke type, FGFR3-related	AD	*FGFR3*	602849	Defined by specific *FGFR3* p.P250R variant
NOS 34-0080	Antley-Bixler syndrome, POR-related	AR	*POR*	201750	
NOS 34-0090	Craniosynostosis Boston type, MSX2-related	AD	*MSX2*	604757	Heterozygous p.P148H variant in a two families
NOS 34-0100	Saethre-Chotzen syndrome, TWIST1-related	AD	*TWIST1*	101400	Variants in *FGFR3*, *FGFR2*, and *TCF12* have been reported to cause phenotypes resembling Saethre-Chotzen syndrome
NOS 34-0110	Shprintzen-Goldberg syndrome, SKI-related	AD	*SKI*	182212	
NOS 34-0120	Baller-Gerold syndrome, RECQL4-related	AR	*RECQL4*	218600	See other phenotypes associated with RECQL4 variants, above
NOS 34-0130	Carpenter syndrome, RAB23-related	AR	*RAB23*	201000	
NOS 34-0140	Carpenter syndrome, MEGF8-related	AR	*MEGF8*	614976	
NOS 34-0150	Craniosynostosis, TCF12-related	AD	*TCF12*	615314	Frequently coronal craniosynostosis
NOS 34-0160	Craniosynostosis, SIX1-related	AD	*SIX1*	see 601205	Frequently sagittal and lambdoid synostosis. See also MIM 608389–Branchiootic syndrome 3, and 605192– deafness, autosomal dominant 23, for other SIX1-related phenotypes
NOS 34-0170	Complex craniosynostosis, ERF-related	AD	*ERF*	600775	Variants in *ERF* also cause Chitayat hyperphalangism syndrome (Group 19)
NOS 34-0180	Non-syndromic midline (metopic / sagittal) craniosynostosis, SMAD6-related	AD?	*SMAD6*	617439	Rare *SMAD6* variants and a common *BMP2* polymorphism may interact to produce craniosynostosis; subject disputed
NOS 34-0190	Non-syndromic midline craniosynostosis, RUNX2-related	AD	*RUNX2*		Gain-of-function variants, duplications, triplications
NOS 34-0200	Structural brain anomalies with impaired ID and craniosynostosis / craniosynostosis type 6	AD	*ZIC1*	618736	
NOS 34-0210	Craniosynostosis and dental anomalies (CRSDA), IL11RA-related	AR	*IL11RA*	614188	
NOS 34-0220	Craniosynostosis, retained deciduous teeth and intellectual disability, IL6ST-related	AR	*IL6ST*	see 600694	Single case reported, with preserved LIF signaling. See Stüve-Wiedemann syndrome, *IL6ST*-related (above, group 24) as well as *IL6ST*-MIM 600694 for other phenotypes associated with *IL6ST*
NOS 34-0230	Cutis laxa with craniosynostosis, short stature, brachydactyly, and syndactyly, LTBP1-related	AR	*LTBP1*	619451	
NOS 34-0240	Bohring-Opitz syndrome, ASXL1-related	AD	*ASXL1*	605039	
NOS 34-0250	Craniosynostosis, radiohumeral fusion and other skeletal defects, CYP26B1-related	AR	*CYP26B1*	614416	*CYP26B1* is a retinoid acid-degrading enzyme, pathogenesis involves retinoic acid-associated morphogenesis

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 34-0260	Cardiac, facial and digital anomalies with developmental delay (CAFDADD), TRAF7-related	AD	*TRAF7*	618164	Multistructure craniosynostosis is one of the features
NOS 34-0270	Craniosynostosis, hypertrichosis, progeroid appearance, bone dysplasia, characteristic face (Fontaine progeroid syndrome, Gorlin-Chaudhry-Moss syndrome), SLC25A24-related	AD	*SLC25A24*	612289	
NOS 34-0280	Curry-Jones syndrome, SMO-related	MOS	*SMO*	601707	Activating variant c.1234C>T (p.L412F)
NOS 34-0290	3MC syndrome, MASP1-related	AR	*MASP1*	257920	Craniosynostosis in 20%–30%
NOS 34-0300	3MC syndrome, COLEC11-related	AR	*COLEC11*	265050	Craniosynostosis in 20%–30%
NOS 34-0310	3MC syndrome, COLEC10-related	AR	*COLEC10*	248340	Craniosynostosis in 20%–30%
NOS 34-0320	Weiss-Kruszka syndrome, ZNF462-related	AD	*ZNF462*	618619	Metopic ridging or CSO (metopic, lambdoid, 9/24)
NOS 34-0330	Au-Kline syndrome, HNRNPK-related	AD	*HNRNPK*	616580	Craniosynostosis and vertebral anomalies in a significant proportion of cases
NOS 34-0340	Char syndrome, TFAP2B-related	AD	*TFAP2B*	169100	Mainly with loss-of-function variants
NOS 34-0350	Syndrome with developmental and speech delay, dysmorphic facies, craniosynostosis and T-cell abnormalities	AD	*BCL11B*	618092	Craniosynostosis in some affected individuals
	Craniosynostosis is not rare and may have a non-genetic pathogenesis in many cases. It can also occur secondarily in any form of rickets. Conditions in which craniosynostosis is an occasional feature have not been included. See also: craniioectodermal dysplasia (several types in the ciliopathy group); SEMD, *RSPRY1*-related; osteocraniostenosis, *FAM111A*-related; Osteogenesis imperfecta with craniosynostosis (Cole-Carpenter syndrome), *P4HB*-related; CDAGS syndrome, *RNU12*-related; syndactyly (Lueken type, with or without craniosynostosis), *IHH*-related; and Multiple synostoses syndrome, *FGF9*-related. Craniosynostosis can also be present in Loeys-Dietz syndromes, Meier-Gorlin syndrome, *CDC45*-related and *GINS2*-related; Hypophosphatasia, *ALPL*-related; Hypophosphatemic rickets, *PHEX*-related; Greig cephalopolysyndactyly syndrome, *GLI3*-related; and others.				
Group 35	**Craniofacial dysostoses**				
NOS 35-0010	Mandibulofacial dysostosis, TCOF1-related (Treacher- Collins, Franceschetti-Klein)	AD	*TCOF1*	154500	
NOS 35-0020	Mandibulofacial dysostosis, POLR1B-related (Treacher Collins, Franceschetti-Klein)	AD	*POLR1B*	618939	
NOS 35-0030	Mandibulofacial dysostosis, POLR1C-related (Treacher-Collins, Franceschetti-Klein)	AR	*POLR1C*	248390	
NOS 35-0040	Mandibulofacial dysostosis, POLR1D-related (Treacher-Collins, Franceschetti-Klein)	AD, AR	*POLR1D*	613717	
NOS 35-0050	Mandibulofacial dysostosis with limb deficiencies, POLR1A-related (Cincinnati type)	AD	*POLR1A*	616462	The original description was "acrofacial dysostosis: a mandibulofacial dysostosis with limb anomalies". The limb anomalies are variable
NOS 35-0060	Mandibulofacial dysostosis with microcephaly, EFTUD2-related (Guion-Almeida type)	AD	*EFTUD2*	610536	
NOS 35-0070	Mandibulofacial dysostosis with alopecia, EDNRA-related	AD	*EDNRA*	616367	
NOS 35-0080	Burns-McKeown syndrome, TXNL4A-related	AR	*TXNL4A*	608572	Some pathogenic variants are in the promoter region; severity is variable

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 35-0090	Postaxial acrofacial dysostosis, DHODH-related (Miller syndrome)	AR	*DHODH*	263750	
NOS 35-0100	Acrofacial dysostosis, SF3B4-related (Nager syndrome)	AD, AR	*SF3B4*	154400, 201170	Both monoallelic and biallelic variants are at the basis of a spectrum that also includes the former "Rodriguez type" of acrofacial dysostosis
NOS 35-0110	Agnathia-Otocephaly complex, PRRX1-related	AD, AR	*PRRX1*	202650	
NOS 35-0120	Frontonasal dysplasia, ALX3-related	AR	*ALX3*	136760	
NOS 35-0130	Frontonasal dysplasia, ALX4-related	AR	*ALX4*	613451	
NOS 35-0140	Frontonasal dysplasia, ALX1-related	AR	*ALX1*	613456	
NOS 35-0150	Frontonasal dysplasia, SIX2-related	AD	*SIX2*	See 604994	
NOS 35-0160	Frontonasal dysplasia with additional malformations (Sweeney-Cox syndrome), TWIST1-related	AD	*TWIST1*	617746	Results from specific amino acid substitutions in TWIST1
NOS 35-0170	Craniofrontonasal syndrome, EFN1B-related	XL	*EFNB1*	304110	
NOS 35-0180	Acromelic frontonasal dysostosis, ZSWIM6-related	AD	*ZSWIM6*	603671	
NOS 35-0190	Richieri-Costa-Pereira syndrome, EIF4A3-related	AR	*EIF4A3*	268305	
NOS 35-0200	Auriculocondylar syndrome, GNAI3-related (type 1)	AD	*GNAI3*	602483	
NOS 35-0210	Auriculocondylar syndrome, PLCB4-related (type 2)	AR, AD	*PLCB4*	614669	
NOS 35-0220	Auriculocondylar syndrome, EDN1-related (type 3)	AR	*EDN1*	615706	
NOS 35-0230	Orofaciodigital syndrome type I, OFD1-related	XL	*OFD1*	311200	
NOS 35-0240	Weyers acrofacial (acrodental) dysostosis, EVC1-related	AD	*EVC1*	193530	See also Group 10
NOS 35-0250	Weyers acrofacial (acrodental) dysostosis, EVC2-related	AD	*EVC2*	193530	See also Group 10
NOS 35-0260	Teebi hypertelorism syndrome, SPECCIL-related	AD	*SPECC1L*	145420	
NOS 35-0270	Craniolenticulosutural dysplasia, SEC23A-related	AR, AD	*SEC23A*	607812	Monoallelic and biallelic inheritance observed
NOS 35-0280	Faciogenital dysplasia, FGD1-related (Aarskog-Scott syndrome)	XL	*FGD1*	305400	
NOS 35-0290	Baraitser-Winter syndrome, ACTB-related	AD	*ACTB*	243310	
NOS 35-0300	Baraitser-Winter syndrome, ACTG1-related	AD	*ACTG1*	614583	
NOS 35-0310	Cerebrofaciothoracic dysplasia, TMCO1-related	AR	*TMCO1*	213980	
NOS 35-0320	Opitz GBBB syndrome, MID1-related	XL	*MID1*	300000	
NOS 35-0330	Arhinia microphthalmia syndrome, SMCHD1-related (Bosma)	AD	*SMCHD1*	603457	
NOS 35-0340	Acrofrontofacionasal dysostosis	AR		201180	

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 35-0350	Hemifacial microsomia	SP, AD		164210	Includes Goldenhar syndrome and Oculo-Auriculo-Vertebral spectrum; genetically heterogeneous; SF3B2 haploinsufficiency identified in ~3% of sporadic and ~25% of familial cases; in some cases a microduplication on 14q23.1
	See also orofaciodigital syndrome type 4 (Mohr-Majewski), *TCTN3*-related; Endocrine-cerebro-osteo dysplasia (ECO), *CILK1*-related; the Cerebro-Costo-Mandibular syndrome, *SNRPB*-related (group 36, below); and Robinow syndrome (see variants in Group 15)				
Group 36	**Vertebral and costal dysostoses**				
NOS 36-0010	Currarino syndrome, MNX1-related	AD	*MNX1*	176450	Possible clinical overlap with caudal regression syndrome (see MIM 600145; the role of heterozygous variants in *VANGL1* remains to be confirmed)
NOS 36-0020	Spondylocostal dysostosis, DLL3-related	AR	*DLL3*	277300	Possible role of CNVs in *TBX6* in modulating the phenotype?
NOS 36-0030	Spondylocostal dysostosis, MESP2-related	AR	*MESP2*	608681	
NOS 36-0040	Spondylocostal dysostosis, LFNG-related	AR	*LFNG*	609813	
NOS 36-0050	Spondylocostal dysostosis, HES7-related	AR	*HES7*	613686	
NOS 36-0060	Spondylocostal dysostosis, TBX6-related	AR, AD	*TBX6*	122600	Possible role of CNVs in *TBX6*
NOS 36-0070	Spondylocostal dysostosis, RIPPLY2-related	AR	*RIPPLY2*	616566	
NOS 36-0080	Vertebral segmentation defect (congenital scoliosis) with variable penetrance, MESP2-related	AD	*MESP2*	608681	
NOS 36-0090	Vertebral segmentation defect (congenital scoliosis) with variable penetrance, HES7-related	AD	*HES7*	613686	
NOS 36-0100	Short stature, cervical segmentation defects, and developmental delay, CDK10-related	AR	*CDK10*	617694	
NOS 36-0110	Klippel-Feil syndrome, GDF6-related	AD	*GDF6*	118100	Role of *GDF6* variants in Klippel-Feil syndrome as well as in AD spondylothoracic dysostosis remains unclear
NOS 36-0120	Klippel-Feil syndrome, MEOX1-related	AR	*MEOX1*	214300	
NOS 36-0130	Klippel-Feil syndrome, GDF3-related	AD	*GDF3*	613702	
NOS 36-0140	Klippel-Feil syndrome, MYO18B-related	AR	*MYO18B*	616549	
NOS 36-0150	Cervico-oculo-acoustic (Wildervanck) syndrome	SP		314600	Congenital perceptive deafness, Klippel-Feil anomaly (see 118100), and abducens palsy with retractio bulbi
NOS 36-0160	Cerebro-costo-mandibular syndrome (rib gap syndrome), SNRPB-related	AD	*SNRPB*	117650	
NOS 36-0170	Cerebro-costo-mandibular-like syndrome, COG1-related	AR	*COG1*	611209	Also known as CDG IIg
NOS 36-0180	Diaphanospondylodysostosis, BMPER-related	AR	*BMPER*	608022	Includes ischiospinal dysostosis, a term that has been used for milder cases
NOS 36-0190	Spondylo-megaepiphyseal-metaphyseal dysplasia (SMMD), NKX3-2-related	AR	*NKX3-2*	613330	

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 36-0200	NAD deficiency syndrome, HAAO-related	AR	*HAAO*	617660	With associated cardiac, limb and renal defects; VACTERL-like
NOS 36-0210	NAD deficiency syndrome, KYNU-related	AR	*KYNU*	617661	In some cases VACTERL-like
NOS 36-0220	NAD deficiency syndrome, NADSYN1-related	AR	*NADSYN1*	618845	In some cases VACTERL-like
NOS 36-0230	VATER/VACTERL association	SP		192350	
NOS 36-0240	VACTERL association with hydrocephalus (VACTERL-H), FANCB-related	XL	*FANCB*	300514	*FANCB*-related Fanconi anemia may present in hemizygous males with the VACTERL-hydrocephalus phenotype
NOS 36-0250	VACTERL association with hydrocephalus (VACTERL-H), ZIC3-related	XL	*ZIC3*	314390	
NOS 36-0260	Uniparental disomy, paternal, for chromosome 14 (UPD14; Kagami-Ogata syndrome)	SP	*14q32?*	608149	Imprinted genes at 14q32 may have a role in this complex phenotype with skeletal malformations such as "coat-hanger ribs"
	VACTERL is nowadays defined as a "Recurrent Constellation of Embryonic Malformations" (RCEM; see Adam et al, AJMG 2020) without a single genetic basis. It may be mimicked by NAD deficiency syndrome, Fanconi anemia and others. The diagnosis is supported by negative genetic analysis. See also spondylocarpotarsal synostosis syndrome, FLNB-related and RFLNA-related, Robinow syndrome (variants in Group 15), and cerebrofaciothoracic dysplasia, TMCO1-related (Group 35)				
Group 37	**Patellar dysostoses**				
NOS 37-0010	Ischiopatellar dysplasia (small patella syndrome), TBX4-related	AD	*TBX4*	147891	See MIM 601360–posterior amelia for the biallelic phenotype
NOS 37-0020	Nail-patella syndrome, LMX1B-related	AD	*LMX1B*	161200	
NOS 37-0030	Genitopatellar syndrome, KAT6B-related	AD	*KAT6B*	606170	
	See also Meier-Gorlin syndromes in the primordial dwarfism group (Group 21), and the pseudoachondroplasia/MED group (Group 9) for conditions with patellar changes; see also ischio pubic-patellar dysplasia as mild expression of campomelic dysplasia, *SOX9*-related; RAPADILINO syndrome, *RECQL4*-related. Patellar hypoplasia is variably present in Clubfoot with or without deficiency of long bones and/or mirror-image polydactyly, *PITX1*-related.				
Group 38	**Limb hypoplasia–reduction defects group**				
NOS 38-0010	Ulnar-mammary syndrome, TBX3-related	AD	*TBX3*	181450	
NOS 38-0020	Holt-Oram syndrome, TBX5-related	AD	*TBX5*	142900	
NOS 38-0030	Holt-Oram/Ulnar Mammary blended phenotype	AD	*TBX3, TBX5*		CNVs involving both *TBX3* and *TBX5* may result in combined phenotype
NOS 38-0040	Posterior Amelia, TBX4-related	AR	*TBX4*	601360	See also ischiopatellar syndrome for the monoallelic TBX4-related phenotype
NOS 38-0050	Cornelia de Lange syndrome, NIPBL-related	AD	*NIPBL*	122470	
NOS 38-0060	Cornelia de Lange syndrome, SMC1A-related	XL	*SMC1A*	300590	
NOS 38-0070	Cornelia de Lange syndrome, SMC3-related	AD	*SMC3*	610759	
NOS 38-0080	Cornelia de Lange syndrome, RAD21-related	AD	*RAD21*	614701	
NOS 38-0090	Cornelia de Lange syndrome, HDAC8-related	XL	*HDAC8*	300882	
NOS 38-0100	Thrombocytopenia-absent radius (TAR) syndrome, RBM8A-related	AR	*RBM8A*	274000	Deletion and common SNP on other allele that has regulatory function

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 38-0110	Thrombocythemia with distal limb defects, THPO-related	AD	*THPO*	187950	Distal limb defects postulated as consequence of vascular occlusions
NOS 38-0120	Okihiro syndrome (Duane syndrome with radial ray anomaly), SALL4-related	AD	*SALL4*	607323	Includes IVIC syndrome
NOS 38-0130	Cousin syndrome, TBX15-related	AR	*TBX15*	260660	
NOS 38-0140	Roberts syndrome, ESCO2-related	AR	*ESCO2*	268300	
NOS 38-0150	Tibial hemimelia-polysyndactyly-triphalangeal thumb (Werner syndrome), ZRS-related	AD	*ZRS*	188740	Monoallelic variants in *ZRS*, a limb-specific enhancer of *SHH* that is located within intron 5 of the *LMBR1* gene
NOS 38-0160	Clubfoot with or without deficiency of long bones and/or mirror-image polydactyly, PITX1-related	AD	*PITX1*	119800	In some patients bilateral patellar hypoplasia (see Group 37)
NOS 38-0170	Acheiropodia, LMBR1-related	AR	*LMBR1*	200500	The Brazilian founder allele is deletion spanning exon 4 of *LMBR1* that probably affects the activity of *ZRS*, the limb-specific enhancer of *SHH*. In a further patient, biallelic deletion of exons 1 to 16 of *LMBR1*, including the *ZRS*
NOS 38-0180	Engrailed-1 related dorsoventral syndrome (ENDOVES), limb-brain type	AR	*EN1*	619218	One single patient with a biallelic frameshift variant described
NOS 38-0190	Engrailed-1 related dorsoventral syndrome (ENDOVES), limb-only type	AR	*MAENLI*	619217	*MAENLI* is a lncRNA regulating *EN1* expression
NOS 38-0200	Tetra-amelia, WNT3-related	AR	*WNT3*	273395	
NOS 38-0210	Tetra-amelia, RSPO2-related	AR	*RSPO2*	618021	
NOS 38-0220	Limb reduction syndrome, WNT7A-related	AR	*WNT7A*	276820, 228930	Includes former Al-Awadi Raas-Rothschild limb-pelvis hypoplasia-aplasia as well as Fuhrmann syndrome
NOS 38-0230	RAPADILINO syndrome, RECQL4-related	AR	*RECQL4*	266280	See also Baller-Gerold syndrome, *RECQL4*-related. See MIM 266280 for explanation of the RAPADILINO acronym
NOS 38-0240	Rothmund-Thompson syndrome, RECQL4-related	AR	*RECQL4*	268400	
NOS 38-0250	Rothmund-Thompson syndrome, ANAPC1-related	AR	*ANAPC1*	618625	
NOS 38-0260	Rothmund-Thompson syndrome, DNA2-related	AR	*DNA2*		
NOS 38-0270	Adams-Oliver syndrome (aplasia cutis congenita and transverse limb defects), ARHGAP31-related	AD	*ARHGAP31*	100300	
NOS 38-0280	Adams-Oliver syndrome (aplasia cutis congenita and transverse limb defects), DOCK6-related	AR	*DOCK6*	614219	
NOS 38-0290	Adams-Oliver syndrome (aplasia cutis congenita and transverse limb defects), RBPJ-related	AD	*RBPJ*	614814	
NOS 38-0300	Adams-Oliver syndrome (aplasia cutis congenita and transverse limb defects), DLL4-related	AR	*DLL4*	616589	
NOS 38-0310	Adams-Oliver syndrome (aplasia cutis congenita and transverse limb defects), EOGT-related	AD	*EOGT*	615297	

