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Hereditary Multiple Exostoses: Genetic, Radiologic, and Oncologic Insights from Twenty-one Patients

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ABSTRACT

Aim: To characterize the clinical, radiological, and genetic features of genetically confirmed hereditary multiple exostoses (HME) in patients presenting with multiple exostoses and to contribute to the understanding of the phenotypic and genotypic spectrum.

Methods: This retrospective cohort study included 21 patients from 13 unrelated families referred to a pediatric genetics clinic for multiple exostoses, with an HME diagnosis confirmed by molecular genetic testing. Clinical findings and available skeletal survey radiographs were reviewed. Identified variants were classified, and segregation analysis was performed when feasible.

Results: Ages at presentation ranged from 2.27 to 59.6 years; 14 patients were female, and 7 were male. The most common reasons for referral were a palpable mass and imaging findings. Skeletal survey radiographs were available for 17 patients, all of whom showed multiple exostoses of variable severity. Exostoses most frequently involved the forearm (ulna and radius), femur, lower leg (tibia and fibula), and humerus; involvement of the hands and pelvis was observed at an intermediate frequency. The feet, ribs, scapula, and clavicle were less commonly affected, and no vertebral lesions were identified. As of the most recent follow-up, no malignant transformation has been identified among patients in our cohort (0%). In one of our patients (P21), a stable, non-growing mass was detected in the mesencephalon. Thirteen distinct variants were detected, five of which were novel. Fifteen patients were classified as *EXT1*-related HME type 1 and six as *EXT2*-related HME type 2. Variant types comprised seven frameshift variants, four nonsense variants, one missense variant, and one splice-site variant; all were classified as pathogenic/likely pathogenic. Among eight probands with segregation testing available, two variants (25%) were confirmed to be de novo.

Conclusion: HME exhibits marked clinical and genetic heterogeneity. Careful assessment of skeletal surveys supports the clinical diagnosis, while molecular confirmation is critical for accurate genetic counseling. The novel variants and the associated phenotypic and radiological findings reported here further expand the disease spectrum.

Keywords: Hereditary multiple exostoses, bone pain, *EXT1*, *EXT2*, osteochondroma

Introduction

In European populations, the reported prevalence of hereditary multiple exostoses (HME) is approximately 1 in 100,000 [1,2]. HME is characterized by the development of osteochondromas, benign cartilage-capped bony tumors that typically arise from the metaphyseal regions of long bones and grow outward from the bone surface. Lesions are most often multiple and, in addition to long bones, may also involve the ribs, clavicle, and pelvis [1-3]. Most patients present with a

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palpable mass, whereas others are referred after lesions are detected incidentally on skeletal radiographs obtained for an alternative indication or during evaluation prompted by a positive family history [2]. The number of osteochondromas, the extent and distribution of skeletal involvement, and the severity of resulting deformities may vary considerably among individuals [1,2]. On average, approximately six lesions are observed per patient; the skeletal distribution of lesions may follow an asymmetric or symmetric pattern across cases [2]. During skeletal growth, osteochondromas enlarge and progressively ossify; after skeletal maturity is reached, growth typically ceases, and the development of new osteochondromas is not expected thereafter [1,2]. Osteochondromas in multiple hereditary exostoses may lead to a broad clinical spectrum, including pain, limb deformities, limb-length discrepancy, scoliosis, reduced skeletal growth, restricted joint range of motion, short stature, early-onset osteoarthritis, and neurological symptoms secondary to peripheral nerve compression [1,2].

Although the primary malignancy risk in HME is well defined as an increased risk of secondary chondrosarcoma, evidence regarding an association with hematologic malignancies (e.g., leukemia) remains limited, with only a few cases reported; the potential contribution of *EXT1/EXT2* through heparin sulfate biosynthesis and related pathways is currently being investigated [4]. Molecular genetic advances have substantially facilitated the genetic diagnosis of this syndrome. Using next-generation sequencing (NGS) and deletion/duplication analyses, genetic testing can identify heterozygous disease-causing pathogenic/likely pathogenic variants or copy-number variations (CNVs) in the *EXT1* and *EXT2* genes, thereby establishing the diagnosis of autosomal dominant HME [1,2,5].

