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Original Article

Bone deformities with hereditary multiple osteochondromas

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ABSTRACT

INTRODUCTION. Hereditary multiple osteochondromas (HMO) is a genetic skeletal disorder caused by defects in exostosin glycosyltransferase 1 (*EXT1*) or 2 (*EXT2*) genes. It develops mainly in the growth period and causes multiple osteochondromas (OC) in the physis of the long bones, leading to discomfort and deformities. This study aimed to investigate the anatomical distribution of OC, the frequency of deformities of the lower limbs, scoliosis and surgeries performed in a cohort of patients with HMO at the time of their enrolment in a regional surveillance programme.

METHODS. The study population included HMO patients from the Centre of Heritable and Complex Diseases (CAKS) in the Region of Southern Denmark. Information on surgical procedures and age at the time of diagnosis was obtained from medical records, while deformities were evaluated on early-onset scoliosis (EOS) scans from time of enrolment in the CAKS.
RESULTS. A total of 54 patients were included and 44 patients (82%) had an EOS scan. All except one (98%) HMO patient had OC in the knees at the time of their EOS scan. A total of 12 patients (27%) had leg length discrepancy, 30 (68%) had genu varum or valgum and 13 (30%) had scoliosis. The HMO patients had undergone a median of 2.0 (0-14) surgeries, where a median of four (1-23) OC were removed, mostly in the lower limb (68%).

CONCLUSIONS. The majority of HMO patients in this cohort suffered from major anatomical burdens, leading to multiple surgeries and deformities. We suggest that a programme, such as the CAKS surveillance programme, may be beneficial to screening and follow-up of OC and deformities in patients with HMO.

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Osteochondromas (OC) are common and benign cartilage-capped bone tumours [1]. They are often singular but can be multiple in genetic disorders [1, 2]. Hereditary multiple osteochondromas (HMO) is a genetic skeletal disorder characterised by multiple tumours that develop mainly in the physis of the long bones in the limbs, but also in the ribs, clavicula and pelvis [2-4]. Tumour growth starts after birth and continues to bone maturity at the end of puberty [3, 5].

HMO is mainly hereditary with autosomal dominant expression and caused by heterozygous variation in one of the two genes coding exostosin glycosyltransferase 1 (*EXT1*) or 2 (*EXT2*). However, approximately 10-20% of the cases appear as a de novo modification [3, 6]. The severity of HMO varies widely, with the *EXT1* reported to manifest more severely [4, 7]. Manifestations include pain, limb deformities, leg length discrepancy (LLD) and scoliosis, etc. [5, 8-10]. Treatment of HMO tends to be conservative, and surgical removal is recommended only in cases of severe symptoms, deformities or malignancy [3, 11].

Previous studies have reported various deformities in the spine and lower limbs, but – to our knowledge – no studies have described in detail the frequency of these deformities, including scoliosis [5, 8, 9]. Furthermore, no previous papers have used surveillance programmes for HMO. This study aimed to investigate the anatomical distribution of OC, frequency of lower limb deformities, scoliosis and surgeries performed in a cohort of patients with HMO at the time of their enrolment in a regional surveillance programme.

Methods

This was a retrospective cohort study based on data from patients diagnosed with HMO who were enrolled in the regional surveillance programme run by the Centre of Heritable and Complex Diseases (CAKS) at Odense University Hospital (OUH) in the Region of Southern Denmark (RSD).

The HMO programme is based on guidelines from the Danish Society of Medical Genetics and the Danish Sarcoma Group [12, 13]. Since 2019, CAKS has continuously offered enrolment to patients from the CAKS who meet the criteria of the HMO programme, including the diagnosis International Classification of Diseases, Tenth Revision (ICD-10) code Q78.6, Online Mendelian Inheritance in Man (OMIM) codes for *EXT1 608177,* 133700 (disease) and *EXT2 608210,* 133701 (disease) and/or Orpha codes 321. Upon inclusion, all patients underwent a full-body low-dose 2D CT (EOS imaging scan) and were offered genetic testing.