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 38-0320	Adams-Oliver syndrome (aplasia cutis congenita and transverse limb defects), NOTCH1-related	AD	*NOTCH1*	616028	
NOS 38-0330	B-cell immunodeficiency-limb anomaly--urogenital malformation syndrome (BILU syndrome), TOP2B-related	AD	*TOP2B*	609296	Also known as Hoffmann syndrome (see MIM 609296)
NOS 38-0340	Scapulo-iliac dysplasia (Kosenow syndrome)	AD		169550	
NOS 38-0350	Hypoglossia-hypodactylia (Hanhart syndrome)	SP		103300	
NOS 38-0360	Poland syndrome	SP, AD		173800	Most commonly sporadic and probably non-genetic; some familial cases reported but no specific gene identified so far
NOS 38-0370	Femoral facial syndrome (FFS)	SP		134780	Some phenotypic overlap with FFU syndrome (below)
NOS 38-0380	Femur-fibula-ulna syndrome (FFU)	SP		228200	
NOS 38-0390	Fibular aplasia, tibial campomelia, and oligosyndactyly syndrome (FATCO)	SP		246570	
NOS 38-0400	Tibial hemimelia (isolated)	SP		275220	Possibly non-genetic etiology
NOS 38-0410	Sirenomelia	SP			Rare cases reported as associated with monoallelic *CDX2* variants with variable expressivity
NOS 38-0420	Fanconi anemia	AR	*(several)*	227650	The complex genetic basis of Fanconi anemia and its complementation groups and loci is acknowledged but not further listed in this Nosology; please refer to MIM or to specialized reviews
	There is overlap between this group and the split hand-foot malformation group. See also Baller-Gerold syndrome, *RECQL4*-related; congenital hemidysplasia, ichthyosis, limb defects (CHILD) syndrome, *NSDHL*-related; as well as the mesomelic and acromesomelic dysplasias groups (above). Some entities in this group (e.g. the Femoral-facial syndrome and the Femur-fibula-ulna [FFU] syndromes) might be considered (RCEM; see the note to VACTERL in Group 36)				
Group 39	**Split hand/foot with and without other manifestations**				
NOS 39-0010	Ankyloblepharon-ectodermal dysplasia-cleft palate (AEC)	AD	*TP63*	106260	See other TP63-related disorders in this group (below)
NOS 39-0020	Ectrodactyly-ectodermal dysplasia cleft-palate syndrome Type 3 (EEC3)	AD	*TP63*	604292	
NOS 39-0030	Ectrodactyly-ectodermal dysplasia-macular dystrophy syndrome (EEM)	AR	*CDH3*	225280	
NOS 39-0040	Limb-mammary syndrome (including ADULT syndrome)	AD	*TP63*	603543	
NOS 39-0050	Split hand-foot malformation, isolated form, type 4 (SHFM4)	AD	*TP63*	605289	
NOS 39-0060	Split hand-foot malformation, isolated form, type 1 (SHFM1)	AD	*DLX5*	220600	Structural variations at locus; also regulatory variants affecting exons of *DYNC1I1* that regulate *DLX5*; association with deafness in a single family may be coincidental; a recessive *DLX5* syndrome may exist
NOS 39-0070	Split hand-foot malformation, isolated form, type 1 (SHFM1)	AD	*DLX6*	183600	
NOS 39-0080	Split hand-foot malformation, isolated form, type 3 (SHFM3)	AD	*10q24*	246560	Duplications at 10q24 encompassing *LBX1, BTRC, POLL, DPCD* and *FBXW4*

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 39-0090	Split hand-foot malformation, isolated form, type 6 (SHFM6)	AR	*WNT10B*	225300	
NOS 39-0100	Split-foot malformation with mesoaxial polydactyly (SFMMP)	AR	*ZAK*	616890	
NOS 39-0110	Split-hand-foot malformation with or without long bone deficiency (SHFLD), BHLHA9-related	AD	*BHLHA9*	612576	Duplications at 17p13.3 that include *BHLHA9*. Phenotypic penetrance is less than 50% and shows markedly variable expressivity; includes the so-called Gollop- Wolfgang complex
NOS 39-0120	Hartsfield syndrome, FGFR1-related	AD	*FGFR1*	615465	
NOS 39-0130	Split hand-foot malformation, EPS15L-related	AD	*EPS15L1*		Structural variants (deletions) at this locus; one consanguineous family with homozygous point variant in *EPS15L1* but inheritance still unclear
NOS 39-0140	Aplasia cutis congenita with ectrodactyly, UBA2-related	AD	*UBA2*		19q13.11 deletions may also cause this phenotype. In OMIM as "aplasia cutis congenita with ectrodactyly skeletal syndrome" (a redundant name)
NOS 39-0150	Focal dermal hypoplasia (Goltz Syndrome), PORCN-related	XLD	*PORCN*	305600	
Group 40	**Polydactyly-Syndactyly-Triphalangism group**				
NOS 40-0010	Preaxial polydactyly, SHH-related	AD	*SHH*	174400	Formerly preaxial polydactyly types 1 and 2 (with triphalangeal thumb); regulatory domain duplication of *ZRS* (limb enhancer of *SHH*) variant or duplication of *ZRS* (limb enhancer of *SHH*)
NOS 40-0020	Preaxial polydactyly, GLI1-related	AR	*GLI1*	174400	
NOS 40-0030	Preaxial polydactyly, GLI3-related	AD	*GLI3*	174700	
NOS 40-0040	Preaxial polydactyly type 3 (PPD3)	AD		174600	
NOS 40-0050	Mirror-image polydactyly of hands and feet (Laurin- Sandrow syndrome), SHH-related	AD	*SHH*	135750	Duplication of *ZRS* (limb enhancer of *SHH*)
NOS 40-0060	Postaxial polydactyly, GLI1-related	AR	*GLI1*	618123	
NOS 40-0070	Greig cephalopolysyndactyly syndrome, GLI3-related	AD	*GLI3*	175700	
NOS 40-0080	Pallister-Hall syndrome, GLI3-related	AD	*GLI3*	146510	
NOS 40-0090	Hypothalamic hamartomas and polydactyly (Pallister-Hall- like) syndrome, SMO-related	AR	*SMO*	241800	
NOS 40-0100	Culler-Jones syndrome, GLI2-related	AD	*GLI2*	615849	Hypopituitarism
NOS 40-0110	Synpolydactyly, FBLN1-related	AD	*FBLN1*	608180	
NOS 40-0120	Synpolydactyly, HOXD13-related	AD	*HOXD13*	186000	
NOS 40-0130	Postaxial polydactyly, isolated (type A10), KIAA0825-related	AR	*KIAA0825*	618498	
NOS 40-0140	Townes-Brocks syndrome, SALL1-related	AD	*SALL1*	107480	
NOS 40-0150	Lacrimo-auriculo-dento-digital syndrome (LADD), FGFR2-related	AD	*FGFR2*	149730	

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 40-0160	Lacrimo-auriculo-dento-digital syndrome (LADD), FGFR3-related	AD	*FGFR3*	149730	
NOS 40-0170	Lacrimo-auriculo-dento-digital syndrome (LADD), FGF10-related	AD	*FGF10*	149730	
NOS 40-0180	Acrocallosal syndrome, KIF7-related	AR	*KIF7*	200990	
NOS 40-0190	Acro-pectoral-vertebral dysplasia (F-syndrome), WNT6-related	AD	*WNT6*	102510	Structural variations of locus resulting in ectopic activation of *WNT6*
NOS 40-0200	Cenani-Lenz syndactyly, LRP4-related	AR	*LRP4*	212780	
NOS 40-0210	Cenani-Lenz-like syndactyly, GREM/ FMN1-related	AD	*GREM1*, *FMN1*	see 212780	Monoallelic duplication of both *GREM1* and *FMN1* loci (one individual)
NOS 40-0220	Oligosyndactyly, radio-ulnar synostosis, hearing loss and renal defects syndrome, FMN1-related	AR	*FMN1*		Biallelic deletion of the *FMN1* gene (one individual)
NOS 40-0230	Mesoaxial synostotic syndactyly with phalangeal reduction (Malik-Percin), BHLHA9-related	AD	*BHLHA9*	609432	
NOS 40-0240	STAR syndrome (syndactyly of toes, telecanthus, anal and renal malformations), FAM58A-related	XLD	*FAM58A*	300707	X-linked dominant (only affected females known, possibly lethal in males)
NOS 40-0250	Syndactyly type 1 (III-IV)	AD		185900	
NOS 40-0260	Syndactyly type 3 (IV-V), GJA1-related	AD	*GJA1*	186100	
NOS 40-0270	Syndactyly type 4 (I-V) Haas type, SHH-related	AD	*SHH*	186200	Duplication of *ZRS* (limb enhancer of *SHH*)
NOS 40-0280	Syndactyly type 5 (Brachydactyly-Syndactyly syndrome; syndactyly with metacarpal and metarsal fusion), HOXD13-related	AD	*HOXD13*	186300, 610713	
NOS 40-0290	Syndactyly (Lueken type, with or without craniosynostosis), IHH-related	AD	*IHH*	185900	Duplication of *IHH* and regulatory region on 2q35; includes syndactyly with craniosynostosis (Philadelphia type)
NOS 40-0300	Metacarpal 4-5 fusion, FGF16-related	XLR	*FGF16*	309630	
NOS 40-0310	Syndactyly with microcephaly and mental retardation (Filippi syndrome), CKAP2L-related	AR	*CKAP2L*	272440	
NOS 40-0320	Synpolydactyly plus syndrome, MAPKAPK5-related	AR	*MAPKAPK5*	619869	In OMIM as neurocardiofaciodigital syndrome
	Note: the Smith-Lemli-Opitz syndrome can present with polydactyly and/or syndactyly. The different variants of Meckel syndrome can have polydactyly and are included under the ciliopathies (see there). The Bardet-Biedl syndromes may have polydactyly as a secondary feature and have not been included in this neither in this group nor in the ciliopathies. See also Clubfoot with or without deficiency of long bones and/or mirror-image polydactyly, *PITX1*-related. The entity called "Crossed polysyndactyly" not included as unclear whether or not it is a distinct entity.				
Group 41	**Defects in joint formation and synostoses**				
NOS 41-0010	Multiple synostoses syndrome, NOG-related	AD	*NOG*	186500, 186570	Includes: Stapes ankylosis with broad thumbs and toes, Tarsal-Carpal coalition syndrome, proximal Symphalangism 1A; see also Brachydactyly type B2, *NOG*-related, in the brachydactyly group
NOS 41-0020	Multiple synostoses syndrome, GDF5-related	AD	*GDF5*	610017	See other *GDF5*-related disorders

Group number/ nr. of disorder	Group/name of disorder	Inheritance	Gene or locus	MIM Nr.	Notes
NOS 41-0030	Multiple synostoses syndrome, FGF9-related	AD	*FGF9*	612961	
NOS 41-0040	Multiple synostoses syndrome, GDF6-related	AD	*GDF6*	617898	
NOS 41-0050	Liebenberg syndrome, PITX1-related	AD	*PITX1*	186550	Structural variants encompassing the *H2AFY* gene resulting in ectopic activation of *PITX1* in upper limb
NOS 41-0060	Short stature, auditory atresia, mandibular hypoplasia, skeletal abnormalities (SAMS) syndrome, GSC-related	AR	*GSC*	602471	
NOS 41-0070	Radio-ulnar synostosis with amegakaryocytic thrombocytopenia, HOXA11-related	AD	*HOXA11*	605432	
NOS 41-0080	Radio-ulnar synostosis with amegakaryocytic thrombocytopenia, MECOM-related	AD	*MECOM*	616738	
NOS 41-0090	Radio-ulnar synostosis with microcephaly (Giuffré-Tsukahara syndrome)	603438			X-linked recessive inheritance suggested
	See also Spondylocarpotarsal synostosis syndrome, *FLNB*-related and RFLNA-related; Cardiospondylocarpofacial syndrome, *MAP3K7*-related; mesomelic dysplasia with acral synostoses (Verloes-David-Pfeiffer type); Baller-Gerold syndrome, *RECQL4*-related; and Antley-Bixler syndrome, *POR*-related				

Note: The numbering system (first column) includes "NOS" for "Nosology, skeletal", followed by the group number and the number of the disorder. The abbreviations are as follows: in the disorder names, SED in spondylo- ephyseal dysplasia; SEMD is spondylo-epi-metaphyseal dysplasia; MED is multiple epiphyseal dysplasia; CDP is chondrodysplasia punctata. In the "Inheritance" column: AD, autosomal dominant; AR, autosomal recessive; XL, X-linked; MOS, somatic mosaicism; SP, sporadic and inheritance unknown. Pseudo-AD and Pseudo-AR refers to genes in the pseudoautosomal regions of chromosome X and Y. The "MIM No." column shows the MIM number of the disorder; when the number is preceded by "see", the MIM number is that of the underlying gene.

1. POJMENOVÁNÍ PROBLÉMŮ A DYADICKÝ PŘÍSTUP JAKO CESTA VPŘED

V letech 2010 až 2020 zaujala technologie masivního paralelního sekvenování centrální místo v genetickém výzkumu a diagnostice. Mezi mnoho poznatků získaných ze sekvenování nové generace (NGS) patří (**1**) velký počet předtím nerozpoznaných vzácných a velmi vzácných nemocí v každé oblasti genetické medicíny, (**2**) fenotypová heterogenita vyplývající z jediného lokusu je mnohem větší, než se dříve předpokládalo, a (**3**) u mnoha dyadických entit jsou jedinci, kteří vykazují všechna fenotypová kritéria popsaná v článku spíše výjimkou než pravidlem.

Na tomto základě bylo navrženo, že fenotypový popisný termín (deskriptor) genetické nemoci („název" onemocnění) již není dostatečný k jednoznačnému rozlišení. Kromě toho pořadové číslování stavů se stejným názvem (jak se používá např. pro osteogenesis imperfecta nebo ataxie v Mendelian Inheritance in Man [MIM]) může být nevyhovující, protože číslo nemá žádnou vnitřní informaci a je proto nutné konzultovat příslušné odkazy. V důsledku toho bylo navrženo, aby byl

místo přiřazení podle čísla (nebo eponymu, viz níže) hlavní fenotypový deskriptor genetické poruchy propojen s názvem odpovídajícího genu, což umožní získat přímější a výstižnější informace, méně náchylné k nejednoznačnostem a chybám: takzvaný dyadický přístup (Biesecker et al., 2021). Za zmínku stojí, že průkopníkem dyadické koncepce byla redakce známého zdroje GeneReviews počínaje rokem 2020 (Dr. M. Adam, osobní sdělení; a Biesecker et al., 2021).

Nozologie nebyla imunní vůči šíření číslovaných seznamů, jako například u osteogenesis imperfecta (Sillence & Rimoin, 1978; Sillence et al., 1979; Van Dijk & Sillence, 2014). V této revizi z roku 2023 se kurátoři rozhodli přijmout dyadický přístup k pojmenováním, protože umožňuje větší přesnost jak v klinice, tak v laboratoři. V některých případech však byly učiněny kompromisy, aby byl zohledněn historický vývoj Nozologie, jakož i pro zachování shody a interoperability s tím, co je považováno za nejdůležitější referenční databázi pro genetické poruchy, MIM (MIM a její online verze OMIM).

2. THE MENDELIAN INHERITANCE IN MAN KATALOG A NOZOLOGIE

Dílo zesnulého Victora McKusicka, MIM, zůstává i nadále nejvýznamnější obecnou referenční databází pro genetické poruchy. Způsob, jakým byl MIM vytvořen a je stále spravován, umožňuje podrobnou dokumentaci historie každé nemoci. Ze stejného důvodu je méně vhodný pro dokumentaci změn, ke kterým dochází v nozografii, například když je jedna porucha podřazena pod jinou; několik nemocí uvedených v MIM bylo podřazeno pod jiné stavy v Nozologii, nebo nejsou v Nozologii vůbec uznávány jako samostatné fenotypové jednotky (např. mezomelická dysplazie, typ Camera; MIM 611886). MIM také hojně využívá eponym k rozlišení příbuzných, ale odlišných poruch (např. nemoc Dyggve-Melchior-Clausen a Smith-McCort dysplazie); u jiných jsou eponymní deskriptory příliš podobné, což vede k diagnostickým nejasnostem (např. Shprintzen-Goldberg a Goldberg-Shprintzen syndromy představují odlišné poruchy). MIM volba těchto eponym nemusí odrážet nejvýznamnější přínos k vymezení fenotypové jednotky. Přijetím dyadického systému jsme se rozhodli popsat každou nemoc názvem genu, který je za ni zodpovědný, a nikoliv eponymem. Zatímco MIM zůstává centrální referenční databází, dyadický systém umožňuje Nozologii seskupovat, shlukovat nebo vyřazovat poruchy na základě jejich molekulárního základu, zejména ve světle poznatků z NGS (viz výše) a je méně vázán historickými omezeními. Přesto se kurátoři Nozologie snažili o zachování pevné vazby na MIM: čísla MIM jsou uvedena u všech nemocí, pokud jsou k dispozici, a pokud nejsou, uvádí se číslo MIM pro zodpovědný gen. Kromě toho jsou uvedeny odkazy na MIM kódy jednotlivých nemocí stejně jako na další nemoci MIM, vzniklé na základě patogenních variant stejného genu.

3. ORPHANET NOMENKLATURA A NOZOLOGIE

V rámci společné spolupráce mezi International Skeletal Dysplasia Society (ISDS), the European Reference Network on Rare Bone Disorders (ERN-BOND) a sítí Orphanet, kterou koordinuje Houda

Ali (kurátorka sítě Orphanet) a Geert Mortier (hlavní kurátor Nosologie 2019) vyústila podrobná analýza databáze Orphanet v porovnání s Nozologií 2019 v seznam zhruba 248 fenotypových jednotek, které se vyskytovaly v databázi Orphanet, ale chyběly v Nozologii 2019. Pro zařazení do Nozologie 2023 musely mít nemoci rozpoznatelný fenotyp a jasný typ dědičnosti nebo molekulární definici. Přibližně 30 z těchto nemocí splňovalo kritéria pro zařazení a proto byly do Nozologie zařazeny. Ostatní poruchy v tomto seznamu byly buď popsány v jediné práci bez molekulárního potvrzení, nebo představují historické popisy s omezeným množstvím dostupných informací, což odráží politiku Orphanetu, který se snaží reprezentovat všechny druhy poruch, které odpovídají definici vzácného onemocnění kvůli výhodě pro jedince postižené ultravzácnými projevy, pokud představují fenotypově jedinečné diagnózy (Ref. https://www.orpha.net/orphacom/cahiers/docs/GB/eproc_disease_inventory_R1_Nom_Dis_EP_04.pdf). Na druhou stranu se ukázalo, že mnoho záznamů v seznamu zřejmě nepředstavuje odlišné fenotypové jednotky z hlediska současných poznatků a kritérií Nozologie. To podnítilo revizní proces týmu sítě Orphanet s cílem přezkoumání a identifikaci záznamů, které je třeba deaktivovat a následně odstranit z nomenklatury vzácných onemocnění sítě Orphanet.