The retrospective study discusses the clinical characteristics, radiological findings, and genetic results of 21 patients from 13 unrelated families with genetically confirmed HME.

Methods

Between February 2022 and December 2025, we enrolled 21 patients from 13 unrelated families who were referred to the Pediatric Genetics Department of Universty of Health Sciences Türkiye, Ankara Etlik City Hospital. The study cohort comprised patients in whom multiple exostoses were identified on radiographs and/or a disease-causing variant was detected in either the *EXT1* or *EXT2* gene by genetic testing. This retrospective study was approved by the Clinical Research Ethics Committee of the University of Health Sciences, Ankara Etlik City Hospital (approval no: AEŞH-BADEK1-2025-349, date: 02.09.2025). Written informed consent for genetic testing was obtained from the patients and their legal guardians prior to testing. Clinical and anthropometric data included medical and family histories, dysmorphic features, age at presentation, sex, weight, height, and head circumference. These measurements were reported as standard deviation scores (SDS) using nationally validated reference standards for children in Türkiye [6]. For participants older than 18 years, height, weight, and head circumference SDS values were calculated using the reference standards for age 18 years [6]. To ensure analytical accuracy, patients who could not be evaluated for specific variables (denoted as “NA: not available” throughout the tables and text) were excluded from percentage calculations for those variables within the cohort. With the exception of four patients (P2, P7, P10, and P18), systematic skeletal survey radiographs were obtained for the remaining 17 patients. The routine skeletal survey protocol included skull radiographs in two projections, anteroposterior radiographs of the upper and lower extremities, hand and foot radiographs, spine radiographs in two projections, a pelvic radiograph, and a posteroanterior chest radiograph. The survey was used to assess the location of skeletal abnormalities (e.g., exostoses) and evaluate radiographic features of spondylar, epiphyseal, and metaphyseal dysplasia. In addition, anthropometric measurements and skeletal survey radiographs of parents with identified exostoses were reviewed.

Diagnostic evaluation was performed using NGS-based clinical exome sequencing (CES) and Sanger sequencing. Genomic deoxyribonucleic acid was extracted from the patient’s peripheral blood following standard procedures. The sequencing library was prepared using the Clinical Exome Solution v3 capture kit (SOPHiA Genetics SA, Switzerland), and sequenced on the MiSeq platform (Illumina Inc., CA, USA). The generated data were interpreted using current databases (PubMed, OMIM, DGV, ClinVar, DECIPHER, and ClinGen), and variant pathogenicity was classified according to the American College of Medical Genetics and Genomics criteria [7]. Variants were reported with reference to the NCBI RefSeq transcripts NM_000127.3 (*EXT1*) and NM_207122 (*EXT2*), respectively. For candidate variants with the potential to explain the observed phenotype, Sanger sequencing was performed for validation in the proband and for segregation analysis in affected parents and siblings. Sanger sequencing was carried out using the Applied Biosystems 3500 Genetic Analyzer (Thermo Scientific, USA).

In this study, genetic diagnoses were established by CES in 12 patients (P1, P3, P6, P9, P11, P13-P17, P19, and P20). Variant confirmation was performed by Sanger sequencing in 19 patients (all except P16 and P19). In some cases, both CES and Sanger sequencing were performed.

Statistical Analysis

No formal statistical analysis was performed in this study. Accordingly, no statistical software was used; the results are presented descriptively.

Results

Of the 21 patients included in the study, 14 (66.7%) were female and 7 (33.3%) were male. The reasons for presentation included family screening, a history of exostoses, a palpable, hard mass in the extremities, joint pain, detection of exostoses on skeletal survey radiographs obtained for screening purposes, short stature, limb bowing, hypoglycemia, and onset of puberty. Age at presentation ranged from 2.27 to 59.6

years. Among patients with available information, no prenatal problems were identified; with respect to birth history, only one patient (P6) was small for gestational age. Only one of the 13 families (P21) was consanguineous.