The study population included all patients registered with HMO in the CAKS database before 12 May 2022. Patient identification numbers, sex, age at inclusion, genotype and family history of HMO were obtained from the database. Data on age at diagnosis and surgical procedures were obtained from all available medical records, including electronic, handwritten and scanned records. The time of diagnosis was defined as the first time the medical records noted that the multiple OC were hereditary. We registered surgical procedures performed due to HMO (excisions and bone deformity corrections) from the date of birth to 12 May 2022.

The anteroposterior EOS scans were reviewed, and involved areas with OC in the lower limbs and scoliosis were registered. The software TraumaCad was used to review the EOS scans and measure angular deformities. The VNA SYD software was used for measuring LLD. Deformities were analysed by measuring the LLD and the mechanical axis of the lower limbs [14].

LLD was defined as a discrepancy of 10 mm or more compared with the contralateral side. Mechanical axis deviation was defined according to Paley [15]. Additionally, we measured the anatomical lateral distal femoral angle, the anatomical medial proximal tibia angle, the anatomical lateral distal tibia angle and the mechanical tibio-femoral axis for each side [15, 16]. Scoliosis was measured by Cobb's method [14]. Only EOS scans with a spine angular deformity exceeding ten degrees that were not caused by LLD were defined as scoliosis. All measurements were made in conformity with international recommendations and compared with standard values [14-16]. Two students and two highly experienced bone deformity surgeons made all measurements and reached a consensus on each measurement. The students were carefully instructed before the measurements were made. The patient data were analysed in four groups according to genetic mutation: *EXT1, EXT2, PNTP11* or unknown. The parents, children and siblings of a genetically tested person were assumed to have the same genetic mutation. All statistical analyses were performed using STATA. All categorical and ordinal variables are presented as numbers with percentages of the total in brackets. None of the analysed continuous variables were normally distributed. As a result, all continuous variables are presented as medians followed by actual complete ranges (lowest and highest value) in brackets. No continuous variables showed normal distribution following log-transformation. Therefore, the non-parametric Kruskal-Wallis test was performed to compare continuous variables between genotypes. Comparison of categorical and ordinal variables between genotypes was done by Fisher's exact test due to a low number of frequencies. Statistical significance was defined as $p < 0.05$.

The study was approved via the CAKS. The dataset is available upon reasonable request.

Trial registration: not relevant.

Results

We identified 55 patients in the database. One patient was only registered due to family history and was therefore excluded from the study. Thus, the study population comprised 54 patients and included 11 families with a total of 35 members (**Table 1**). Among the 54 patients, 28 (51%) were male, and the median age at diagnosis was 13.5 years (1-69 years). A genotype was available for 42 patients (78%).

TABLE 1 Age at diagnosis, age at inclusion, gender, probands and family information, stratified by genotype.

	Genotype				
	EXT1	**EXT2**	**PTPN11**	**unknown**	**all**
n	16	24	2	12	54
Age, median (range), yrs					
At diagnosis	14.5 (4-69)	11 (1-64)	7 (2-12)	12 (1-51)	13.5 (1-69)
At inclusion in the CAKS	52 (15-73)	24.5 (1-78)	17.5 (2-33)	23.5 (6-57)	26.5 (1-78)
Men/women, n	6/10	13/11	1/1	8/4	28/26
Probands, n	8	1	0	10	19
Families/of members, n	3/8	6/23	1/2	1/2	11/35

CAKS = Centre of Heritable and Complex Diseases.

The median follow-up time was 28 years (2-79 years). The 54 patients had 282 OCs surgically removed, the median being 4.0 (0-23) per patient, and the median number of surgeries with excisions was 2.0 (0-14) (**Table 2**). A total of 14 patients underwent other types of surgical procedures, such as angular corrections, bone lengthening or surgeries due to osteoarthritis. The median number of surgeries performed was 2.5 (0-17) per patient.