4. NOZOLOGIE A CLINGEN INICIATIVA

Iniciativa ClinGen (https://clinicalgenome.org/affiliation/40065/) v současné době pracuje na souboru genů spojených s kosterními nemocemi s cílem poskytnout sílu důkazů pro asociace gen – nemoc, s použitím přísně ověřených kritérií pro hodnocení patogenity variant v genech, u nichž byla zjištěna definitivní souvislost s onemocněním. To již učinila u jiných skupin genetických poruch, jako jsou kardiomyopatie a další. Několik současných kurátorů Nozologie se na tomto úsilí podílí. Nicméně samotný počet genů, které způsobují konstituční nemoci kosterní soustavy je takový, že sekce ClinGen pro geny kostních dysplazií bude vyžadovat čas, než bude moci být dokončena. V této souvislosti zůstane Nozologie se svým seznamem ověřených genů a nemocí (i když ne v rozsahu stanoveném v iniciativě ClinGen) v dohledné době nejlepším dostupným zdrojem. Za zmínku stojí, že přístup ClinGen je mnohem více „řádný" než Nozologie, a to do té míry, že fenotypy způsobené patogenními variantami na jednom lokusu musí mít významné kvalitativní rozdíly, aby bylo možné je považovat za samostatné nozologické položky (fenotypové jednotky); pouhý kvantitativní rozdíl (typicky více či méně závažný projev) nestačí k odůvodnění oddělení. To nás může vést k zamyšlení nad tím, co představuje „dysplazii" nebo „syndrom". Někteří z nás také přispěli k vývoji „Nozologie vrozených metabolických vad" a následné „Mezinárodní klasifikace dědičných metabolických poruch" (ICIMD) (Ferreira et al., 2019, 2021). Tato nozologie aplikuje zásadu „jeden gen – jedna nemoc", pokud neexistují kvalitativní rozdíly. Tuto zásadu je však obtížnější aplikovat na kosterní nemoci. Například děti postižené metylmalonovou acidémií mohou mít různé koncentrace metylmalonové kyseliny v moči, ale budou považovány za pacienty se stejnou poruchou (MIM 251000). Bylo by obtížnější tvrdit, že plod s achondrogenezí typu 1B (MIM 600972) a dítě s recesivní mnohočetnou epifyzární dysplazií (MIM 226900) mají stejnou poruchu, i když odpovědný gen je stejný a fenotypy představují opačné konce tíže v rámci stejného spektra, protože morfologické znaky a klinická prognóza jsou tak radikálně odlišné.

5. ZMĚNY VE SROVNÁNÍ S PŘEDCHOZÍMI REVIZEMI

Některé změny ve struktuře Nozologie si zaslouží zmínku. Celkový počet skupin se snížil ze 42 na 41. Toto snížení souvisí s restrukturalizací několika skupin. Konkrétně dřívější skupiny „Perlecan" a „Aggrecan" byly začleněny do nové skupiny „Proteoglycan core protein disorders" a dřívější skupiny „Neonatální osteosklerotické dysplazie" a „Jiné sklerotické kostní nemoci" byly sloučeny do skupiny (neosteopetrotických) „Osteosklerotických nemocí". Do současné Nozologie byla přidána nová skupina „Skeletální poruchy signalizační kaskády parathormonu". Dvě skupiny brachydaktylií (izolované nebo jako součást syndromů; nyní skupiny 18 a 19) byly shledány jako lépe organicky umístěny hned za akromezomelickou a akromelickou skupinou (skupiny 16 a 17). Několik skupin bylo přejmenováno. Skupina „Osteopetróza a příbuzné nemoci" se nyní jmenuje „Osteopetróza a příbuzné nemoci osteoklastů", aby se zdůraznila skutečnost, že osteopetrózy představují poruchy počtu nebo funkce osteoklastů. „Osteogenesis Imperfecta a skupina snížené kostní denzity" byla přejmenována na „Osteogenesis Imperfecta a skupina fragility kostí", aby se zohlednila skutečnost, že fragilita skeletu je charakteristickým znakem těchto poruch bez ohledu na minerální denzitu (protože malá podskupina pacientů s osteogenesis imperfecta může mít vysokou kostní hmotu). Název skupiny „Syndromy nadměrného (vysokého) vzrůstu s postižením skeletu" byl změněn na výstižnější „Syndromy nadměrného (vysokého) vzrůstu a segmentálního přerůstání". Skupina „Syndromy s kraniosynostózou" byla přejmenována na „Syndromy, jejichž součástí je kraniosynostóza", neboť ačkoli poruchy v této skupině často zahrnují kraniosynostózu, tento nález nepředstavuje vždy nejvýznamnější příznak. Další změny v názvosloví skupiny zahrnují změnu „Brachydaktylie (bez extraskeletálních projevů)" na „Izolované brachydaktylie"; „Brachydaktylie (s extraskeletálními projevy)" na „Brachydaktylie jako součást syndromů"; „Ciliopatie s velkými změnami skeletu" na „Skeletální nemoci způsobené abnormalitami cilií a ciliární signalizace"; „Skupina abnormální mineralizace" na „Poruchy mineralizace kostí"; a „Ektrodaktylie s a bez jiných projevů" na „Rozštěpená ruka/noha s jinými projevy a bez nich". Některé poruchy byly přeřazeny. Například trichorinophalangeální dysplazie typu 1/3 byla přesunuta ze skupiny „Akromelických dysplazií" do skupiny „Brachydaktylie jako součást syndromů". Celkový počet nemocí se zvýšil ze 461 na 771 a počet genů ze 437 na 552. Přestože jsme si vědomi problémů spojených s číselnými seznamy (jak je uvedeno výše), zařadili jsme systém číslování včetně zkratky „NOS" (pro „Nosology, skeletal"), číslo skupiny a pořadové číslo v rámci skupiny, přičemž jsme dbali na to, aby byly ponechány mezery, které by mohly umožnit v budoucnu zařadit další poruchy. Takový systém číslování by se mohl ukázat jako užitečný při křížovém odkazování s MIM, Orphanet a s dalšími databázemi.

6. JAKÁ JE UŽITEČNOST NOZOLOGIE?

Od svých prvních revizí je Nozologie užitečná pro pediatry, genetiky, radiology a další odborníky jako pomůcka diferenciální diagnostiky. Její původní struktura skupin nemocí s podobnými radiologickými rysy odrážela diagnostický přístup klinického genetika a ještě více radiologa k steochondrodysplaziím. V průběhu let po zařazení brachydaktylií, kraniosynostóz, kraniofaciálních dysostóz, syndaktylií, redukcí končetin a dalších dysostóz jakož i primordiálního malého vzrůstu a syndromů s nadměrným růstem, rozšířily její použitelnost pro diferenciální diagnostiku v rámci těchto skupin

nemocí. Revize z roku 2010 uvádí, že „Cílem je poskytnout genetické, pediatrické a radiologické komunitě seznam genetických nemocí skeletu, který může být nápomocný při diagnostice konkrétních případů, při vymezení nových poruch a při budování mostů mezi klinickými lékaři a vědci, kteří se zajímají o skeletální biologii. Nozologie by měla být užitečná pro diagnostiku pacientů s genetickými onemocněními skeletu, zejména s ohledem na očekávanou záplavu informací spojenou s novými technologiemi sekvenování; při vymezování klinických jednotek a nových nemocí tím, že poskytuje přehled o zavedených nozologických jednotkách; a pro vědce, kteří hledají klinické koreláty genů, proteinů a drah zapojených do biologie skeletu." O třináct let později může mít Nozologie další úlohu v molekulárně – genetickém diagnostickém testování. V předtestové fázi může Nozologie informovat o tom, které geny zařadit do diagnostického panelu připraveného na míru pro konkrétní klinickou situaci. Současné diagnostické pracovní postupy často zahrnují ověření věrohodnosti variant nalezených v panelu nebo exomu (reverzní fenotypizace). Rovněž v rámci posttestové fáze může být Nozologie užitečná pro rychlou referenci a orientaci.

Nozologie je také ilustrací složitosti lidského genomu, o čemž svědčí obrovské množství genů a genových produktů potřebných pro normální vývoj a růst kostry. Přiložená tabulka s více než 750 položkami je se svými řádky a sloupci jako hudební partitura pro orchestr vývoje a růstu kostry, která může být inspirací pro genetiky a vědce v základním výzkumu. Možná právě hybridní povaha Nozologie, která kombinuje klinická, rentgenologická a molekulární kritéria, je silnou stránkou, nikoli slabinou, protože umožňuje kolegům z různých oborů přístup k údajům. Je jasné, že žádná nozologie v medicíně není dokonalá ani úplná. Jsou vždy dynamické a vyvíjejí se. Nicméně časté citace předchozích verzí Nozologie naznačují, že navzdory mnoha kompromisům, které byly nutné při její přípravě, se Nozologie stala pro lékařskou a vědeckou komunitu užitečná a široce přijatá. Díky neustálému pokroku ve vymezování genetických stavů začíná Nozologie zastarávat v okamžiku, kdy je publikována. Ať se tato nová verze setká se stejně benevolentním přijetím a ať je také časem nahrazena novými a úplnějšími verzemi.

Příspěvky autorů

Všichni autoři vytvořili koncepci práce na revizi, podíleli se na revizi několika skupin poruch a podíleli se na diskusi a rozhodování. Sheila Unger, Carlos R. Ferreira a Andrea Superti-Furga uspořádali příspěvky, sestavili konečnou tabulku a vypracovali návrh rukopisu. Tabulka a rukopis pak byly revidovány všemi autory a následně dokončeny Sheilou Unger, Carlosem R. Ferreirou a Andrea Superti-Furgou.

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Sdílení dat se na tento článek nevztahuje, protože nebyla vytvořena ani analyzována žádná nová data v této studii.

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PALEOPATOLOGICKÁ ANALÝZA NA PANONSKÉM AVARSKÉM POHŘEBIŠTI TEREHEGY-MÁRFA Z 9. STOLETÍ

PALEOPATHOLOGICAL ANALYSIS AT THE TEREHEGY--MÁRFA PANNONIAN AVAR BURIAL SITE FROM THE 9TH CENTURY

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ABSTRACT

The aim of the work is a paleopathological study of skeletal remains from the 9th century discovered in 1961 at the Pannonian Avar burial ground of Terehegy-Márfa in today's Hungary and deposited by the Jannus Pannonius Museum (JPM) in Pécs.

At the Terehegy-Márfa, Pannonian Avar´s burial site, a collection of 10 individuals was paleopathologically examined: 3 males (M); 2 females (F); 3 children (CH); 2 unidentified individual (N). No injuries were found in this collection.

Workload was found in 2 instances out of 10 (20%) with maximum strain of the skeletons on the spine *spondylolysis* (M aged 20-29 in grave 2 and F, aged 20–30, in grave 5).

Congenital anomalies occurred in the form of *ossa suturaria*, *dental anomalies* and *assymetry of mandibular condyles*.

Anaemia in the form of *cribra orbitalia* was discovered in 4 cases out of 10 individuals (40%) in graves 1,2,5 and 8 and in all the instances it was of type 2. *Scurvy*, vitamin C deficiency, was recognized in 4 cases out of 10 (40%) in graves 2,4,6,7, through cribra formations on the palate and the sphenoid bone of the skull.

Dental disabilities occurred in 5 cases out of 10 (50%), usually it was *tooth loss in life* due to *periodontitis*. *Infections* occurred in 4 cases out of 10 (40%), in the form of meningitis (grave no.1, M? and grave no 8, CH infans I(to 7 years), *periostitis* and tooth *abscess.*

In terms of pathology, *congenital anomalies* and *dental diseases prevailed* (50%) in the collection followed by *anemia*, *scurvy* and *nonspecific infections*.

An exceptional find in terms of social relations and ethnology was placement of a cow bell, probably used as a rattle, with the child (infans I) in grave no. 4.

Key words: Avars, congenital anomalies, plagiocephaly, meningitis, Central Europe

INTRODUCTION

In 1961, Jozsef Bosnyák, a resident of Márfa, discovered a grave while digging a carcass pit. The postman, Jozsef Varga, from Pécs, took the objects found in this grave to the Jánus Pannonius Museum (JPM).

The rescue excavation was carried out by Attila Kiss between September 3rd and 15th, 1962.

The archaeological finds were registered under inv. no. 62.181 1–57 in the catalogue of the Archaeological Department. Skeletal material was registered under inv. no. 69.5 1–10 in the anthro-

Figure 1: Terehegy N45,8561873 E18,1947984. Access to the road to the Acemetery from the road between the villages of Marfa and Terehegy (November 2022).

pological collection. The horse skeleton discovered in grave no. 6 was presented in the Magyar Agricultural Museum as it was recovered in situ (**8**). The burial site is situated on a low hill on the border between the villages of Márfa and Terehegy, about 1100 m southeast of Márfa and Terehegy (**fig. 1**). It is likely that the excavated graves belonged to a much larger burial site.

The aim of this work was a paleopathological study of skeletal remains from the 9th century discovered in 1961 at the Pannonian Avar burial ground of Terehegy-Márfa in today's Hungary and deposited by the Jannus Pannonius Museum (JPM) in Pécs.

METHODS

The basis of the paleopathological study was the standard determination of sex and classification of individuals into individual age categories (**19**; **5**). Paleopathological findings were assessed mainly according to the criteria of Steinbock, Campillo (**18**, **4**), Ortner and Putschar (**14**, **15**), Vyhnánek (**19**), Horáčková, Strouhal and Vargová (**7**), Smrčka et al. (**17**) and Lewis (**10**). The basic investigative methods of paleopathological diagnosis were mainly detailed macroscopic study.

Figure 2: Meningitis in grave no. 1

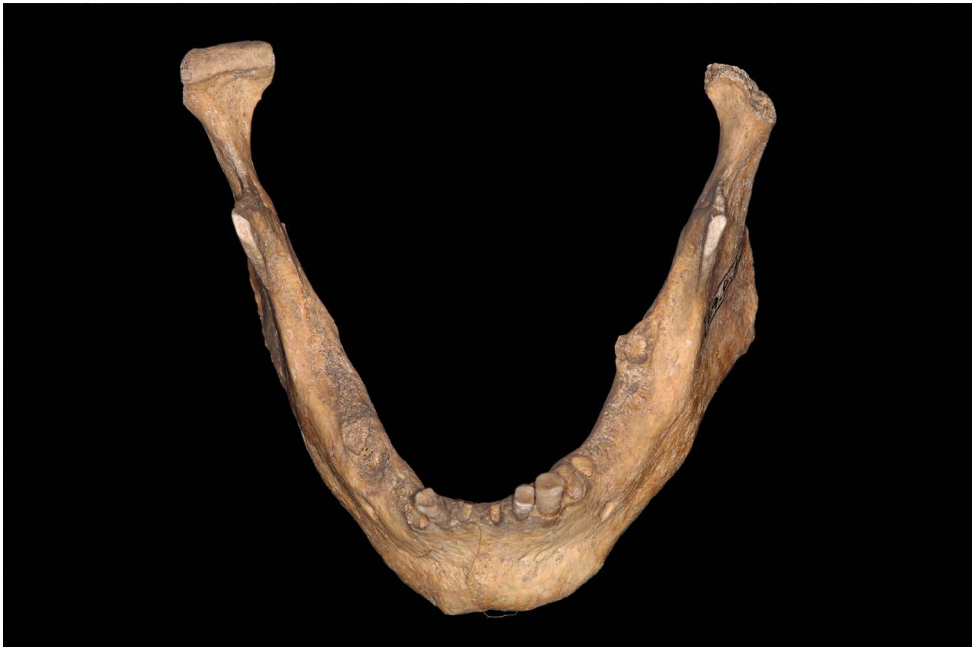

Figure 3: Tooth loss in life, grave no. 2.

RESULTS

Paleopathological Analysis

In **grave no. 1** (inv. no. 69.6.1) a man of unknown age was buried. His skull is in fragments. In the left orbit, there are type 2 *cribra orbitalia*. The right orbit has not been preserved just like the right part of the mandible. The interior of the skull in the frontal region is flaking, there is suspected *periostitis* on the bone fragments *inside the skull*. There is green colouration in the occipital region due to Cu ions. There is *striated periostitis* on the left side of the mandible. The man suffered from suspected *anaemia(cribra orbitalia)* and the cause of his death could have been *meningitis* (central arrow showing flaking parts, under right not preserved orbit – **fig. 2**). The bone material of the axial skeleton was in fragments. Two types of arrowheads were found in the grave, trilateral, characteristic for the late Avar period.

In **grave no. 2** (inv. no. 696.2) a man, aged 20–29, was buried. His skull is well-preserved including the lower jaw. There are *intra sutural bones* in the lambdoid suture on the right and in the sagittal suture. There was an *abscess of the incisor* in the maxilla and tooth *loss occurred* during his *life* from the *1st premolar*. In the lower jaw, *tooth loss in life* also occurred *from the premolars* (**fig. 3**).

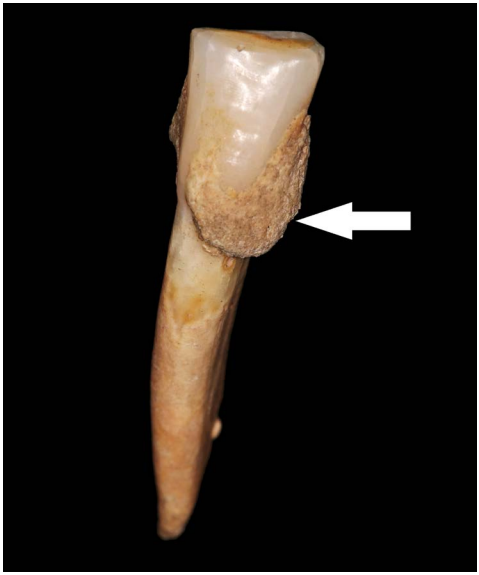

Figure 4: Dental calculus in grave no. 3

At the same time, in the lower jaw there is *asymmetry of the caput mandibulae,* greater on the right, smaller on the left, though only partially preserved. On the skull there are porotic signatures of *scurvy*, vitamin C deficiency, in the foramen jugulare region, on the mandible and fossa pterygoidea.

In the axial skeleton, *spondylosis* was found on the spine, with a maximum in the lumbar spine, where osteophytes reach up to 4 mm. On the surface of vertebral bodies of the four thoracic vertebrae there are defects indicative of disability, that are probably caused by nucleus pulposus. This finding is typical of Scheuermann´s morbus.

In **grave no. 3** (inv. no. 69.6.3), a skeleton of unknown sex and age and with a skull in fragments was found. There was *calculus* on the teeth (**fig. 4**). The axial skeleton is also in fragments.