Based on anthropometric evaluation, two patients (P4, P16) had a body weight ≤-2 SDS, and one patient (P14) had a head circumference <-2 SDS. Five patients (P3-P5, P7, P17) were classified as having short stature (height ≤-2 SDS). Three patients (P5, P11, P17) exhibited variable dysmorphic facial features. None of the patients reported hearing- or vision-related complaints, and no developmental or cognitive impairments were observed.

Cranial imaging was performed in selected patients; brain magnetic resonance imaging (MRI) findings were normal in P1 and P6, the latter of whom was followed for complex febrile seizures. Chiari type 1 malformation was identified in P14, and a benign-appearing, non-growing mass in the mesencephalon was observed in P21. Abdominal ultrasonography was performed in five patients (P1, P3, P15, P17, P21), and findings were normal in all patients. On echocardiography, minimal mitral regurgitation was detected in P14 (who was subsequently diagnosed with acute rheumatic fever) and in two other patients (P15 and P21). A secundum atrial septal defect was identified in P7. Echocardiography was normal in P3 and P17. In addition, epileptiform activity was detected on EEG in P6. One patient (P21) was receiving treatment for anorexia nervosa and an anxiety disorder.

Genetic testing identified a point mutation in either *EXT1* or *EXT2* in all patients. No CNV-related etiology was detected. Overall, 13 distinct pathogenic or likely pathogenic variants were identified in 15 (71.4%) patients with *EXT1* and *in* six (28.6%) patients with *EXT2*. Of these variants, seven were frameshift, four were nonsense, one was missense, and one affected a splice site. Eight variants had been previously reported in ClinVar, whereas the remaining five were novel. Family segregation analysis was performed on eight probands; only two (25%) were found to harbor *de novo* variants. For P14, P16, and P19, parental inheritance was suspected; however, segregation analysis could not be performed. In P15, segregation analysis in the mother was negative, whereas paternal testing could not be undertaken because the father was deceased. The medical history indicated that the father did not report similar symptoms. The patients' clinical and anthropometric characteristics are summarized in Table 1. Skeletal survey radiographs from 17 patients were evaluated for exostoses, and the findings are presented in Table 2 and Figures 1-3. The genetic analysis results are compared in Table 3.

Discussion

HME is a syndrome that is predominantly caused by pathogenic/likely pathogenic variants in the *EXT1* or *EXT2* genes and typically shows an inherited pattern, with sporadic cases occurring less frequently [8-11]. Whereas the diagnosis was historically based on clinical findings, the widespread use of molecular testing now facilitates diagnostic confirmation and enables provision of appropriate genetic counseling, including discussion of preimplantation genetic testing options for families [1]. Hematologic, renal, central nervous system, and cardiac findings may rarely accompany the condition. These manifestations are often not intrinsic features of the disease; rather, they may result from compressive mass effects due to lesions in uncommon locations or may reflect incidental/secondary conditions [1,3,12-14]. In our cohort, exostoses were most frequently identified in the forearm (ulna and radius), the femur, the lower leg (tibia and fibula), and the humerus. They were observed with moderate frequency in the hand and pelvis. More rarely, exostoses were detected in the foot, ribs, scapula, and clavicle, but no vertebral exostoses were observed in any patient. When interpreting radiographs, priority should be given to the extremities; however, it should be kept in mind that exostoses may also occur in other anatomical regions.