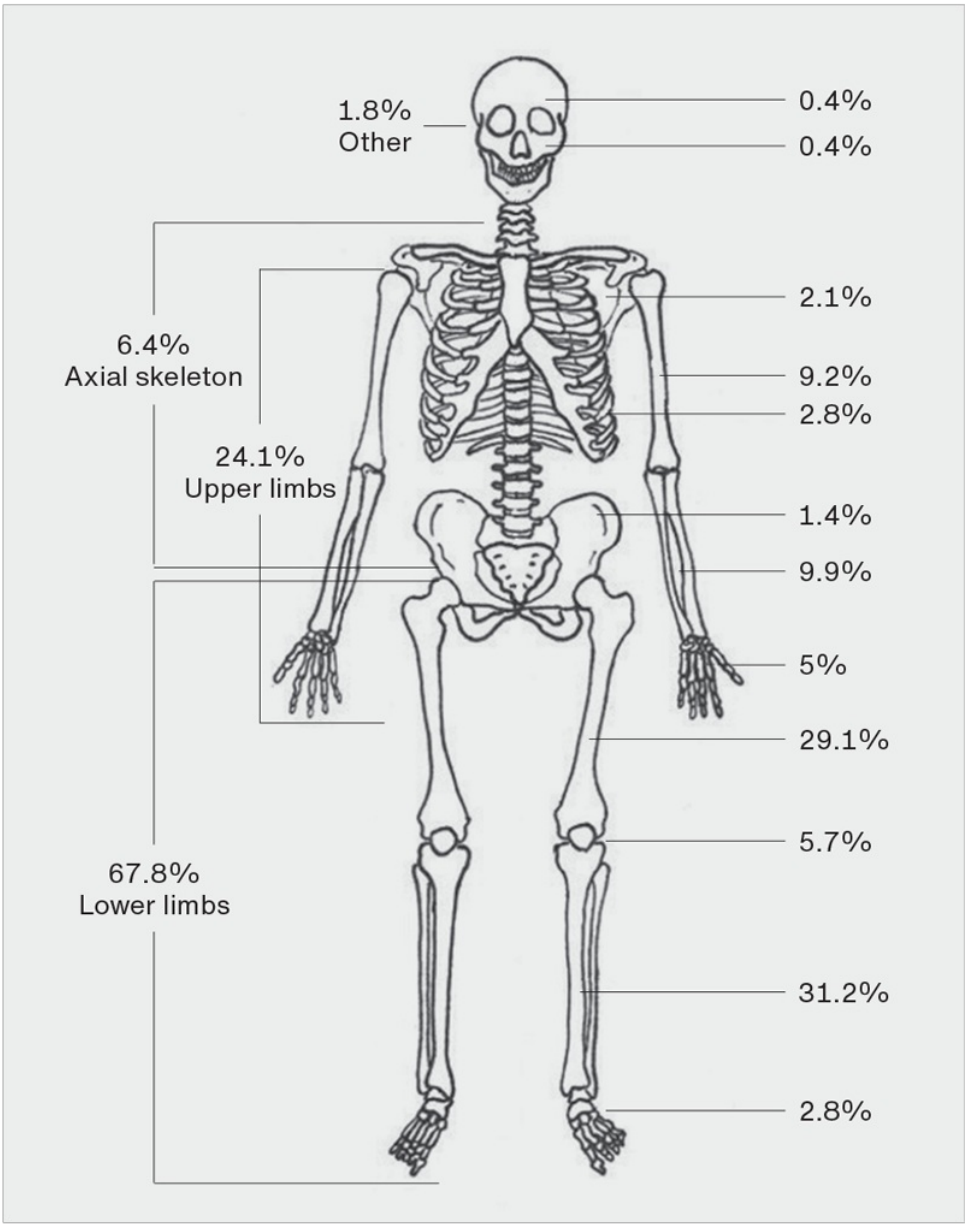
TABLE 2 The median number of surgically removed osteochondromas per patient, the median number of surgeries with excision of osteochondromas per patient, the median number of total surgeries per patient and the location of surgically excised osteochondromas, stratified by genotype of hereditary multiple osteochondroma (HMO).