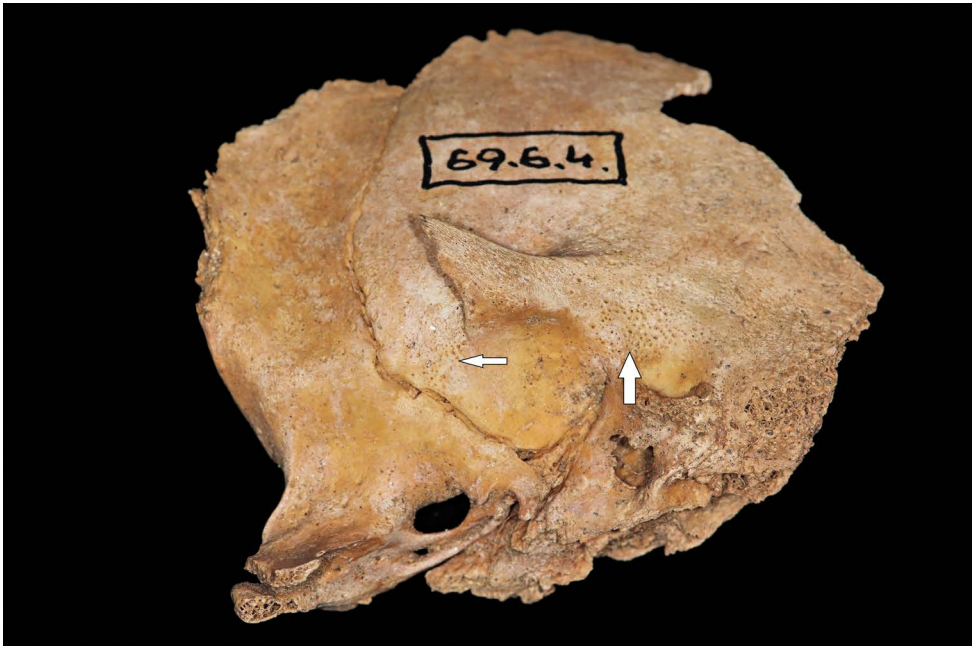

Figure 5: Signs of scurvy in the infratemporal fossa, grave no. 4.

Figure 6.1: Rotation of the cuspid, grave no. 5 (F; aged 20–30)

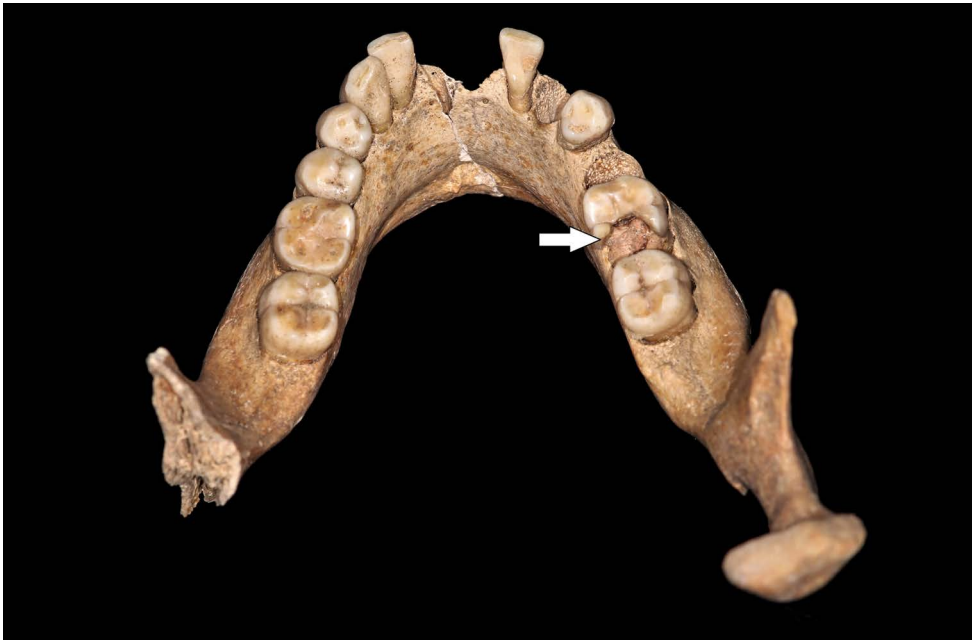

Figure 6.2: Dental caries in the right M1, grave no. 5

In **grave no. 4** (inv. no. 69.6.4) a child, infans I (to 7 years), was buried. It had suffered from suspected *scurvy*, vitamin C deficiency. Signs of scurvy were identified as *cribra formations* affecting almost the entire bony portion of the right half of the palate as well as the infratemporal fossa (**fig. 5**).

An iron cow bell was found near the child in grave no. 4, a unique find among Avar period finds. At the Terehegy burial site it was found near a child's skeleton and its role could have been the same as rattles in children's graves.

F. Mora's (**4**) ethnographic data show that parents were informed of where their child was playing by the sound of the rattles the child carried, and thus were aware of the child's movements. When the child died, the bell was placed in his grave.

In **grave no. 5** (inv. no. 69.6.5), a woman, aged 20–30, whose skull and lower jaw have been preserved, was found. In both orbital roofs there is *cribra orbitalia*, type 2 bilaterally. The woman suffered from suspected anaemia. There is a *congenital anomaly* in the maxillary teeth, a *rotated right cuspid* (**fig. 6.1**). A large *caries* was found on the first right molar (M1) in the mandible (**fig. 6.2**) There is *periostitis* on the anterior part of the mandible on the right (on level with the M1 with caries). There is *spondylosis* on the axial skeleton in the lumbar spine. It is also found on the sacrum. In both cases with osteophytes of up to 7 mm in size.

Figure 7: Cusp of Carabelli, grave no. 6 (M; aged 20–40)

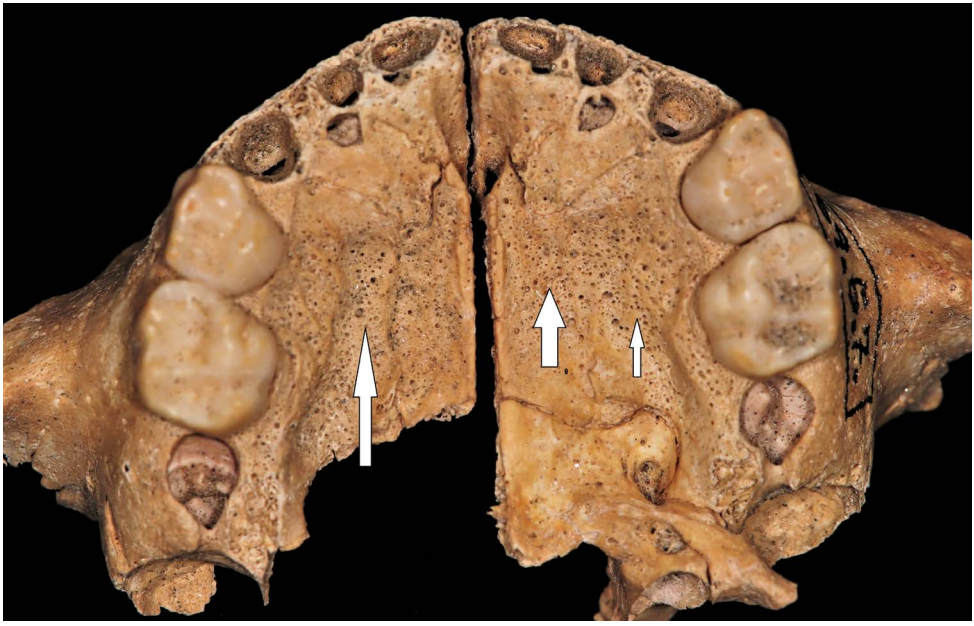

Figure 8: Cribra in the palate of the child from grave no. 7

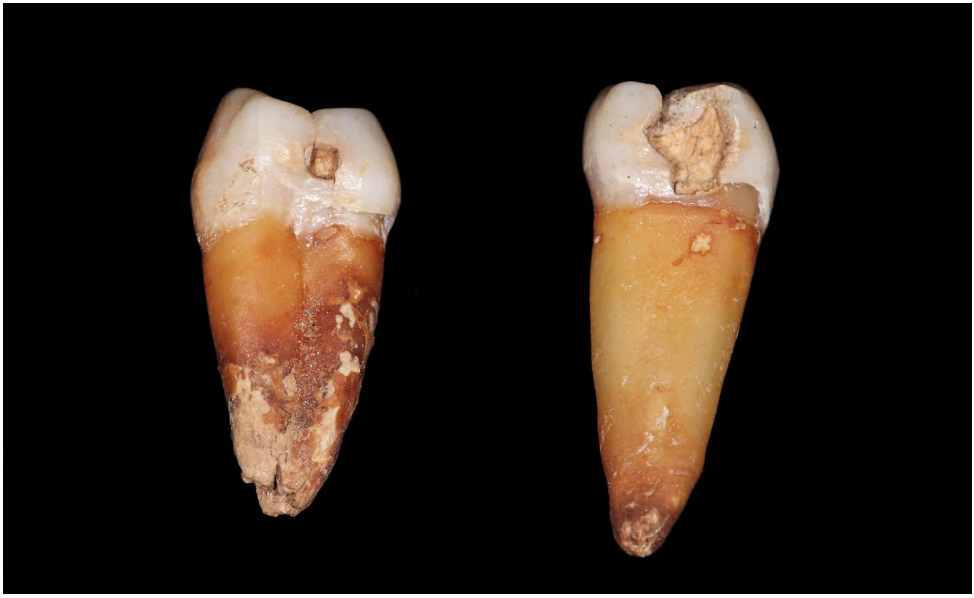

Figure 9: Dental caries in the premolars in grave no. 9

In **grave no. 6** (inv. no. 69.6.6) there is a skull of a man aged 20–40. The skull is in fragmentary condition. In the lower jaw, there are exposed tooth necks with thickened alveolar margins, due to *periodontitis*. In the upper jaw, there are signs of suspected *scurvy* manifested as *palatal cribra*, exposure of tooth necks and alveolar margins. In the maxilla, there is a congenital dental defect on the left M2, *cusp of Carabelli* (**fig. 7**). In the grave, next to the man, there also was a skeleton of a horse (1.5 – 2-year-old tarpan-taku crossbreed, according to S. Bökönyi in Kiss 1977), with stirrups and a bridle bit. The horse skeleton lay on the left side of the man in the same orientation. The top part of a spearhead of a type belonging to the Late Avar period was also discovered in the grave.

In **grave no. 7** (inv. no. 69.6. 7) a child, infans I (to 7 years), was inhumed whose orbits have not been preserved. The child's fragmentary skull shows signs of *scurvy*, manifested by palatal *cribra* (**fig. 8**) mainly on the side of the oral cavity, less so from the nasal cavity and also loss of the front teeth of the upper jaw.

In **grave no. 8** (inv. no. 69.6.8) there also is a child, infans I (to 7 years), with type 2 *cribra orbitalia* in the right orbit. The child suffered from suspected anaemia, but concomitant intracranial lesions on the frontal and parietal bones are indicative of *meningitis*.

In **grave no. 9** (inv. no. 69.6.9) there was an individual of unknown sex and age with dental caries on the premolars from the mesial aspect (**fig. 9**).

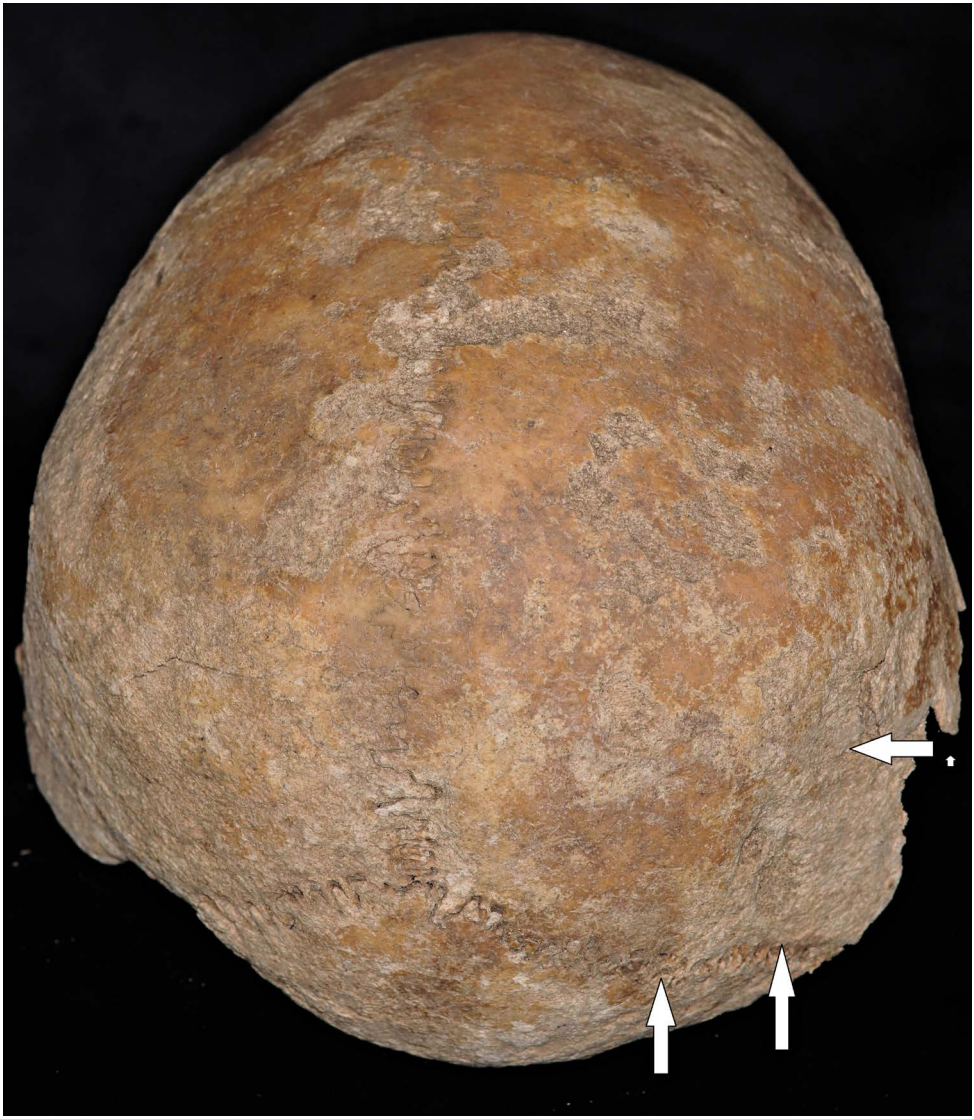

Figure 10: Posterior plagiocephaly in grave no. 10 (F, aged 40–60)

In **grave no. 10** (inv. no. 69.6.) there was woman, aged 40–60, with darkened sutures on a pentagonal skull with right *posterior plagiocephaly* (**fig. 10**). The deformity may have originated as a positional, postural plagiocephaly in infancy, but it cannot be ruled out that the deformity may have been caused by lying the skull in a moist, mycotic and acidic environment.

At the burial site of Terehegy-Márfa, 10 individuals were found – 3 males (M), 2 females (F), 3 children (CH) and 2 unidentified individuals (N). No injuries were found in this collection. In terms of *workload*, it appears that in this collection spine was predominantly affected (**13**).

Spondylosis occurred in 2 individuals out of 10 (20%) (M aged 20–29 in grave 2 and F, aged 20–30, in grave 5).

Congenital anomalies were discovered in 5 cases out of 10 (50%). These congenital defects mostly affected the skull, with intra sutural bones (*ossa suturaria*), *asymmetry of mandibular condyles* and *tooth anomaly* (**2**, **3**). In grave 10 (F, aged 40–60) right *posterior plagiocephaly* was discovered. However, it cannot be excluded that the deformity may have been caused by lying the skull in a moist, mycotic and acidic environment.

In grave 2 (M, aged 20–29) *intra sutural bones* with asymmetrical condyles were found. In terms of dental anomalies, there was a congenital *rotation of a cuspid* in grave 5 (F, aged 20–30) and *cusp of Carabelli* in grave no. 6 (M, aged 20–40) (**10**).

Anaemia in the form of *cribra orbitalia* (**11**) was discovered in 4 instances out of 10 (40%) – in Terehegy graves 1, 2, 5, and 8. In all the instances it was of type 2.

Scurvy, vitamin C deficiency, identified as *cribra formation* was found in 4 cases out of 10 (40%) – in Terehegy graves 2, 4, 6, and 7. Some form of tooth disease was discovered in 5 instances out of 10 (50%) such as *tooth loss in life* (grave no. 2, M 20–29), *dental calculus* (grave no. 3, N?), *dental caries* (grave no. 5, F 20–30, and grave no. 9, N?) and *periodontitis* (grave no. 6, M 20–40). *Infections* were found in 4 cases out of 10 (40%) in the form of *meningitis* (grave no. 1; M?, and grave no. 8, CH infans I). There also was *periostitis* (grave no. 5, F 20–30) and a *tooth abscess* (grave no. 2, M 20–29).

In terms of bone pathology, *congenital anomalies* and *dental diseases* prevailed (50%) in the Terehegy collection followed by *anaemia*, *scurvy* and *nonspecific infections*.

An exceptional find in terms of social relations and ethnology was the placement of a cow bell, probably used as a rattle, with the child (infans I) in grave no. 4 (**12**).

DISCUSSION

Trauma

We did not find any injuries in the skeletal assemblage in Terehegy-Márfa. But we found in another Avar burial site in the nearby Pécsvárad, from the 9th century, so far from a paleopathological point of view unpublished.

At the Pécsvárad burial site, a collection of 27 individuals was paleopathologically examined: 9 males (M); 10 females (F); 7 children (CH); 1 unidentified individual (N), together with the bone remains of several animals (horse and sheep).

Traumas occurred in 3 cases out of 27 (11.1%). In grave no. 1 it was (F 14-20-year-old) an *execution*, interpersonal violence, inflicted with the blunt part of a war axe by a right-handed horseman.

Congenital anomalies

Plagiocephaly was found in Terehegy, not congenital, but probably postural formed in childhood. In Pécsvárad, scaphocephaly was found from cranisynostoses.

Regarding Terehegy's right-sided posterior plagiocephaly, we can assume that it is a consequence of laterality, which leads to the so-called malpositioned skull deformity in early infancy. However, we cannot exclude that the deformity may have been caused by the storage of the skull in a moist, mycotic and acidic environment.

At the Pécsvárad, occurred in 9 cases congenital anomalies out of 27 (33.3%), in the form of craniosynostoses, intra sutural bones in the cranial sutures, dental anomalies and vertebral fusions. In grave no. 4, a 40-60-year-old male had a boat-shaped skull, *scafocephaly*. In grave no. 11, a female, aged 14–20, had a *congenital fusion of thoracic vertebrae* caused by ossification of the anterior ligaments of the vertebral bodies. In children, girls in graves no. 21 (4-7-year-old) and no. 28 (7-14-year-old), *intrasutural bones* were present.

Infections

The same infections were not found in Terehegy. In contrast, we found in Pécsvárad *brucellosis*, transmitted by goats, their milk and milk products. In Pécsvarád skeletons of horses and goats were found among the animals, but only horses in Terehegy. Brucellosis was also found in the Austrian Avar cemetery of Vösendorf (**13**). Brucellosis was associated with the expansion of goat herds and milk production (**6**). Infections at the Pécsvárad occurred in 5 cases out of 27 (18.5%). In one instance out of 27 (3.7%) it was *brucellosis* (grave no. 5; M 40-60-year-old) (**1**, **15**) and one instance was *meningitis* (grave no. 24; CH 7-14-year-old).

Anemia (cribra orbitalia)

Anemia manifesting as cribra orbitalia is usually attributed to iron deficiency (**11**, **10**). Its occurrence in Terehegy and Pécsvárad was high. We found *anemia* (cribra orbitalia) also in the Avar burial site in the nearby Pécsvárad, from the 9th century, in 12 out of 27 individuals (44.4%).

Lászlo Orolyia (2018) anthropologically analyzed individuals from the Kőlked-Feketekapu with 681 graves. Kőlked-Feketekapu Avar Age site can be dated from the last decade of the 6th century

to mid-8th century. Anthropological analysis has identified moderately preserved skeletal remains of 466 individuals, of which 150 were infants.

The frequency of *cribra orbitalia* was highest between 2–6,5 years" (**9**). László found porotic type with 84 individuals (54,9%), cribrotic with 48 individuals (31,4%) and trabecular with 21 individuals (13,7%) (**9**).

CONCLUSION

The original pathological findings on the 9th century Avar skeletal remains of 10 individuals from Terehega-Márfa provide insight into the congenital skull and spinal defects, defects and dental diseases that were common in this period and locality, as well as diseases caused by non-specific infections, vitamin deficiencies and malnutrition.