Scoliosis has been reported in approximately 30% of individuals with HME, with some studies describing even higher rates [2,3,15]. In our series, the prevalence of scoliosis was 17.6% (3/17), lower than rates reported in the literature. On the other hand, the detection of heparan sulfate (HS) expression in human fetal vertebrae and intervertebral discs suggests that HS may influence axial skeletal development [16]. Moreover, the literature has also demonstrated that HME is a risk factor in the etiology of scoliosis [15]. The reported prevalence of scoliosis may vary depending on several factors, including the number and size of exostoses, patient age at assessment, and the Cobb angle threshold used to define scoliosis. In addition to axial deformities, cases of compressive myelopathy due to intraspinal exostoses—although less frequent—have also been reported [17]. Therefore, for patients with HME who present with symptoms suggestive of neurological deficits, we recommend advanced imaging modalities. In the long bones, osteochondromas are typically asymptomatic and most commonly present as cosmetic concerns or palpable, firm masses. When symptomatic, they may lead to complications related to mechanical compression of adjacent anatomical structures, including bursitis, tendinitis, neuropathy, and arterial or venous thrombosis, as well as pseudoaneurysm formation; in rare cases, chronic compartment syndrome has also been reported [18,19]. Exostoses that impair joint range of motion may increase shear forces across the joint during movement. In addition, cartilaginous hypertrophy secondary to HS deficiency is considered a potential risk factor for early-onset osteoarthritis [20]. HME can affect long-bone growth, leading to short stature, limb-length discrepancies, and angular deformities of the extremities. The most common deformities include coxa valga, genu valgum, and ankle valgus. Radial and ulnar deviation and progressive deformity may result in elbow dislocation. Additional deformity-related manifestations include shortening and angular deformities of the metacarpal and metatarsal bones, as well as hip-related pathology such as acetabular dysplasia, femoroacetabular impingement, hip subluxation or dislocation, and patellar dislocation, reflecting a broad spectrum of orthopedic conditions associated with HME [21-23].

Table 1. Clinical and anthropometric characteristics of the patients

Patient	Sex	Age (years)	Weight (kg/ SDS)	Height (cm/SDS)	Head circum-ference (cm/SDS)	Gestational age/birth weight	Presenting complaint (s)	Comorbidities US: ultrasonography ECHO: echocardiography EEG: electroencephalography
F1P1	Female	9.24	27/-0.54	127 /-1.09	53/0.38	38 weeks 3500 g	Puberty started	Brain MRI: normal, abdominal US: normal, non-dysmorphic
F1P2 (father)	Male	47.00	NA	NA	NA	NA	Family screening, exostosis history	Non-dysmorphic
F2P3	Female	10.92	26.1/-1.88	126/**-2.77**	52/-0.91	38 weeks 3000 g	Short stature, limb bowing	Abdominal US: normal ECHO: normal non-dysmorphic
F2P4 (sibling)	Male	9.83	22/**-2.29**	125/**-2.00**	53/-0.29	NA	Short stature, limb bowing	Non-dysmorphic
F2P5 (mother)	Female	35.00	NA	136/**-4.62**	NA	NA	Short stature	Dysmorphic features
F3P6	Female	5.54	20/0.14	112/-0.07	50/-0.62	37 weeks 1800 g	Recurrent febrile seizures	Abnormal EEG findings, brain MRI: normal, Hypoglycemia, non-dysmorphic
F3P7 (sibling)	Female	2.46	NA/-1.46	**NA/-2.74**	NA/-0.78	38 weeks 2400 g	Family screening, short stature	ECHO: Secundum atrial septal defect, non-dysmorphic
F3P8 (mother)	Female	30.00	NA	NA	NA	NA	Family screening, exostosis history	Non-dysmorphic
F4P9	Male	2.87	12/-1.58	91/-1.19	51/0.68	38 weeks 3400 g	Exostoses identified; family history present	Non-dysmorphic
F4P10 (mother)	Female	30.00	NA	NA	NA	NA	Family screening, exostosis history	Non-dysmorphic
F5P11	Female	4.84	16/-0.87	109/0.21	51/0.27	40 weeks 3300 g	Palpable hard mass in the extremities	Dysmorphic features
F6P12	Female	13.34	40/-1.71	151.5/-1.2	54.5/-0.27	38 weeks normal	Palpable hard mass in the extremities	Non-dysmorphic
F6P13 (father)	Male	50.20	73/0.12	165 /-1.82	57/-0.47	NA	Family screening, exostosis history	Non-dysmorphic
F7P14	Female	15.00	48/-1.17	160/-0.28	**52/-2.62**	38 weeks normal	History of acute rheumatic fever, arthralgia	Non-dysmorphic brain MRI: chiari type I malformation, ECHO: minimal mitral regurgitation
F8P15	Male	2.27	NA/**-0.91**	NA/**-0.50**	NA/1.16	38 weeks 3000 g	Palpable hard mass in the extremities	Abdominal US: normal, non-dysmorphic ECHO: minimal mitral regurgitation
F9P16	Female	11.23	27/**-2.0**	137/-1.5	55/0.30	38 weeks normal	Palpable hard mass in the extremities	Don-dysmorphic
F10P17	Female	13.84	31/-4.05	142/**-3.03**	54/-0.84	39 weeks 3500 g	Short stature	Dysmorphic features abdominal US: normal ECHO: normal
F10P18 (father)	Male	59.60	NA	NA	NA	NA	Family screening, exostosis history	Non-dysmorphic