	Genotype				
	EXT1 (N_1 = 16)	EXT2 (N_2 = 24)	PTPN11 (N_{11} = 2)	unknown (N_u = 12)	p value
Surgery, median (range), n/person					
Excised osteochondromas	3.0 (0-23)	4.0 (0-21)	2.5 (0-5)	3.5 (0-16)	0.748[a]
Surgeries with excisions	2.5 (0-14)	2.0 (0-10)	1.5 (0-3)	2.5 (0-11)	0.751[a]
All surgeries due to HMO	3.0 (0-15)	2.0 (0-10)	1.5 (0-3)	2.5 (0-17)	0.762[a]
Location of surgically excised osteochondromas, n					
Upper limbs:					0.083[b]
Humerus	11	10	0	5	
Antebrachium	10	12	2	4	
Fingers	5	5	1	3	
Subtotal	26	27	3	12	
Axial skeleton:					0.075[b]
Scapula	4	2	0	0	
Costa	2	1	0	5	
Pelvis	3	0	0	1	
Subtotal	9	3	0	6	
Lower limbs in total:					0.010[b]
Femur	24	44	0	14	
Tibia/fibula	25	43	0	20	
Foot	3	2	0	1	
Unknown	4	5	0	4	
Subtotal	56	96	0	39	
Other[c], n	1	2	0	2	1.000[b]
Total	92	126	5	59	

a) Kruskal-Wallis test.
b) Fisher's exact test.
c) Maxillaris dxt., orbita dxt., unknown location.

A total of 191 OC were surgically excised from the lower limbs, corresponding to 68% of all excised OC (**Figure 1** and Table 2). Only 68 (24%) OC were excised from the upper limbs, 18 (6.3%) from the axial skeleton and five (1.8%) from other parts of the skeleton. We found that 84% of the excised OC were in the long bones, with the highest proportions being located to the lower leg (31%), the femur (29%) and the forearm (9.9%).

FIGURE 1 Percentage distribution of surgically excised osteochondromas in segments (left side) and anatomical location (right side) (n = 54).



Overall, 44 out of 54 patients (82%) had EOS scans available. Among the 44 patients, 43 (98%) had OC in the proximal crus, 41 (93%) in the distal crus, 39 (89%) in the distal femur and 38 (86%) in the proximal femur (**Table 3**). Most had bilateral involvement in the lower limb. We found a significant difference in the frequency of OC in the proximal femur between genotypes, with the highest proportion being recorded in the *EXT2* group and the lowest in *EXT1* group (p = 0.025). LLD was identified in 12 (27%) patients, with a median discrepancy of 13 mm (11-26 mm) (Table 3). Genu varum was seen in seven (16%) patients (six patients unilaterally), with a median lateral deviation from the mechanical axis of 17.5 mm (15-42 mm). Genu valgum was seen in 23 (52%) patients, with a median medial deviation from the mechanical axis of 19 mm (10-48 mm).

TABLE 3 Locations of segmental involvement, leg length discrepancy and genu valgum/varum, due to deviation of the mechanical axis, abnormal anatomic angles in the lower limbs and scoliosis, stratified by genotype of hereditary multiple osteochondroma.