In terms of bone pathology, congenital anomalies and dental diseases predominated in the cohort (50%), followed by anaemia, scurvy and non-specific infections.

An exceptional finding in terms of social relations and ethnology was the deposition of a cowbell, probably used as a rattle, on a child (Infans I) in grave 1.

Acknowledgements

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MOLECULAR GENETIC DIAGNOSIS OF CONGENITAL CONTRACTURAL ARACHNODACTYLY AND COMPLEX TREATMENT OF A CZECH GIRL

MOLEKULÁRNĚ GENETICKÁ DIAGNOSTIKA VROZENÉ KONTRAKTURÁLNÍ ARACHNODAKTYLIE A KOMPLEXNÍ LÉČBA ČESKÉ DÍVKY

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SUMMARY

The authors summarize the findings of Congenital contractual arachnodactyly (Beals-Hecht syndrome) and present clinical, radiographic and molecular genetic findings and results of surgical therapy and rehabilitation in a Czech girl followed interdisciplinarily (orthopedic and plastic surgeon, cardiologist, anthropologist, osteologist, geneticist and physiotherapist) from 3 years of age to adulthood.

The diagnosis of severe congenital contractural arachnodactyly was established after birth on the basis of clinical-genetic examination at the Pediatric Clinic of the University Hospital Hradec Kralove. Associated anomalies of the cardiovascular, respiratory, digestive, urogenital, nervous systems, etc. were excluded.

The current molecular genetic analysis of blood and bone tissue samples of the patient revealed the same pathogenic intronic variant c.3724+2T>C (rs863223570) in the *FBN2* gene in heterozygous state, which is causative in our patient. The inheritance of the identified mutation is autosomal

dominant. This case report extends the clinical experience and molecular genetic findings of Beals-Hecht syndrome.

Keywords: Beals-Hecht syndrome, clinical findings, radiological characteristics, treatment, molecular genetic testing – blood and bone, pathogenic intronic variant of the *FBN2* gene.

INTRODUCTION

Beals-Hecht syndrome, known as congenital contractural arachnodactyly (CCA), is a rare autosomal dominant congenital connective tissue disorder. CCA is classified as group 31 "Overgrowth (high growth) and segmental overgrowth syndromes" along with Marfan syndrome, etc., according to the NOSOLOGY OF GENETIC BONE DISORDERS: 2023 REVISION (**23**).

Synonyms are used in the literature: Beals syndrome; Beals-Hecht syndrome (**1, 10**); Arachnodactyly, contractile Beals type; multiple contractures with arachnodactyly; ear anomalies-contracture-bone dysplasia with kyphoscoliosis; distal arthrogryposis type 9.

Clinical findings

Tall, slender Marfanoid habitus; arm span exceeds height; long, slender fingers and toes with arachnodactyly and contractures of proximal interphalangeal joints (PIP), ulnar deviation of fingers; flexion contractures involving mainly large joints (elbow, knee joints with subluxation of the patella); metatarsus varus; joint stiffness and muscle hypoplasia. Contractures are present in all affected children at birth, may be mild and tend to improve with time, but almost always present with permanently bent fingers and toes (camptodactyly) (**5, 22, 14**).

Beals-Hecht syndrome is caused by a defect in fibrillin as in Marfan syndrome (MFS). While MFS is caused by pathogenic variants (i.e. mutations) in *FBN1* gene, Beals-Hechte syndrome is caused by pathogenic variants in *FBN2* gene. Although the clinical features can be similar to Marfan syndrome (MFS), differences between the two syndromes exist. The characteristic feature is the crumbled appearance of anthelix, which in most cases distinguishes CCA from MFS. On the other hand, patients with CCA do not typically have serious ocular and cardiovascular complications seen in MFS. However, some more severe forms of CCA are associated with cardiovascular (e.g. interrupted aortic arch, atrial or ventricular septal defects, aortic root dilatation) and/or gastrointestinal anomalies (e.g. duodenal or esophageal atresia). Ectopia lentis is very rare in CCA, but general ocular complications are estimated to be present in 20% of patients with CCA.

In addition, CCA is often associated with short neck and kyphoscoliosis, which often worsens gradually and may require surgical treatment (**22, 3, 8,9, 17, 14, 19**).

The frequency of CCA in population is unknown, the number of patients reported has increased following the identification of *FBN2* mutation. To date about 70 cases with CCA have been described (**2**).

Radiological features

Gracile bones, mild osteopenia, slight bowing of the long bones, elongation of the proximal phalanges of the fingers and toes, vertebral malformations, hypoplastic tibia and bowing of fibula can be observed.

Inheritance

Inheritance is autosomal dominant (AD). The penetrance for CCA is likely up to 100% with variable expression. CCA is linked to the gene encoding the protein fibrillin 2 on chromosome 5q23-31 (**24, 25, 22**). Parental somatic and germline mosaicism have been observed in families with affected siblings with CCA (**22**). New data suggests that severe CCA can be also inherited in an autosomal-recessive manner by compound heterozygosity of a hypomorphic and a null allele of the *FBN2* gene (**13**).

Differential diagnosis

Infantile Marfan syndrome, homocystinuria, various arthrogryposis syndromes including lethal congenital contracture syndrome (AR) and fetal akinesia syndrome.

CASE REPORT

A female newborn (b.w. 3530 g, b.l. 56 cm) was hospitalized at the *Children's Clinic of the University Hospital in Hradec Králové* for limb contractures (flexion contractures of hip, knee and elbow joints, contractures of fingers with ulnar deviation of the 2^{nd}–5^{th} fingers of both hands, pedes equinovari bil. and digiti mallei) and facial changes (brachycephalic skull, asymmetrical nose deviated to the right, asymmetrical nostrils, abnormal auricles, very long limbs and chest).

Clinical-genetic and *laboratory examinations* did not reveal associated systemic defects. USG examination of the heart, brain and abdomen, ocular and neurological examination were normal. Diagnosis of Beals-Hecht syndrome i.e. congenital contractural arachnodactyly (CCA) or arachnodactyly syndrome with contractures, severe form, was made according to above mentioned clinical signs. Since both parents were healthy, *de novo* mutation (or gonadal mosaicism in one of the parents) was presumed.

Treatment

Since birth, orthopaedic (plaster redress bandages, splints, braces) and rehabilitation treatment of equinovarus contractures and flexion contractures of upper and lower extremities was performed. Residual deformities and contractures were an indication for surgical treatment already in toddlerhood (MUDr. J. Charvát, PhD in Nový Bydžov): At 20 months of age, tenotomy of m. rectus femoris bil. and prolongation of hamstrings bil. were done. At the age of 2.5 years, osteotomy of metatarsus I.-V pedis l. dx. was performed. At the same time, osteotomy correctiva calcanei l. sin. propter varo-

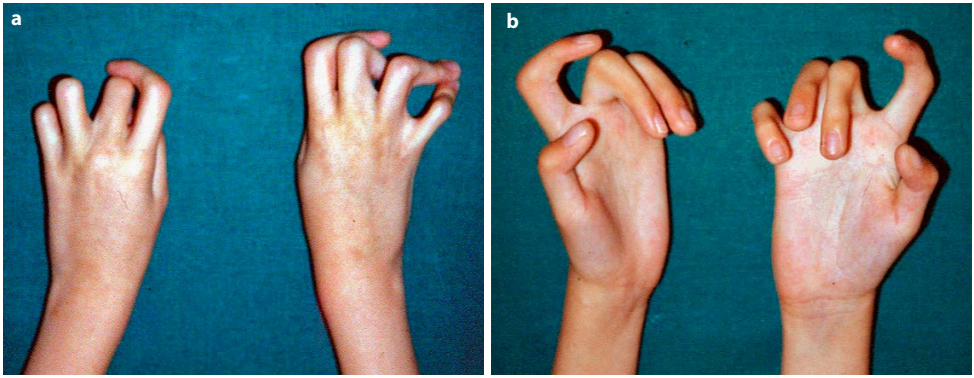


Fig. 1a, b. 3 years. Flexion contractures of the fingers of both hands: contractures in the PIP joints around 110°; **a.** dorsal view of the hands; **b.** volar view.

sity of the heel and tenotomy m. abductoris hallucis l. sin. and also resectio phalangis proximalis digiti II. pedis l. sin.

From the age of 3 years she was followed up at the *Centre for Defects of Locomotor Apparatus in Prague* for flexion contractures of the fingers of both hands – see **Fig. 1a, b** (*110° contracture in the PIP joints with passive extension only up to 90° – so-called tenodesis effect*). At the age of 3 years and 2 months, surgical treatment of the 3rd–5th fingers of the right hand was performed (exstirpatio tendines m. digitorum superficialis manus and partial dissection of the collateral ligaments of the PIP joints with transplantation of skin defects).

At 3 years and 8 months, the same procedure was performed on the 2nd–5th fingers of the left hand – see **Fig. 2a, b**.

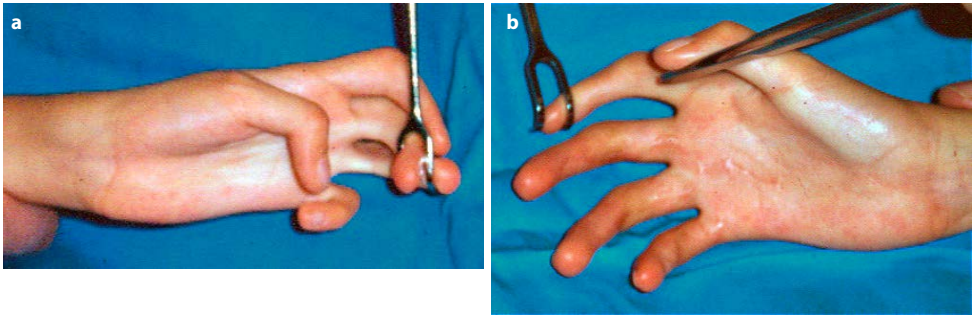


Fig. 2a, b. 3 years 2 months. **a**. left hand just before surgery – passive extension only up to 90° (so-called tenodesis effect); **b**. result of surgery of the right hand performed 6 months ago.

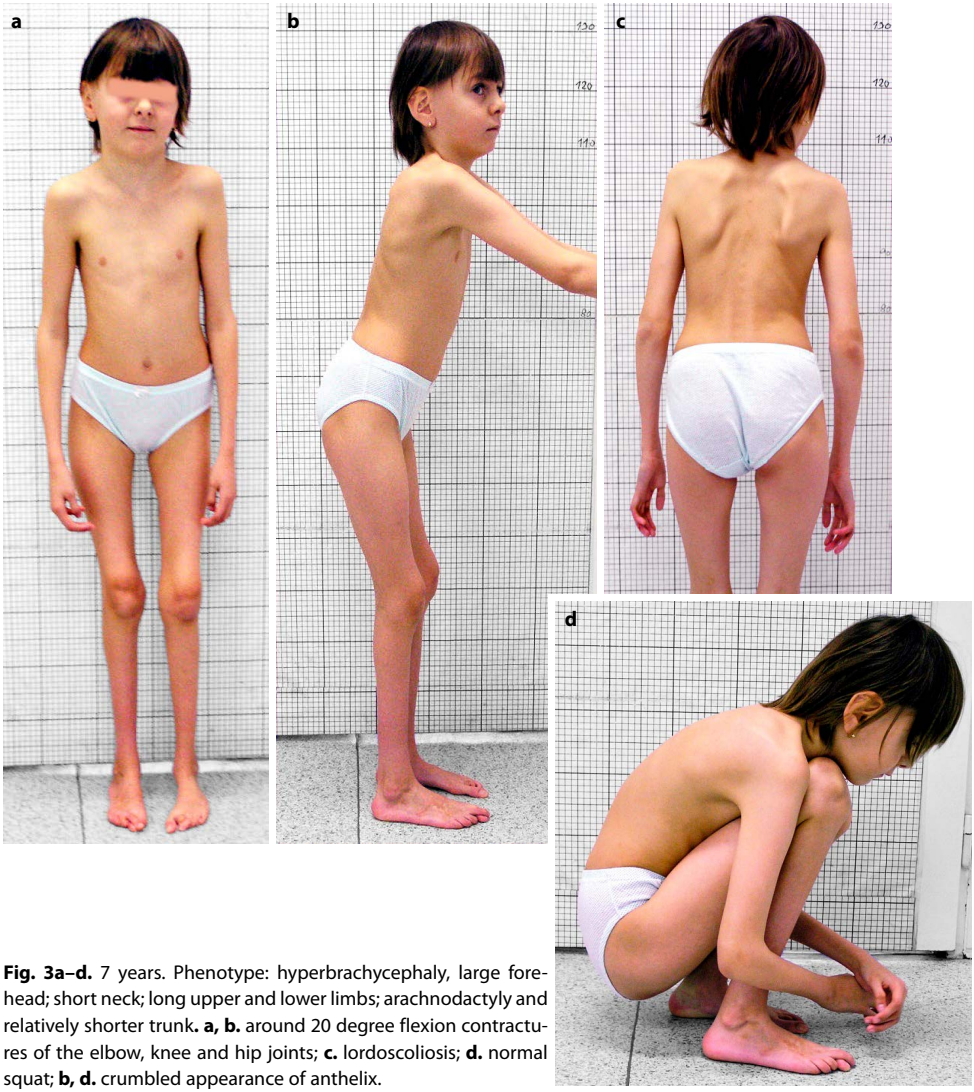
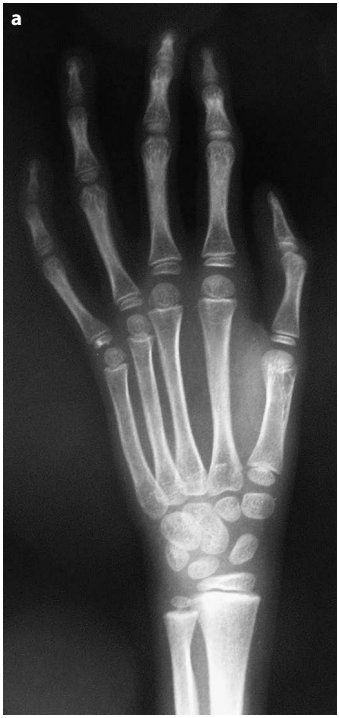


Fig. 3a–d. 7 years. Phenotype: hyperbrachycephaly, large forehead; short neck; long upper and lower limbs; arachnodactyly and relatively shorter trunk**. a, b.** around 20 degree flexion contractures of the elbow, knee and hip joints; **c.** lordoscoliosis; **d.** normal squat; **b, d.** crumbled appearance of anthelix.

Figures 3a–d show the phenotype of a seven-year-old girl with CCA. The asthenic girl with low weight was walking slightly forward with her knees bent and her legs rotated inwards. **Figures 4a–d**, X rays show gracile skeleton.



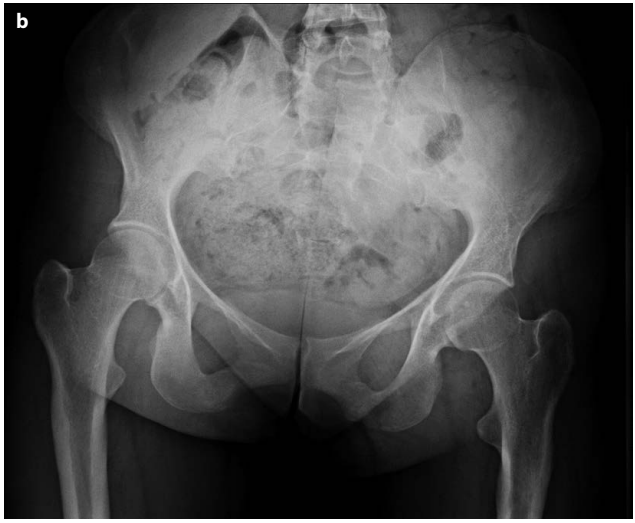


Fig. 4a–d. X-rays of graciel skeleton: **a**. 11 years – left hand –long and thin fingers; **b**. 25 years – pelvis in standing – coxa valga anteverta, shortening of the left lower limb by 3 cm;

Osteological examination at 7 and 12 years showed normal markers of calciophosphate metabolism. Markers of bone turnover were within the normal range of age-matched controls.

DXA densitometry (pediatric SW) – lumbar spine (L1–L4) at 5 years confirmed lower bone density (Z-score: -1.3), at 6.5 years density was normal (Z-score: -0.5). At 12 years L1–L4 (Z-score -1,0), but after correction to the height Z-score was -1,63. At 13 years DXA densitometry: Whole body – Z-score total: -1.9; lumbar spine – Z-score total: -0.4; right hip – Z-score total: -0.9; left hip – Z-score total: -1.1.

Conclusion: bone density during growth period was lower.

The mid- and long-term results of hand surgery are shown in the **Fig. 5a–e.**

At 7 years, medial metatarsal arthrotomy I and basal metatarsal osteotomy II–V l. sin. were performed to correct the metatarsus varus deformity. The foot deformities are shown in **Fig. 6a–c.** The result of the performed left foot surgery is shown in **Fig. 6d–f.**

At the age of 10 years she underwent surgery of flexor contracture of the 3^{rd}–5^{th} toe of the right foot (tenotomy of m. flexoris digitorum profundus).

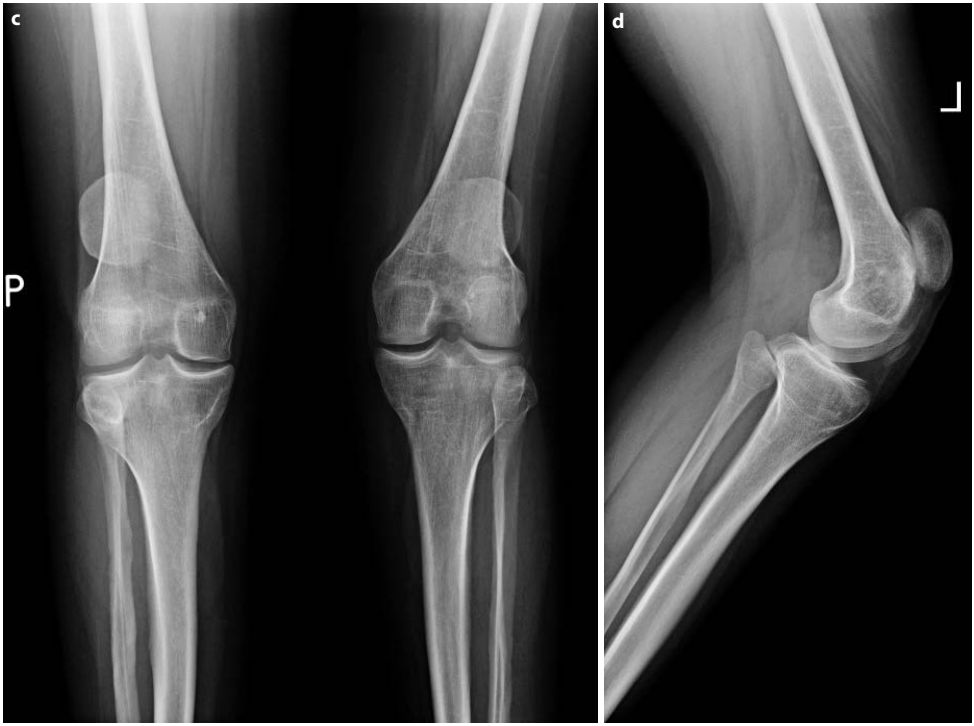


Fig. 4a–d. X-rays of gracile skeleton: **c**. 17 years – knee – AP projection: genus valgum l. sin., **d**. left knee – lateral projection – patella alta – is also seen in **c.**

At 12 years, based on clinical and anthropological evaluation and bone age, bilateral ventral drilling hemiepiphyseodesis of the distal femoral physis was performed to address 20° flexion contracture.

At 12.5 years, medial drilling hemiepiphysiodesis of the distal left femoral physis was indicated to address knee valgosity. Soon after ventral epiphysiodesis, however, the growth of the lower limbs stopped and the expected correction did not occur.