Table 1. Continued

Patient	Sex	Age (years)	Weight (kg/ SDS)	Height (cm/SDS)	Head circum-ference (cm/SDS)	Gestational age/birth weight	Presenting complaint (s)	Comorbidities US: ultrasonography ECHO: echocardiography EEG: electroencephalography
F11P19	Female	18.21	NA	169/1.00	NA	NA	Palpable hard mass in the extremities	Non-dysmorphic
F12P20	Male	2.99	15,8/0.5	94/-0.69	51/0.65	38 weeks 3250 g	Palpable hard mass in the extremities	Non-dysmorphic
F13P21	Female	17.79	50/-1.33	158/-0.85	56/-0.05	38 weeks 2650 g	Palpable hard mass in the extremities	Brain MRI*, abdominal US: normal ECHO: minimal mitral regurgitation non-dysmorphic

*: A well-circumscribed solid lesion is identified in the left mesencephalon, measuring 1.2 cm (AP) ×1.1 cm (TV) ×1.1 cm (SI). The lesion is T2-hyperintense and T1-hypointense, demonstrates no appreciable contrast enhancement, and shows no acute diffusion restriction. There is mild superior extension toward the left thalamo-mesencephalic junction
NA: Not available, F: Family, P: Patient, US: Ultrasonography, ECHO: Echocardiography, EEG: Electroencephalography, MRI: Magnetic resonance imaging

Three of our patients (3/21, 14.3%) underwent surgery for osteochondromas. Patient P3 underwent bilateral hemiepiphysiodesis of the distal femur, proximal tibia, and distal tibia to address bilateral knee and ankle valgus deformities. In Patient P5, MRI was performed because of pain in the left iliac wing and right distal medial femur and demonstrated a cartilage cap thickness of 3 mm; excision was subsequently performed for pain palliation. Patient P21 underwent excision of painful osteochondromas located at the right distal medial femur and the lateral aspect of the proximal tibia.

Malignant transformation is one of the most concerning complications of osteochondromas. The association between HME and skeletal malignancies is well established, and approximately 5-10% of patients may develop low-grade chondrosarcoma with limited metastatic potential [24,25]. The most common sites of malignant transformation include the proximal femur, proximal humerus, scapula, and pelvis [26]. Less frequently, osteosarcoma, fibrosarcoma, and malignant fibrous histiocytoma have also been reported [27]. In addition, hematologic malignancies, cerebellar astrocytoma, atypical teratoid/rhabdoid tumor, and cancer of the lung, thyroid, and colon have been described in these patients [27-32]. As of the most recent follow-up, no malignant transformation has been identified in any patient in our cohort (0%). In one of our patients (P21), a non-growing, stable mass was detected in the mesencephalon.