	Genotype				
	EXT1 (N_1 = 15)	EXT2 (N_2 = 19)	PTPN11 (N_{11} = 1)	unknown (N_u = 9)	p value
Anatomical involvement, uni-/bilateral, n					
Proximal femur	1/14	4/11	0/0	1/7	0.025[a]
Distal femur	1/12	3/14	0/0	0/9	0.220[a]
Proximal crus	1/14	2/17	0/0	0/9	0.056[a]
Distal crus	2/13	6/12	0/0	2/6	0.041[a]
Deformities					
Leg length discrepancy:					
n (%)	4 (27)	5 (26)	0	3 (33)	0.751[a]
Median (range), mm	12 (11-13)	16 (14-26)	-	13 (12-23)	0.151[b]
Genu varum, uni-/bilateral, n	0/0	4/1	0/0	2/0	0.832[a]
Genu valgum, uni-/bilateral, n	7/4	5/0	1/0	4/2	0.339[a]
Abnormal aLDFA:					
Uni-/bilateral, n	7/5	5/12	1/0	5/3	0.682[a]
Median (range), °	85 (77-94)	86 (79-94)	85	86 (78-90)	0.145[b]
Abnormal aMPTA:					
Uni-/bilateral, n	5/1	5/1	0/0	3/2	0.988[a]
Median (range), °	92 (82-93)	91 (80-92)	-	92 (83-96)	0.938[b]
Abnormal aLDTA:					
Uni-/bilateral, n	8/7	8/10	1/0	5/3	0.978[a]
Median (range), °	81 (55-85)	80.5 (68-8)	85	81 (77-96)	0.807[b]
Scoliosis: > 10°:					
Patients, n (%)	5 (33)	4 (21)	0	4 (44)	0.983[a]
Median (range), °	15 (10-30)	13.5 (11-18)	0	12 (11-15)	0.572[b]

aLDFA = anatomical lateral distal femoral angle; aLDTA = anatomical lateral distal tibia angle; aMPTA = anatomical medial proximal tibia angle.
a) Fisher's exact test.
b) Kruskal-Wallis test.

Scoliosis was verified on the EOS scan in 13 (30%) patients, with a median Cobb's angle of 13° (11-30°). Angular deformity of the distal femur was seen in 38 (86%) patients, of the proximal tibia in 17 (39%) patients and of the distal tibia in 42 (95%) patients (Table 3).

Discussion

This study assessed the occurrence of OC, deformities of the lower limb and scoliosis at the time of their enrolment in a regional HMO surveillance programme. Furthermore, the study described the burden of surgeries in the HMO patients registered in available medical records. The clinical expression of HMO varied

between patients.

Among 44 patients with EOS scans, this study showed that 89% of the patients had OC involvement in the distal femur, 98% in the proximal crus and 98% in the knees. Due to the difficulty in distinguishing between OC in the tibia and fibula, caused by synostosis, this study examined OC on the crus as a single unit. However, our findings correlate well with those of Schmale et al., who found OC involvement in 70% of patients at the distal femur, 71% at the proximal tibia and 27% at the proximal fibula; i.e., approximately 94% of patients had OC at least one of the three locations involving the knee [8]. OC can lead to severe symptoms and growth disturbances that result in LLD and bone deformities [4, 6, 11]. Several patients had undergone surgery during their childhood and/or adolescence, 27% of 44 patients with EOS scans had LLD and 52% had genu valgum. The LLDs resulted from a discrepancy in the length of the femur and/or the tibia. Schmale et al. found LLD in only 10% of their patients by measuring during a physical examination, which is different to our study. Still, some of their samples were identified through family history, thus including milder cases [8]. In our study, valgus deformities were found in the ankles in 93% and in the proximal crus of 30%, whereas varum deformities were found in the distal femur in 80% of the patients. These proportions were higher than in the study by Schmale et al., where 2% had ankle deformities and 8% had knee deformities [8]. These overall findings reflect the OC locations in the lower limb and highlight the effect HMO has on bone growth. In our study, previous surgery might have produced the lower severity and number of bone deformities.