The outcome of irreversible ventral bilateral hemi-epiphysiodesis and medial hemiepihysiodesis of the distal physis of the left femur was continuously evaluated clinically, radiologically, and anthropologically. The result is documented in **Fig. 7a–d.**

At 17 years of age, a wedge osteotomy of the tibia (10°) and external rotation of the tibia (10°) was indicated due to persistent valgus in the proximal 1/3 of the left tibia and internal torsion. However, the planned procedure was not performed until the patient was 24 years old due to her studies.

The growth of the proband was regularly monitored by an anthropologist – see **Fig. 10 a, b.**

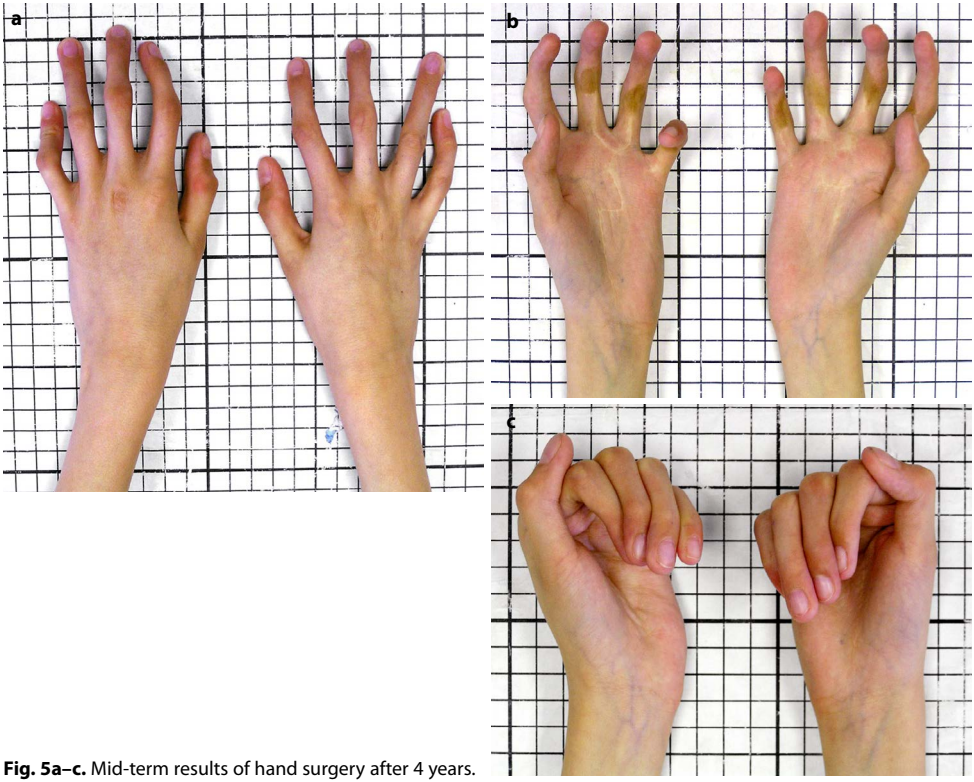


Fig. 5a–c. Mid-term results of hand surgery after 4 years.

At the age of 7 years (**Fig. 3**) the girl was tall (body height 130 cm – 90th percentile) with marked disproportion between trunk and limbs. Similar to Marfan syndrome, the shoulders were narrow and the pelvis was relatively wide, and arachnodactyly was present. However, during childhood before the onset of puberty, growth slowed slightly and the final height of 171 cm (72. percentile) is within the limits of hereditary growth potential. At the same time, during growth period, we observed a spontaneous alleviation of Marfanoid disproportions. (**Fig. 10c**). The age at menarche of 12.6 years was consistent with healthy peers. However, bone age appeared to be delayed by 0.5–1.5 years in the long term. Bone age assessment may have been biased (underestimated) by slender skeletal built, and thus the calculation of remaining growth was overestimated. Therefore, epiphyseodesis did not lead to the expected correction of the left knee valgosity.

At 23 years of age (**Fig. 8**), she reached a height of 171 cm, and a sitting height of 89.5 cm indicated relatively longer lower limbs, but within the norm. Arm span was 179.5 cm. BMI of 20.3 was normal for age.

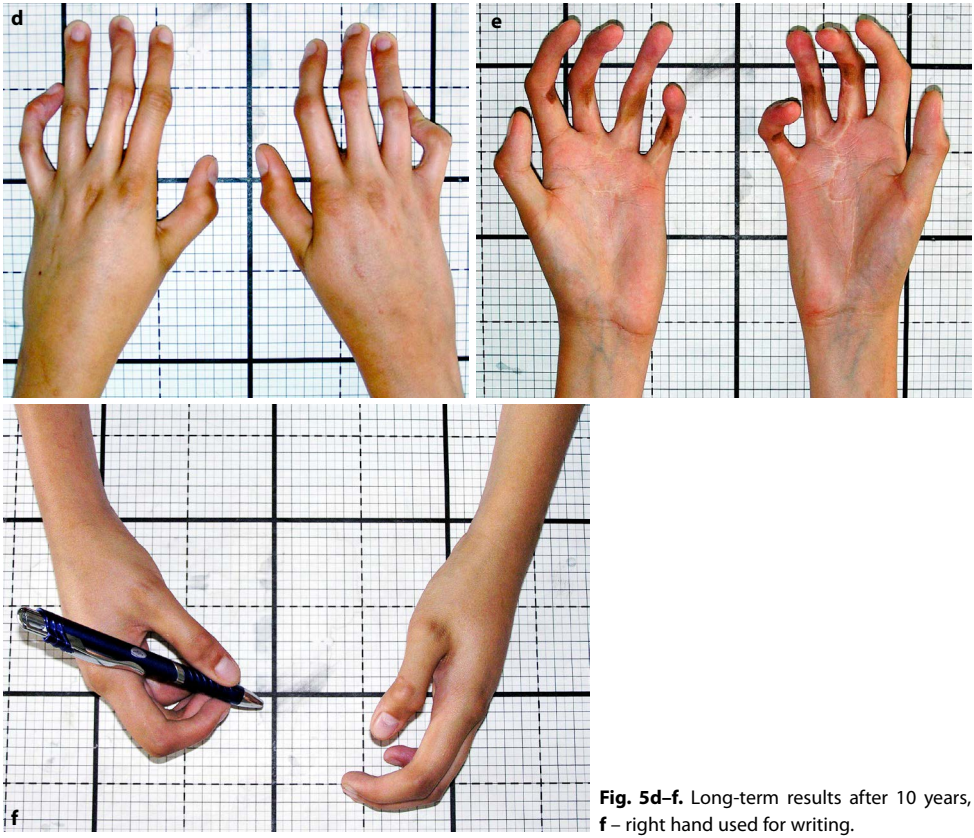


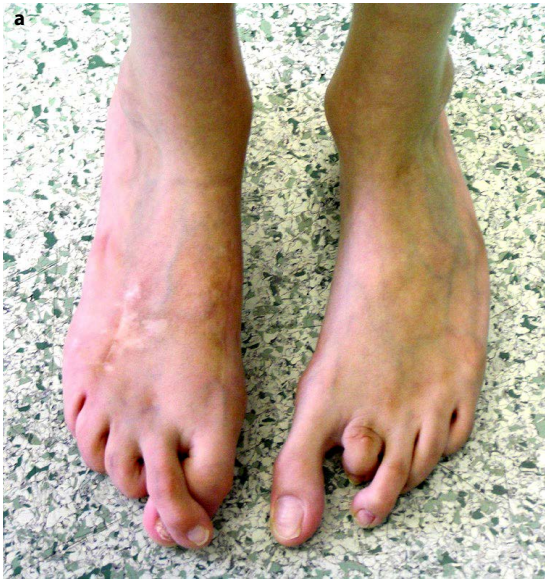
Fig. 5d–f. Long-term results after 10 years, **f** – right hand used for writing.

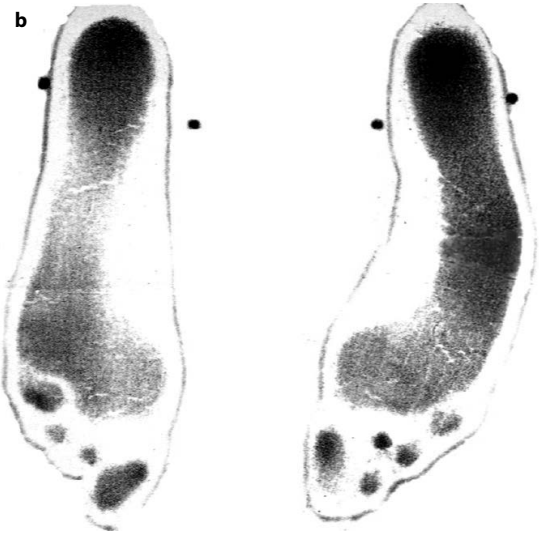
After the last surgery, the girl was followed by an orthopaedic surgeon for a year due to delayed healing of the osteotomy.

The typical phenotype and X-rays before and after the last surgery are documented in the images – see **Fig. 7d, 8a–c** and **Fig. 9a–d.**

Proband is still followed up by an orthopedic and plastic surgeon, a cardiologist (aortic root dilatation) and an osteologist on an outpatient basis. Rehabilitation is focused on static scoliosis of the spine due to a 3 cm shortening of the left lower limb. The correction of the lower limb discrepancy is solved with special shoe inserts.

Besides above mentioned skeletal abnormalities clinical-genetic examination at the age of 23.5 years revealed crumbled ears brachycephalic skull, backward running forehead, face (right eyebrow higher than the left one) and tip nose asymmetry (see **Fig. 8c, d),** teeth crowding and relatively short neck.





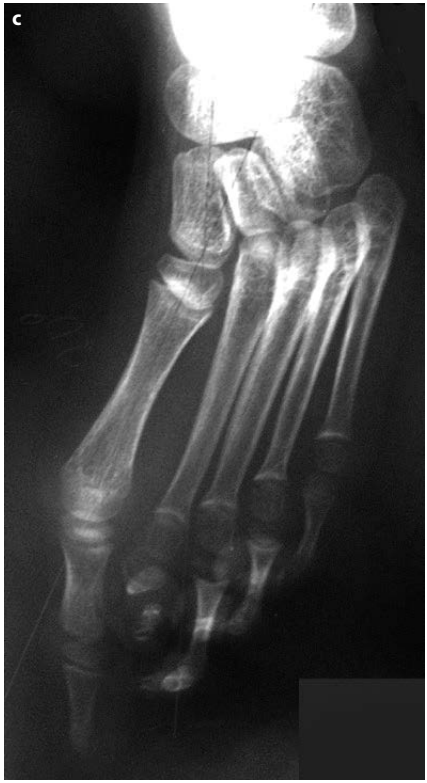


Fig. 6a–c. Foot deformities, podograms and radiographs: 7 years metatarsus varus l. sin. before surgery – 20 degrees of adduction of the forefoot, long and thin toes, hypermobile 2nd toe on the left foot. On the right foot, 2nd toe crossed big toe, which is in valgus position

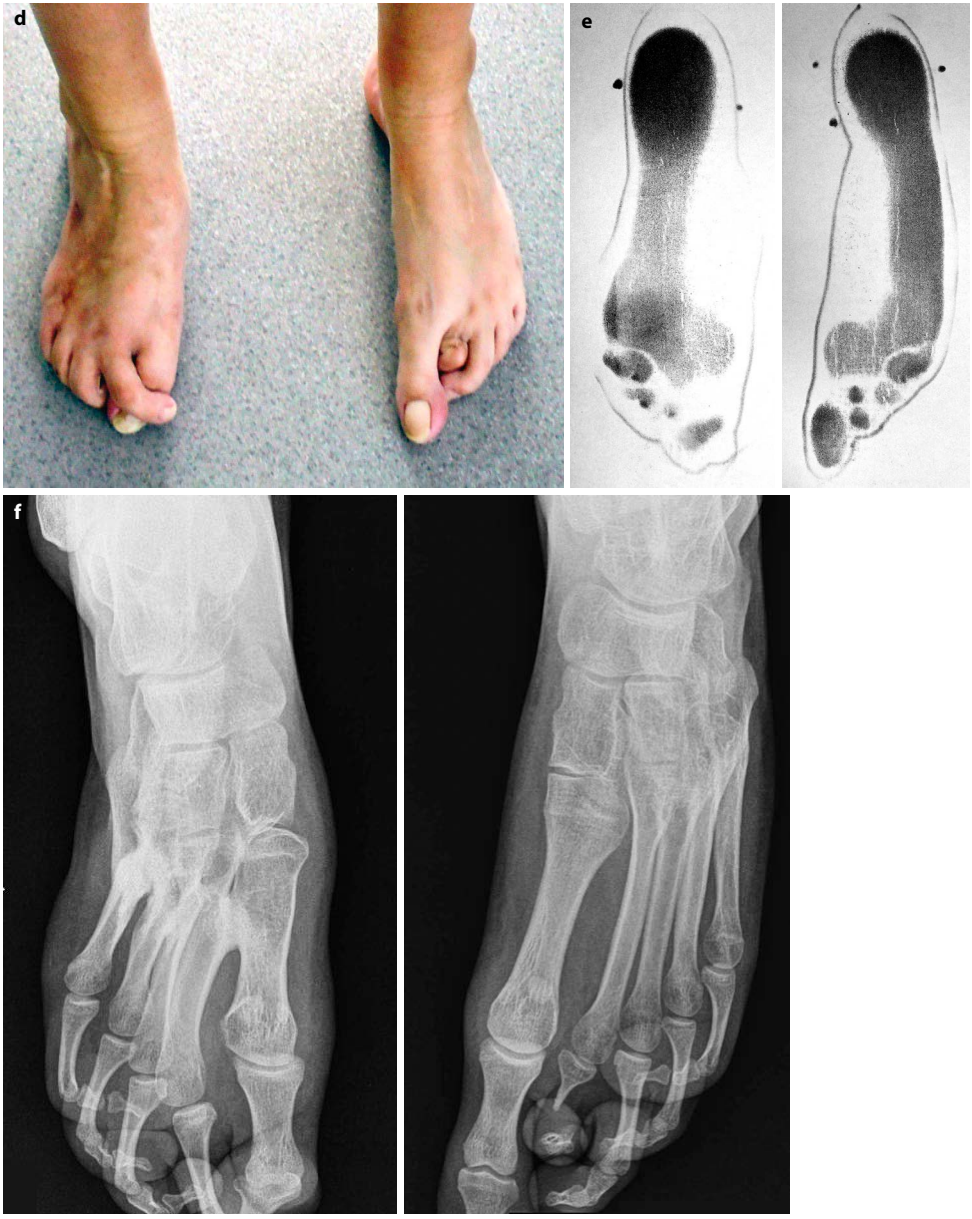


Fig. 6d–f. 17 yrs. Result of the surgery performed on the left foot after 10 years: **d**. deformity of the foot; **e**. podograms; **f**. radiographs after 7 years.

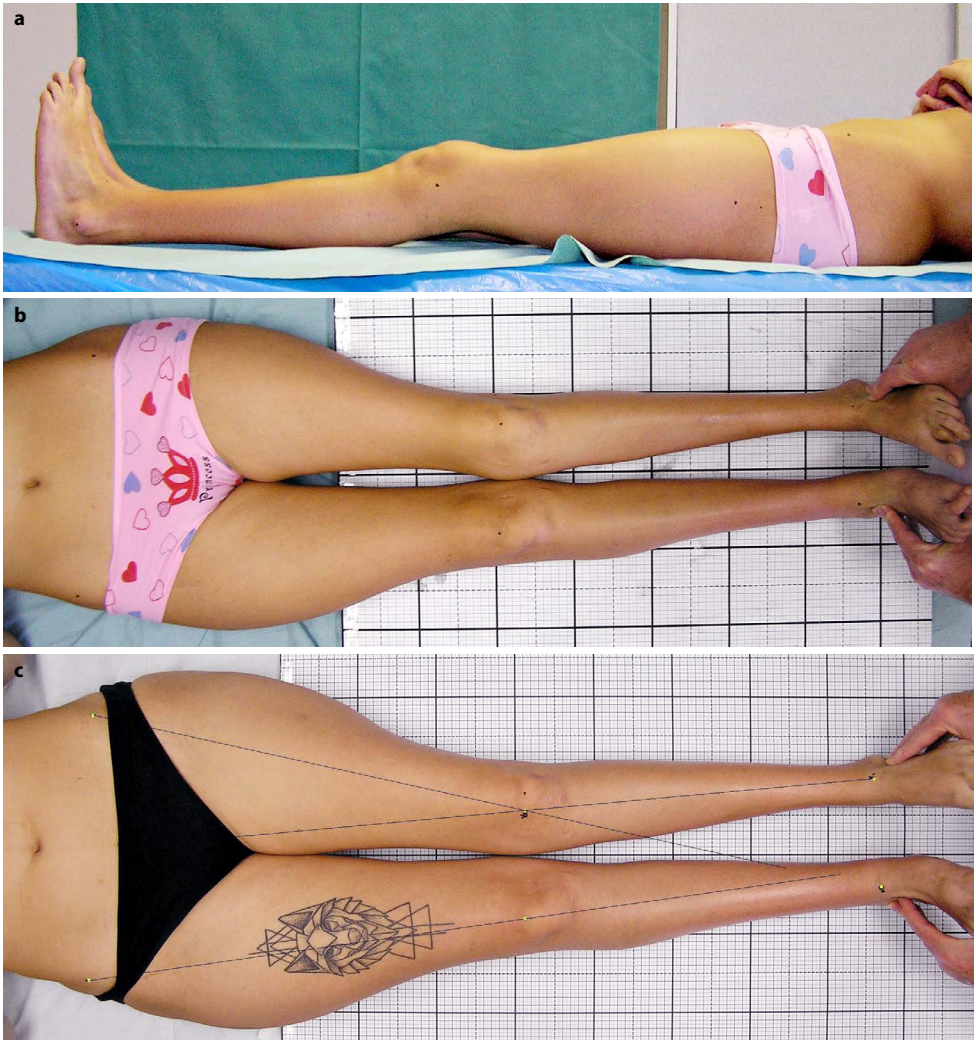


Fig. 7. 15.5 years. **a–c**. lower limbs supine: **a.** 10-degree flexion contracture of the knee and hip joints; **b.** 15.5 years and **c.** 23.5 years – valgus of the left knee around 15 degrees (inner ankle deviates from the vertical by 5 cm).

d

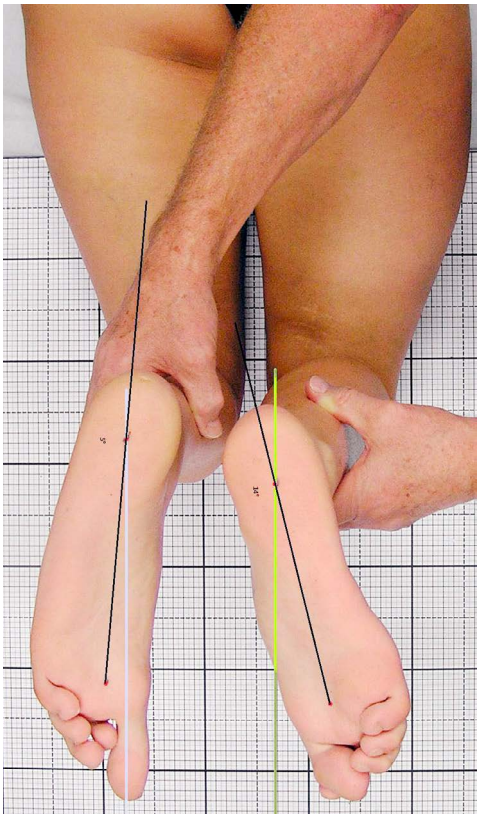


Fig. 7. 15.5 years. **d.** 23.5 years – less internal torsion of the left tibia.