The *EXT* gene family, comprising *EXT1* and *EXT2*, functions as a tumor suppressor and encodes critical glycosyltransferases involved in HS biosynthesis. HS proteoglycans, formed by the attachment of HS chains to core proteins, play an important role in regulating bone and cartilage development [25,33,34]. Heterozygous variants in *EXT1*/*EXT2* reduce HS levels by approximately 50%; however, this reduction alone is not sufficient for osteochondroma formation [35]. The development of a tumorigenic cell is consistent with Knudson's "two-hit" hypothesis, requiring an additional somatic event affecting the second allele (e.g., loss of heterozygosity, or a second pathogenic mutation) [1,8]. Loss-of-function variants in these genes provide the biological basis for osteochondroma development [1,2]. Variants in *EXT1*, compared with those in *EXT2*, have been reported to be associated with a more severe phenotype, a higher number of osteochondromas, and an increased risk of malignant transformation [1,36]. In this genetically heterogeneous syndrome, no underlying genetic etiology is identified in approximately 10-13% of cases, whereas variants are reported in *EXT1* in 65-70% and in *EXT2* in 30-35% of cases [1]. In our study, consistent with the literature, variants were most frequently detected in *EXT1* (15/21; 71.4%) and less commonly in *EXT2* (6/21; 28.6%). Although variants can be distributed throughout the genes, some reports indicate that exons 1 and 6 in *EXT1* and the first eight exons in *EXT2* constitute mutational "hot spot" regions [1]. Consistent with the literature, 80% of patients carrying an *EXT1* variant had variants in these two exons (60% in exon 1 and 20% in exon 6), whereas all patients with *EXT2* variants

Table 2. Distribution of exostoses across the skeletal system in patients

Patient	Femur	Lower leg (tibia and fibula)	Humerus	Forearm (ulna and radius)	Hand	Foot	Rib	Clavicle	Vertebra	Pelvis	Scapula
F1P1	+	+	+	+	+	+	-	-	-	+	-
F1P2	No imaging available										
F2P3	+	+	+	+	+	-	-	+	-	+	-
F2P4	+	+	+	+	+	-	+	+	-	+	+
F2P5	+	+	+	+	-	-	-	-	-	+	+
F3P6	+	+	+	+	+	-	-	-	-	-	-
F3P7	No imaging available										
F3P8	+	+	-	+	+	+	-	-	-	-	-
F4P9	+	+	+	+	-	-	-	-	-	-	-
F4P10	No imaging available										
F5P11	+	+	+	+	+	-	-	-	-	-	-
F6P12	+	+	+	+	-	-	-	-	-	-	-
F6P13 (Baba)	+	+	+	+	-	-	-	+	-	-	+
F7P14	+	+	-	-	-	-	-	-	-	-	-
F8P15	+	+	-	+	-	-	-	-	-	-	-
F9P16	-	-	+	+	-	-	-	-	-	-	-
F10P17	+	+	+	+	-	-	-	-	-	+	-
F10P18	No imaging available										
F11P19	+	+	+	+	-	-	-	-	-	-	-
F12P20	-	+	-	+	+	+	+	-	-	-	-
F13P21	+	+	+	+	-	-	-	-	-	-	-
	15/17	16/17	13/17	16/17	7/17	3/17	2/17	3/17	0/17	5/17	3/17