This study found that 30% of patients with HMO had scoliosis, reflecting that HMO affects more than the long bones. Unfortunately, we have no reliable radiological information to conclude whether the scoliosis was due to OC in spinal bone. Matsumoto et al. reported a much higher proportion (72%), with scoliosis possibly indicating more severe HMO in their study [9]. In our study, the frequency of genu valgum and scoliosis tended towards higher values in the *EXT1* group than in the *EXT2* group, although this was not statistically significant.

The PTPN11 genotype is a loss-of-function variant that leads to OC [17]. In this study, while statistically insignificant, the two patients with PTPN11 had the lowest number of surgeries performed and the lowest number of OCs removed. Except for two abnormal angles, no bone deformities were found, indicating a minor HMO burden in the PTPN11 group. As described, these findings were not statistically significant, which may be due to the limited sample size. A larger study population may confirm whether the PTPN11 phenotype is milder as far as disease burden is concerned.

The median number of excised OC was slightly higher for patients with the *EXT2* than the *EXT1*. Still, the range of excised OC and median number of surgeries was higher in the *EXT1* group, but neither was statistically significant. This suggests that these genotypes are associated with similar severity of symptoms and a considerable individual variability. Patients had a median of four excised OC, mostly from the femur and crus. Wicklund et al. similarly reported a mean of 3.5 excised OC with the most frequent locations being the femur, tibia and humerus [5]. However, in our study, not all medical records could be found in the databases, and thereby, some surgeries were not registered, which may indicate an even larger number. We have no reliable information on the scope of this bias.

Some of the medical records of patients included in this study indicated an unknown number of relatives with multiple OC who were not included in the CAKS database. We did not investigate whether CAKS had identified all patients with HMO in the RSD. However, the national prevalence of HMO (approximately 1-2 per 50,000 inhabitants) aligns with the current findings, as the RSD had 1,228,362 citizens in 2022, corresponding to 25-49 patients with HMO [13, 18]. The prevalence of HMO in Denmark might be underestimated due to a lack of knowledge about HMO, family history or patients with mild or no symptoms. Schmale et al. found that approximately 10% of patients had no family history of HMO, which could contribute to an underestimation of the prevalence [8].

The strength of the present study was the limited recall bias owing to the collection of data from medical records going back to birth. The CAKS programme ensured systematic evaluation and continual follow-up of the development of HMO, providing a solid database for this and future studies.

Study limitations include the missing EOS scans in the database and any missing data in the medical records of some patients. The medical records contained old handwritten records that were difficult to read, some records omitted surgical data, and we had limited access to data for the limited number of patients from other regions. The follow-up varied due to age differences. For younger patients, we believe that data regarding surgery are reliable. However, information may be missing in elderly patients. Furthermore, we found that some patients' follow-ups were erroneously terminated, resulting in missing consultations for a few years. We did simple statistical analyses across the different genotypes. Almost all analyses were non-significant. We believe that the low statistical power caused by the small number of patients caused the recorded lack of statistical significance. A larger sample size would potentially have enabled us to investigate the impact of different genes and to compare the severity of symptoms and the number of OC.

The CAKS surveillance programme aims to collect information on HMO cases to ensure that patients receive the most appropriate treatment and thus attain their highest possible level of functioning [10-12]. This requires complete information; and although the guidelines require an EOS scan at inclusion into the CAKS database, this was occasionally lacking and needs improvement.

We found that an overwhelming majority of patients with HMO had major anatomical changes that required multiple surgeries. We believe that a national surveillance programme targeting patients with HMO should be initiated to ensure proper follow-up and treatment.