Molecular genetic analysis

Recent *molecular genetic analysis* performed from patient's blood revealed pathogenic intronic variant c.3724+2T>C (rs863223570) of the *FBN2* gene (intron 28) in the heterozygous state. This mutation destroys the canonical splice donor site and is predicted to cause abnormal gene splicing. The mutation is predicted to lead to either an abnormal protein or no protein product. This mutation has already been reported in genetic databases as pathogenic variant **(6).** Genetic testing was performed by massive parallel sequencing using clinical exome panel followed by Sanger sequencing. Since pathogenic variants in the *FBN2* gene are associated with Beals-Hecht syndrome, we consider intronic variant c.3724+2T>C in *FBN2* gene in the heterozygous state as causal in our patient. The inheritance of identified mutation is autosomal dominant.

Subsequently, a bone tissue sample from the diaphysis of the tibia was tested using Sanger sequencing. The same pathogenic intronic variant c.3724+2T>C (rs863223570) in the *FBN2* gene was confirmed in a heterozygous state, as expected.

DISCUSSION

The main differential diagnosis is Marfan syndrome (MFS), namely its neonatal form. These disorders of the connective tissue share numerous common characteristics, such as a so-called marfanoid appearance constituted by tall, slender, asthenic appearance and skeletal features such as arachnodactyly, dolichostenomelia, pectus deformities, and kyphoscoliosis (**7, 9**). The overlap in the clinical features has a molecular basis; CCA and MFS result from mutations in two homologous genes, *FBN2* and *FBN1*, respectively (**9, 25, 22, 17**).

Fibrillins are large (350 kDa) cysteine-rich glycoproteins that assemble into beaded structures in the extracellular matrix (ECM) of connective tissues (**19**). These molecules play a key role in microfibril formation especially in elastic but also in non-elastic tissues (**20, 11, 22**).

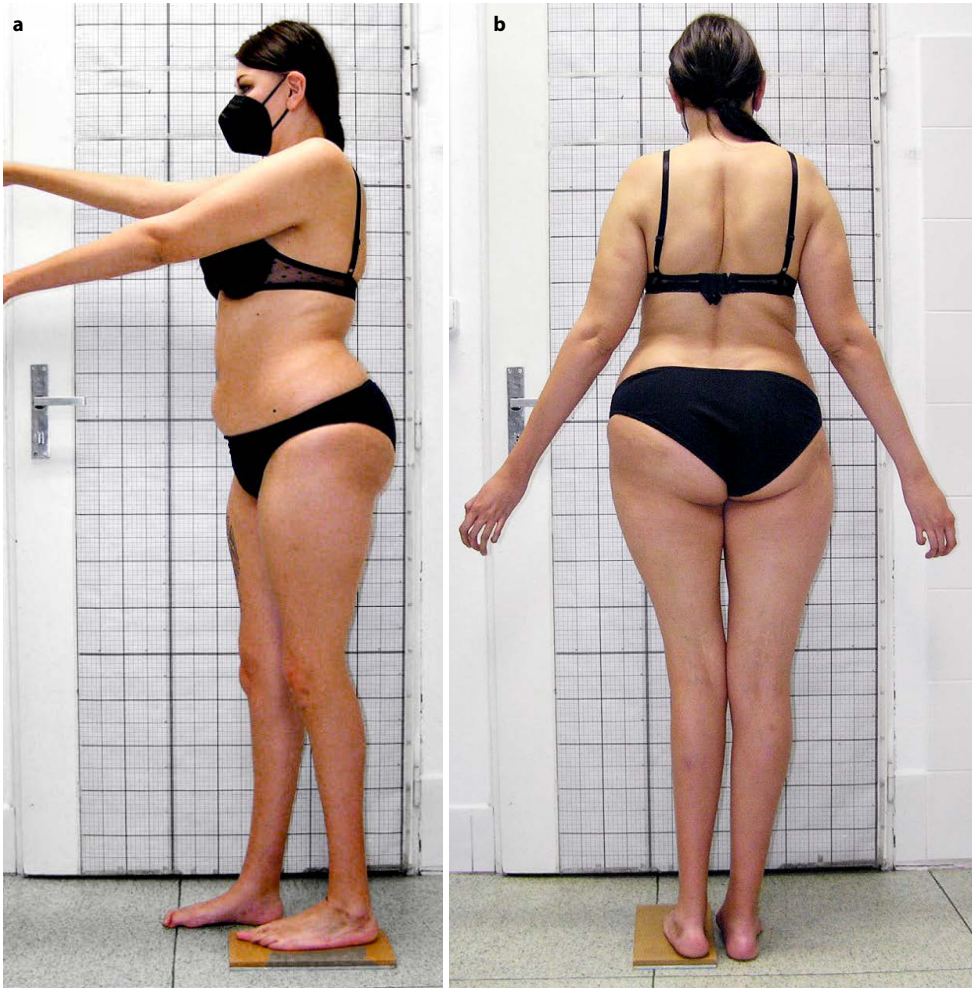


Fig. 8a–b. Phenotype before the last operation at 23.5 years: long upper and lower limbs; shortening of the left lower limb; lordoscoliosis of the lumbar spine; valgosity of the left knee; arachnodactyly; relatively shorter trunk; crumbled appearance of anthelix.

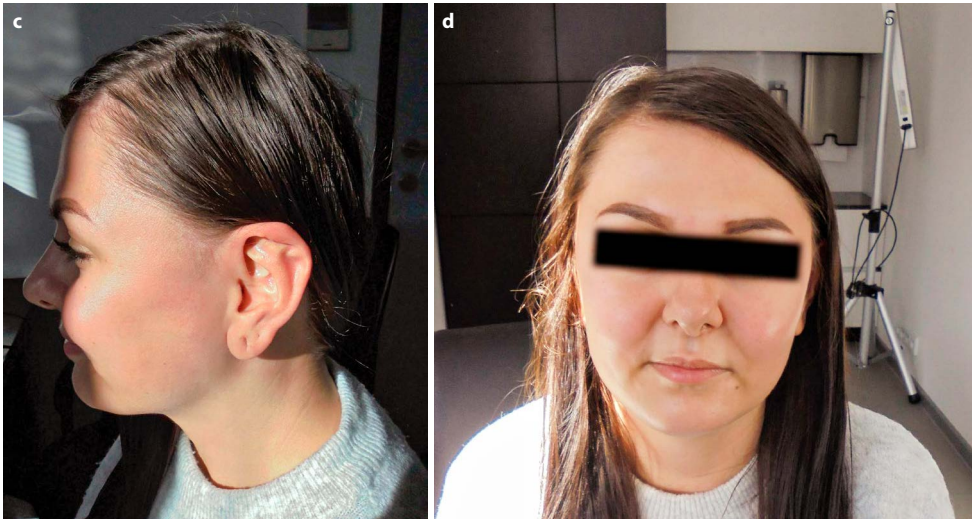


Figure 8c, d. c. crumbled anthelix of ear, backward running forehead; **d.** tip nose asymmetry, right eyebrow higher than the left one

Fibrillin microfibrils provide mechanical and functional support to human cells, tissues, and organs. In elastic tissues (lungs, blood vessels, skin, and ligaments) microfibrils serve as a scaffold for elastin deposition and modification during elastic fiber formation. In nonelastic tissues (ciliary zonule and cornea, tendon, perichondrium, and renal glomerulus) microfibrils provide tensile strength (**19**). Mutations affecting the structure, assembly and stability of FBN microfibrils have been associated with impaired biomechanical tissue properties (**20)**.

In addition to the structural role, equally important is the role of microfibrils in the control of cell signalling pathways through storage and activation of growth factors, including TGF-β, bone morphogenic proteins (BMPs), and growth differentiating factors (GDFs). Interacting with other components of ECM, fibrillin networks regulates bioavailability of growth factors, ECM formation, cell behaviour and the immune response, and thus play a crucial role in development and homeostasis of tissues, including bone (**12, 21, 19, 16, 15, 4, 20**)**.** Altered TGF-β signalling is a major contributor to the pathology of fibrillinopaties (**11, 18**). Schematic representation of the role of fibrillin in the regulation of the TGF-β signalling pathway is shown in **Figure 11**. Loeys-Dietz syndrome caused by mutations in the *TGFBR1/2, SMAD3, SMAD2, TGFB2* and *TGFB3* genes also exibits a Marfan-like phenotype (**15**).

The fibrillin proteins are encoded by three genes, that is, *FBN1* (chromosome 15q15-21.3), *FBN2* (chromosome 5q23-31), and *FBN3* (chromosome 19p13.3-13.2), and have a highly conserved domain architecture (**19**). Fibrillin 3 is the least important. It is absent in some mammals and is not known to be associated with any disease in humans. Fibrillin-1 and 2 are expressed in the developing and mature tissues in a spatial and temporal-specific manner. Already at the time of the discovery of fibrillin 2 gene, Zhang pointed to preferential accumulation of the gene product

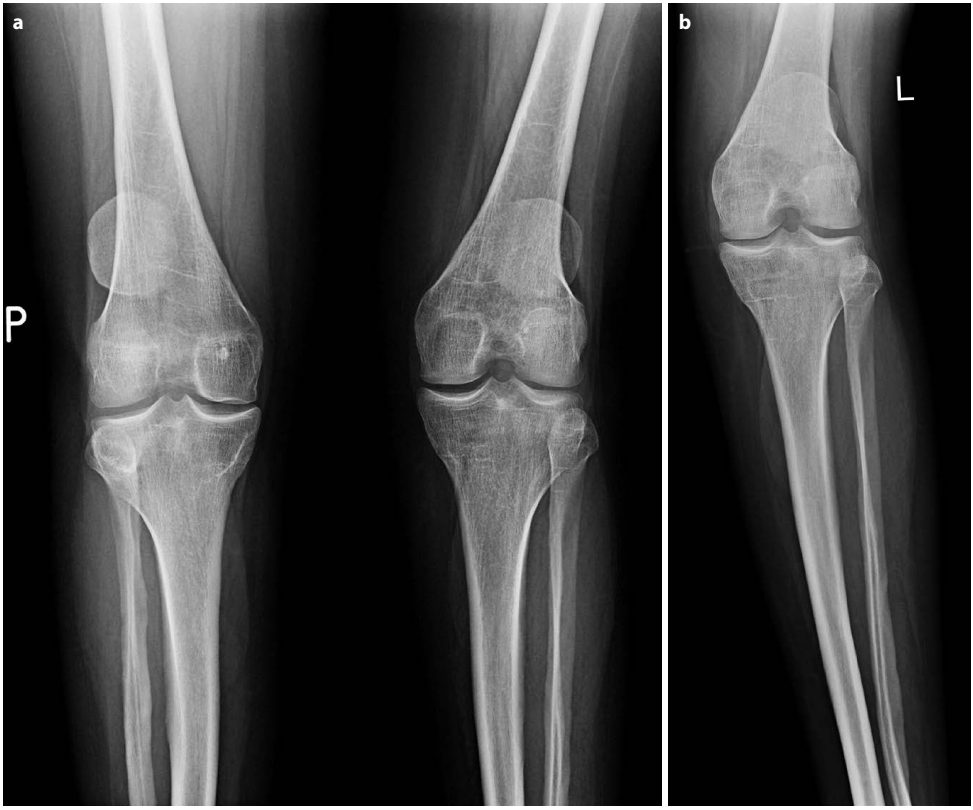


Fig. 9a, b. X-rays of the knee joints and left tibia at 17 years: valgus in the proximal 1/3 of the tibia;

in elastic fiber-rich matrices (**25**). Research in recent years has shown that FBN2 makes up the inner core of microfibrils which are surrounded by abundant fibrillin-1. Fibrillin 2 plays an important role in embryonic development, while fibrillin-1 provides the major structural force bearing support in many tissues and organs. Postnatally, fibrillin 2 synthesis is reduced and fibrillin1 expression dominates (**18, 16, 22**). Differential transcription of the fibrillin genes largely explains the differences in the clinical course of MFS and CCA. CCA manifests itself at birth, but during childhood the signs of the disease (with the exception of scoliosis) usually do not progress. Contractures tend to improve with time, and in our patient we have demonstrated a reduction in disproportion (**Fig. 10c**).

MFS-causing variants are spread across the *FBN1* gene, and the most severe „neonatal" forms are most often caused by variants between exons 25–33 encoding TB3-cbEGF18). Most CCA-causing variants cluster between exon 23 and exon 34 (cbEGF10–cbEGF20) of *FBN2* which roughly corresponds to the "neonatal" region of *FBN1* (**8, 11, 14**). However, pathological variants resulting in

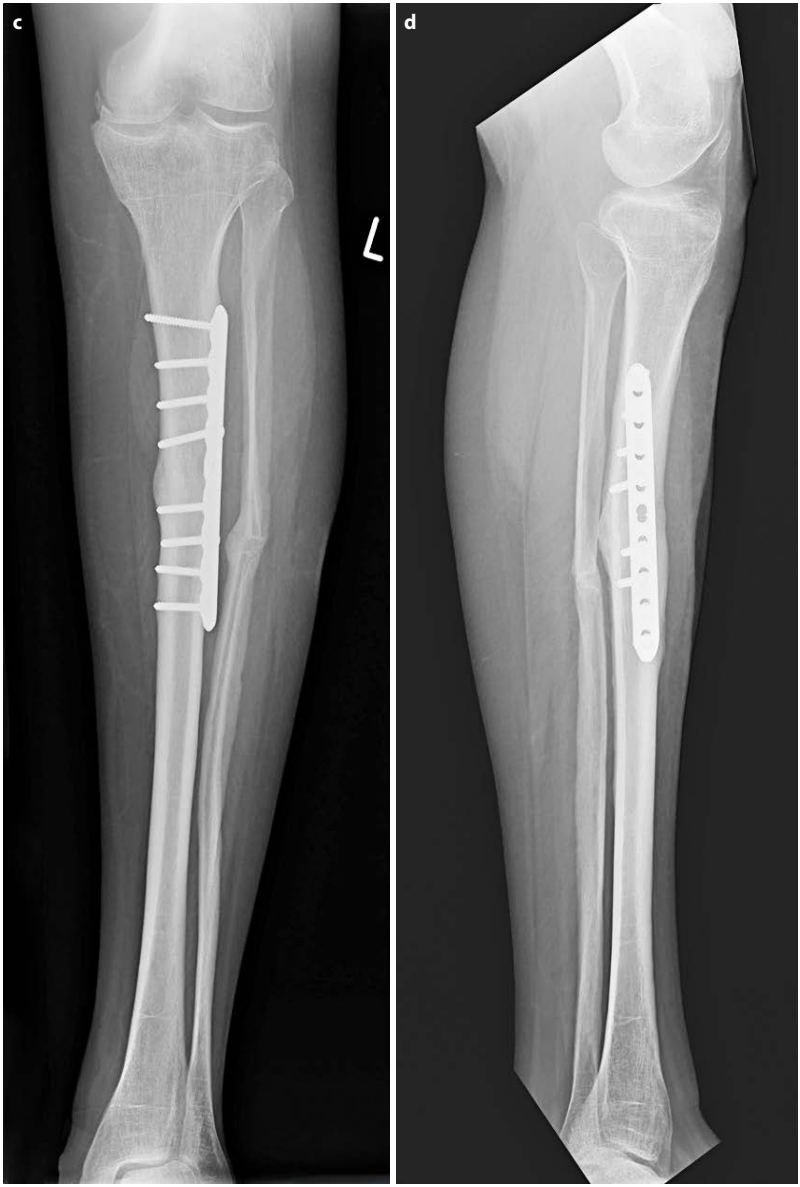


Fig. 9c, d. Result of wedge osteotomy and external rotation of the left tibia performed at 25 years (1 year after surgery). See good healing – remodeling of the tibial osteotomy and fibula and correction of the tibia in both the frontal and sagittal planes (where the goal was also correction of residual flexion contracture of the left knee joint at the tibial osteotomy site).

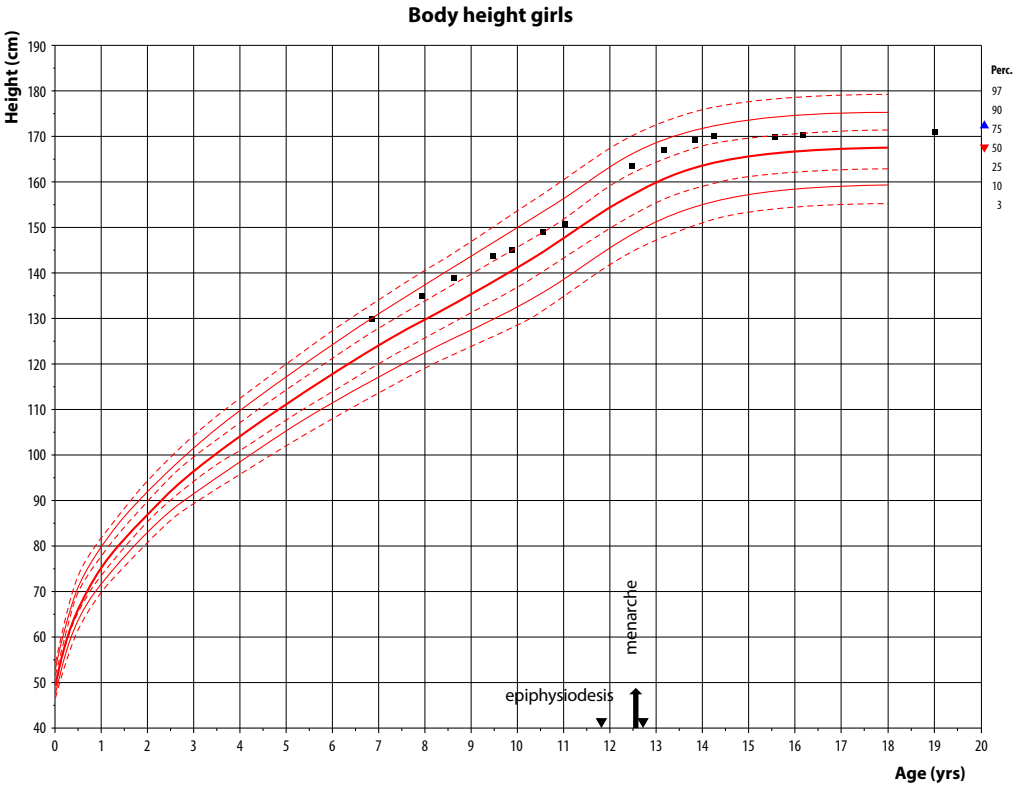


Fig. 10a. Growth curve.

haploinsufficiency of the gene or splice-site alterations and abnormal mRNA have been described, as in our patient (**19**).

Disturbed TGF-β signalling can also have the opposite phenotypic effect – short stature, brachydactyly, heart valve thickening. In case of fibrillin 1, this is geleophysic dysplasia, acromicric dysplasia, Weill-Marchesani syndrome and Stiff skin syndrome. Acromelic dysplasia is also known for fibrillin 2. Nearly all these "acromelic" variants cluster within the TB4-TB5 region (transforming growth factor beta binding-like domains). To date, the pathophysiological mechanisms underlying these contrasting clinical syndromes remain largely unknown (**19**).

It cannot be excluded that other variants of the fibrillin2 gene with different phenotypes will be found. While loss of fibrillin1 is lethal at birth, fibrillin2 null mice have syndactyly (**11**) and osteopenia (**18, 15**).

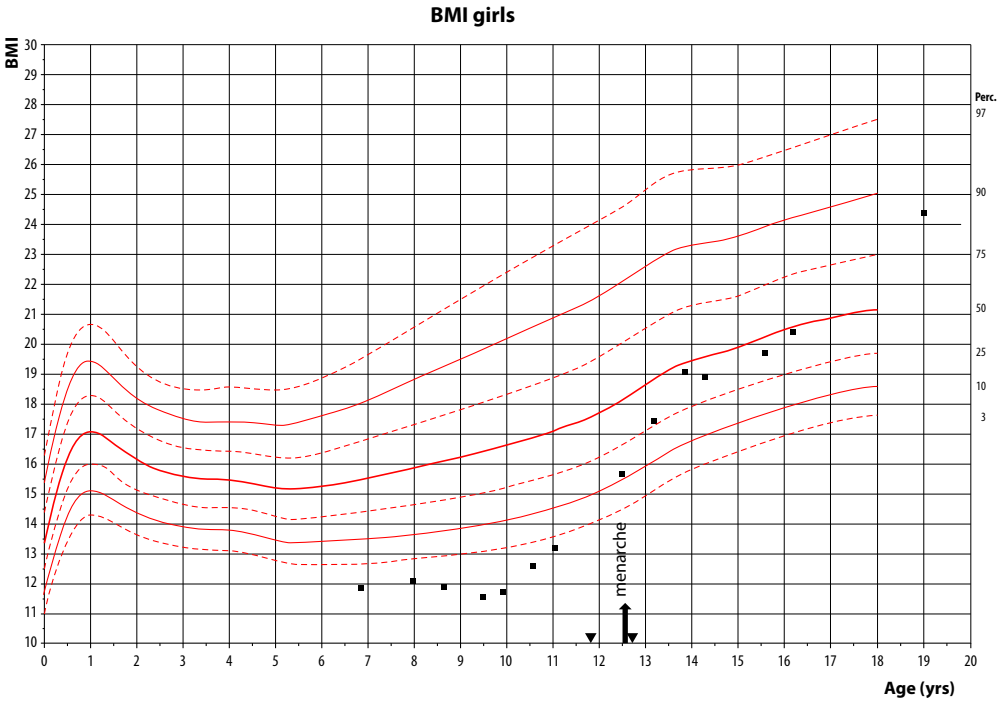


Fig. 10b. Developmet of BMI

Since the symptoms in CCA can be very variable and formal diagnostic criteria for CCA have not been established, molecular genetic testing plays a key role in differential diagnosis CCA, MFS and arthrogryposes.

CONCLUSION

The authors present the clinical, anthropological, radiological and molecular genetic findings of CCA (Beals-Hecht syndrome) in a proband followed from 3 years to adulthood and the results of orthopaedic (conservative and surgical) and complex rehabilitation treatment.

The diagnosis was made after birth on the basis of clinical and genetic examination. Associated diseases were excluded.

Recent molecular genetic analysis performed from the patient's blood and also from a bone tissue sample revealed the same pathogenic intronic variant c.3724+2T>C (rs863223570) in the *FBN2* gene in a heterozygous state, which is causative in our patient. The inheritance of the identified mutation

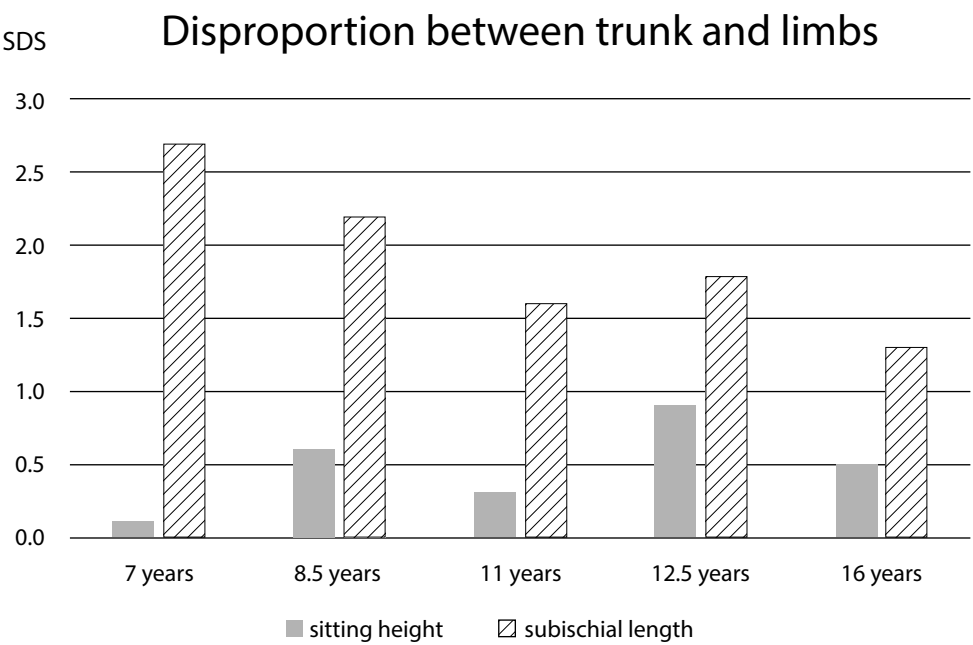


Fig. 10c. Morphogram showing the disproportion between trunk and limbs. Note the decreasing difference between SDS of sitting height and subischial leg length.

is autosomal dominant. Each child of our patient has a 50% chance of inheriting the *FBN2* pathogenic variant. Prenatal testing or preimplantation genetic testing of embryos is possible to prevent CCA in the patient's future offsprings. The decision to undergo this procedures is up to the patient and her partner based on genetic counselling.

The patient continues to be followed by an orthopaedic and plastic surgeon, cardiologist and osteologist. Although no complications related to pregnancy or delivery have been reported in women with CCA, cardiac surveillance during pregnancy is recommended. This case report adds to the clinical and molecular genetic knowledge of Beals-Hecht syndrome.

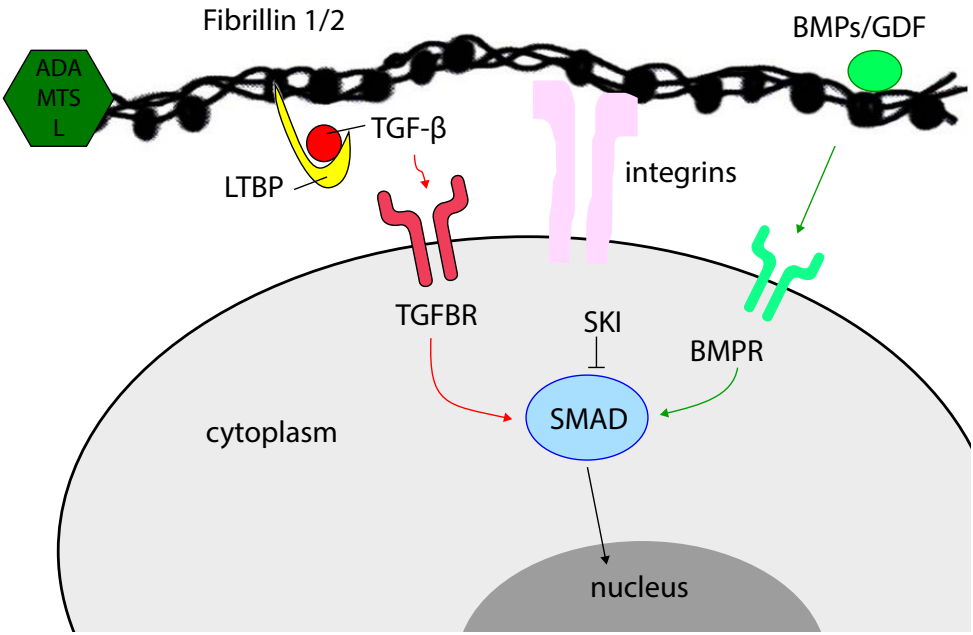


Fig. 11. Schematic figure representing growth factor sequestration by fibrilllin network. ADAMTSL – a disintegrin-like and metalloprotease with thrombospondin type 1 motif TGF-b transforming growth factor b, LTBP – latent TGF-β binding protein, BMPs – bone morphogenetic proteins, GDF – growth and differentiation factors, TGFBR – TGF-β receptor, BMPR – BMP receptor, SMAD – transcription factor, SKI – gene named after Sloan-Kettering Institute. Fibrillin network fragmentation leads to an uncontrolled TGF-β release (according to **20, 15**).

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INFORMACE O SPOLEČNOSTI PRO POJIVOVÉ TKÁNĚ ČLS J. E. PURKYNĚ (SPT)

Vážená paní kolegyně, vážený pane kolego,

dovolujeme si Vás informovat o možnosti stát se členem **Společnosti pro pojivové tkáně** (SPT), která v roce 2004 navázala na plodnou desetiletou činnost Společnosti pro výzkum a využití pojivových tkání vedenou panem prof. MUDr. M. Adamem, DrSc. Posláním SPT je podpora rozvoje výzkumu pojivových tkání, šíření nových poznatků týkajících se všestranných analýz tkání z obecného pohledu, moderních klinických přístupů k diagnostice a léčbě. Dalším posláním SPT je usnadnění styků mezi jednotlivými odborníky navázáním spolupráce s různými vědeckými, odbornými, výrobními a farmaceutickými společnostmi.

Vědecké poznání a aplikace nejnovějších poznatků v klinické praxi nabyly v posledních letech nebývalého zrychlení, a to nejenom v zahraničí, ale i u nás. Tato skutečnost bezprostředně souvisí s kvalitativním rozvojem poznání i v nebiologických vědách a v moderních inženýrských přístupech. Stále více se prokazuje, že vše se vším souvisí – není náhodou, že nové poznatky a objevy vznikají na rozhraní oborů a různých vědních disciplín. Lidská společnost v posledních desetiletích dosáhla nové civilizační kvality – ve vědě a v jejich aplikacích zcela jistě, avšak v morálce a etice ne tak příliš. Biomedicína je v současné době rozsáhlou interdisciplinární vědou, která bez kooperace s jinými vědními obory by byla odsouzena ke stagnaci. Proto cílem SPT je nejenom integrovat odborníky v biomedicíně, ale i v technických sférách.

Prioritní snahou SPT je presentovat odborné veřejnosti a specialistům v klinické praxi nejnovější poznatky v oblasti pojivových tkání. SPT je i společenskou organizací klinických pracovníků, vědců, pedagogů, která si klade za cíl společensky sblížit nejenom pracovníky v aktivní službě, ale i kolegyně a kolegy v důchodovém věku a v neposlední řadě i studenty a mladé doktorandy z vysokých škol, universit a akademických ústavů.

SPT organizuje během každého roku alespoň dvě odborná a společenská setkání, kde vedle odborných přínosů je kladen důraz také na společenské – přátelské diskuse všech vás, kteří nechtějí stagnovat a kteří nechtějí přemýšlet o nových poznatcích izolovaně a osamoceně.

Pro uhrazení nejzákladnějších nákladů na korespondenci se členy společnosti, jejich informovanost a pořádání odborných kolokvií, symposií a společenských odborných setkání byl stanoven **roční členský příspěvek pro aktivní kolegyně a kolegy 200 Kč** a **pro studenty a důchodce 100 Kč.**
SPT vydává časopis Pohybové ústrojí – pokroky ve výzkumu, diagnostice a terapii, do kterého se i vy můžete aktivně zapojit odbornými články a vašimi zkušenostmi. **Pro současné odběratele časopisu PU a další zájemce doporučujeme přihlásit se na http://www.pojivo.cz/en/newsletter/, zadat jméno a e-mailovou adresu, na kterou bude časopis posílán. Na webové doméně SPT ČLS JEP http://www.pojivo.cz/cz/pohybove-ustroji/ naleznete ve formátu PDF všechna jednotlivá čísla a dvojčísla časopisu (včetně Suplement) vydaná od roku 1997 (bezplatný přístup).**
Milí kolegové, nestůjte opodál a připojte se k české inteligenci – v oblasti pojivových tkání, ke které i Vy zcela jistě patříte. V naší krásné české zemi je třeba, aby prameny poznání byly stále živé a permanentně udržované. Poslání každého z nás není náhodné. Jsme velice zavázáni našim předkům, kteří rozvíjeli kvalitu odbornosti v naší zemi. Nepřipusťme útlum vědy u nás. Nenechme se zmanipulovat programovanou lhostejností, vyrůstající z neodbornosti, závisti a z patologického prosazování ekonomicko-mocenských zájmů.

Těšíme se na Vás a na Vaše zkušenosti – přijďte mezi nás!

Za výbor společnosti:

Prof. MUDr. Ivo Mařík, CSc. – předseda
Prof. MUDr. Josef Hyánek, DrSc. – čestný předseda
Prof. Ing. Miroslav Petrtýl, DrSc. – místopředseda
RNDr. Martin Braun, PhD – vědecký sekretář
Ing. Jana Zelenková – pokladník

Přihlášku do Společnosti pro pojivové tkáně ČLS JEP, z.s. najdete na adrese:
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INFORMATION ABOUT SOCIETY FOR CONNECTIVE TISSUES CMA J. E. PURKYNĚ (SCT)

Dear Sir/Madam, dear Colleagues,

We have great pleasure to inform you about the possibility of joining the **Society for Connective Tissues** (SCT) that was established in 2004 in order to continue the ten-year fruitful activities of the Society for Research and Use of Connective Tissue headed by Professor M. Adam, MD, DSc. The activities of the SCT are aimed at supporting the research development in the field of connective tissues, the dissemination of knowledge related to the all-purpose analyses of the tissues in general, and the application of the up-to-date approaches to the diagnostics and clinical practice. Further, the SCT is determined to facilitate contacts between the respective specialists by means of collaboration with various research, professional, production and pharmaceutical companies.

In the last few years, the scientific knowledge and the application of the latest findings in the clinical practice have accelerated on an unprecedented scale, not only abroad, but also in this country. This fact is closely connected with the qualitative development of the knowledge in the non-biological sciences and in the up-to-date engineering approaches. The fact that all things are mutually connected is becoming more and more evident. It is fairly obvious that the new knowledge and discoveries arise on the dividing line between the different fields and disciplines of science. In the last few decades, the human society has reached the new qualities of civilization. This applies, in particular, for the disciplines of science and their applications; however, this statement can hardly be used with reference to the moral and ethical aspects of the human lives. At present, the biomedical science is a wide-ranging interdisciplinary science which, in case of lack of cooperation with other scientific disciplines, would be condemned to stagnation. That is the reason why the SCT is aimed at integrating the specialists both within the biomedical science and within the engineering fields.

The priority objective of the SCT is to present the professional public and specialists involved in the clinical practice with the latest knowledge in the field of connective tissues. The SCT is also a civic society whose aim is to bring people close together by joining members of the clinical staff, researchers and teachers including the retired ex-colleagues and, last but not least, the undergraduates and PhD students from universities and academic establishments.

The SCT is planning to organize at least two professional and social meetings each year. Beside the professional contribution of these meetings, emphasis will be laid on social activities – informal

discussions of all those who do not want to stagnate and who do not want to acquire the new knowledge in solitary confinement.

The annual membership fee is 200 Czech crowns for full workers, and 100 Czech crowns for students and pensioners. This membership fee shall be used to cover the basic costs on correspondence with the members of the Society in order to inform them about organizing colloquiums, symposiums and social meetings.

The SCT is also engaged in publishing of the interdisciplinary journal entitled **Locomotor System – Advances in Research, Diagnostics and Therapy**. You are invited to contribute to the journal writing professional articles, exchanging experience or, simply sharing your opinions. You can find the volumes of Locomotor System journal at http://www.pojivo.cz/cz/pohybove-ustroji/ since 1997 (free of charge). Since 2013 only electronic edition of the journal is available. That is why we recommend to all subscribers and those interested apply at http://www.pojivo.cz/en/newsletter, enter personal data, titles and e-mail address where the journal will be mailed.

Dear Colleagues, do not stand aside (suffering from terrible lack of time) and join the professional people in the field of connective tissues to whom you undoubtedly belong. In this beautiful country, the sources of knowledge should be kept alive and maintained permanently. Our role in this process is not accidental. We are much obliged to our ancestors who had developed the qualities of proficiency in this country. Do not allow the decline of science. Do not let the programmed indifference arising from lack of professionalism, enviousness, and pathological promotion of economic and power interests manipulate us.

We are looking forward to meeting you. We will be pleased if you join us and share your experience with us.

On behalf of the committee of the Society for connective tissues:

Professor Ivo Marik, MD, PhD – chairman
Professor Josef Hyánek, MD, DSc – honorary chairman
Professor Miroslav Petrtýl, MSc, DSc – vice-chairman
Braun Martin, Dr, PhD – research secretary
Zelenková Jana, Eng – treasurer

Membership application form of the Society for Connective Tissues, Czech Medical Association J.E. Purkynje, Prague you can find on the following link:
http://www.pojivo.cz/cz/wp-content/uploads/2020/02/PrihlaskaCLS_JEP_SPT_form.pdf

Membership application form of the Orthopaedic-Prosthetic Society, Czech Medical Association J.E. Purkynje, Prague you can find on the following link:
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TÉMATIKA PŘÍSPĚVKŮ

K uveřejnění v časopise Pohybové ústrojí se přijímají rukopisy prací z oblasti pohybového ústrojí člověka, které se týkají především funkce, fyziologického i patologického stavu kosterního a svalového systému na všech úrovních poznání, diagnostických metod, ortopedických a traumatologických problémů, příslušné rehabilitace a léčebné i preventivní péče. Předmětem zájmu jsou týmové práce z oboru dětské ortopedie a osteologie, dále problémy z oboru biomechaniky, patobiomechaniky a bioreologie, biochemie a genetiky. Redakce časopisu má zájem publikovat články kvalitní, vysoké odborné úrovně, které přinášejí nové poznatky, jsou zajímavé z hlediska aplikací a nebyly doposud nikde uveřejněny s výjimkou publikace ve zkrácené formě.

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Rukopisy zasílejte na adresu:

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SUBJECT MATTER OF CONTRIBUTIONS

The journal Locomotor System will publish the papers from the field of locomotor apparatus of man which are above all concerned with the function, physiological and pathological state of the skeletal and muscular system on all levels of knowledge, diagnostic methods, orthopaedic and traumatologic problems, rehabilitation as well as the medical treatment and preventive care of skeletal diseases. The objects of interest are interdisciplinary papers on paediatric orthopaedics and osteology, further object of interest are problems of biomechanics, pathobiomechanics and biorheology, biochemistry and genetics. The journal will accept the original papers of high professional level which were not published elsewhere with exception of those which appeared in an abbreviated form.

The editorial board will also accept the review articles, case reports and abstracts of contributions presented at national and international meetings devoted largely to locomotor system. The papers published in the journal are excerpted in EMBASE / Excerpta Medica and Bibliographia medica Čechoslovaca.

MANUSCRIPT REQUIREMENTS

Manuscripts should be submitted in text editor Microsoft Word in format *.doc, docx or *.rtf. While no maximum length of contributions is prescribed, the authors are encouraged to write concisely. The first page of paper should be headed by the title followed by the name(s) of author(s) and his/her (their) affiliations. Furthermore, the address of the corresponding author should be indicated to receive correspondence and proofs for correction. Papers are reviewed by two (and/or three) reviewers.

The second page should contain a short Abstract(up to 250 words) followed by the key words (no more than 6). The proper text of original paper is laid out into introduction, material and methods, results, discussion and if need be acknowledgement. The reviews, discussions and news from conferences are without summaries and their lay-out depends on the character of communication. The paragraphs should not begin with any spaces from the left margin nor tabs and should contain at least four rows.

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Authors should supply illustrations and tables on separate sheets in the document. They should be numbered in the same order as is their desired location in the text. The figures should include the relevant details. Pictures should have resolution min. 150 dpi, drawings and graphs in bitmap resolution 600 dpi. They should be saved as tif or jpg format, tables and graphs in Microsoft Excel or as vector graphics in formats *.eps or *.pdf. Figure legends should be provided for all illustra-

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The references of books should contain the names and initials of the first three authors, with eventual supplement „et al.", title of book, number of edition, place of publishing, name of publisher, year of appearance and number of pages, for instance: Frost HM. The Laws of Bone Structure. 4. ed. Springfield: C.C.Thomas, 1964, 167 p.

The references of papers published in journals should be arranged as follows: the names and initials of the first three authors (eventually after the name of the third author introduce et al.), title of the paper, journal name or its abbreviation, year, volume, number and page numbers, for instance: Sobotka Z, Mařík I. Remodelation and Regeneration of Bone Tissue at Some Bone Dysplasias. Locomotor System 1995: 2, No.1:15–24.

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Manuscripts and contributions should be sent to the Editor-in-chief:

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