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REFERENCES

1. Fletcher CDM, Unni KK, Mertens F, eds. World Health Organization Classification of Tumours. Pathology and genetics of tumours of soft tissue and bone. Lyon: IARC Press, 2002:228-30
2. Stieber JR, Dormans JP. Manifestations of hereditary multiple exostoses. J Am Acad Orthop Surg. 2005;13(2):110-20. https://doi.org/10.5435/00124635-200503000-00004
3. Wuyts W, Schmale GA, Chansky HA, Raskind WH. Hereditary multiple osteochondromas. In: Adam MP, Ardinger HH, Pagon RA et al., eds. GeneReviews. Seattle: University of Washington, 1993.
4. Alvarez CM, De Vera MA, Heslip TR et al. Evaluation of the anatomic burden of patients with hereditary multiple exostoses. Clin Orthop Relat Res. 2007;462:73-9. https://doi.org/10.1097/BLO.0b013e3181334b51
5. Wicklund CL, Pauli RM, Johnston D, Hecht JT. Natural history study of hereditary multiple exostoses. Am J Med Genet.

1995;55(1):43-6. https://doi.org/10.1002/ajmg.1320550113

6. Jamsheer A, Socha M, Sowi&;ska-Seidler A et al. Mutational screening of EXT1 and EXT2 genes in Polish patients with hereditary multiple exostoses. J Appl Genet. 2014;55(2):183-8. https://doi.org/10.1007/s13353-014-0195-z
7. Clement ND, Porter DE. Hereditary multiple exostoses: anatomical distribution and burden of exostoses is dependent upon genotype and gender. Scott Med J. 2014;59(1):35-44. https://doi.org/10.1177/0036933013518150
8. Schmale GA, Conrad EU 3rd, Raskind WH. The natural history of hereditary multiple exostoses. J Bone Joint Surg Am. 1994;76(7):986-92. https://doi.org/10.2106/00004623-199407000-00005
9. Matsumoto Y, Matsumoto K, Harimaya K et al. Scoliosis in patients with multiple hereditary exostoses. Eur Spine J. 2015;24(7):1568-73. https://doi.org/10.1007/s00586-015-3883-4
10. El-Fiky TAM, Chow W, Li YH et al. Hereditary multiple exostoses of the hip. J Orthop Surg (Hong Kong). 2009;17(2):161-5. https://doi.org/10.1177/230949900901700207
11. D'Arienzo A, Andreani L, Sacchetti F et al. Hereditary multiple exostoses: current insights. Orthop Res Rev. 2019;11:199-211. https://doi.org/10.2147/ORR.S183979
12. Center for Arvelige og Komplekse Sygdomme (CAKS). Patientforløbsbeskrivelse. Multiple osteochondromer version 2021.11.01. CAKS2021. Updated 1 Nov 2021. http://ipaper.ipapercms.dk/RegionSyddanmark/OUH/Odense_Universitetshospital/Klinisk_Genetisk_Afdeling/168314/?page=4 (7 Mar 2025)
13. Danske Multidisciplinære Cancer Grupper. Multiple endokondromer og osteokondromer - udredning og opfølgning med henblik på malignisering. Danske Multidisciplinære Cancer Grupper, 2023. www.dmcg.dk/siteassets/kliniske-retningslinjer---skabeloner-og-vejledninger/kliniske-retningslinjer-opdelt-pa-dmcg/dsg/dsg_multiple_enchon_osteochon_v2.0_admgodk130123.pdf (7 Mar 2025)
14. Borgwardt A, Borre M, Elberg JJ et al. Kirurgi. 2nd ed. Copenhagen: FALD's Forlag, 2016:667-8, 937
15. Paley D. Principles of deformity correction. 1st ed. Springer Science & Business Media, 2002:8-10
16. Luís NM, Varatojo R. Radiological assessment of lower limb alignment. EFORT Open Rev. 2021;6(6):487-94. https://doi.org/10.1302/2058-5241.6.210015
17. Bowen ME, Boyden ED, Holm IA et al. Loss-of-function mutations in PTPN11 cause metachondromatosis, but not Ollier disease or Maffucci syndrome. PLoS Genet. 2011;7(4):e1002050. https://doi.org/10.1371/journal.pgen.1002050
18. Danmarks Statistik. Befolkningen den 1. i kvartalet efter område, køn, alder og civilstand. www.statistikbanken.dk/FOLK1A (7 Mar 2025)