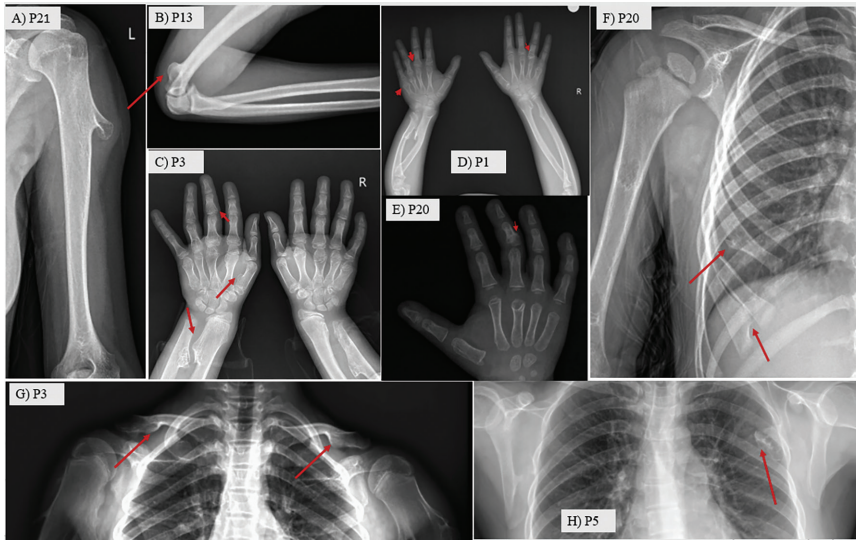

Figure 1. Representative examples of multiple exostoses/osteochondromas involving the upper extremities, clavicles, and ribs in patients with hereditary multiple exostoses. Red arrows indicate the lesions. A) P21: Exostosis of the proximal humerus. B) P13: Exostosis around the elbow (at the level of the proximal forearm). C) P3: Multiple exostoses of the hand and wrist, involving the metacarpals, phalanges, and distal forearm bones. D) P1: Multiple exostotic foci in both hands and the forearm, predominantly at the metacarpal/phalangeal level. E) P20: Exostosis at the level of the phalanx. F) P20: Rib-localized exostoses on the shoulder girdle and chest radiograph. G) P3: Bilateral clavicular exostoses on a shoulder girdle radiograph. H) P5: Exostosis in the scapular region on a shoulder girdle/chest radiograph

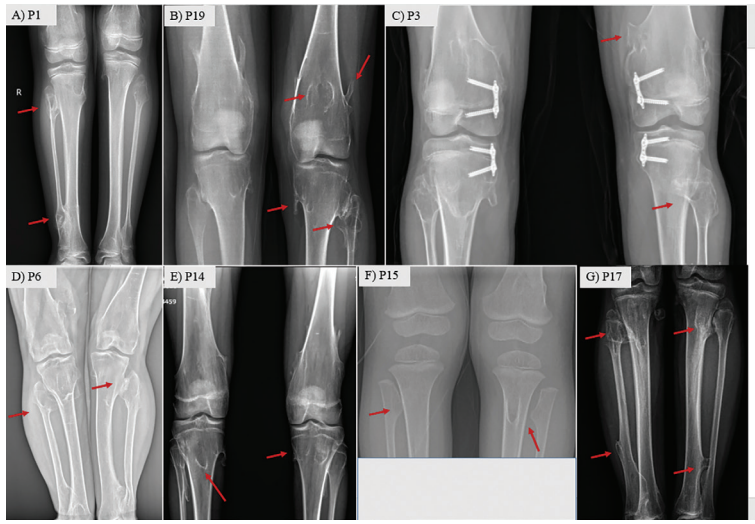

Figure 2. Representative examples of multiple exostoses/osteochondromas involving the lower extremities (distal femur, proximal tibia/fibula, and peri-knee region) in patients with hereditary multiple exostoses. Red arrows indicate the lesions. A) P1: Multiple exostoses along the tibia at the proximal and distal metaphyseal levels. B) P19: Multiple exostoses around the knee involving the distal femur and proximal tibia/fibula. C) P3: Exostoses around the knee at the distal femur and proximal tibia, with orthopedic fixation hardware *in situ*. D) P6: Multiple exostoses around the proximal tibia/fibula. E) P14: Prominent exostosis around the knee, most evident at the proximal fibular metaphysis. F) P15: Multiple exostoses at the level of the proximal tibia and fibula. G) P17: Multiple exostotic foci along the tibia and fibula

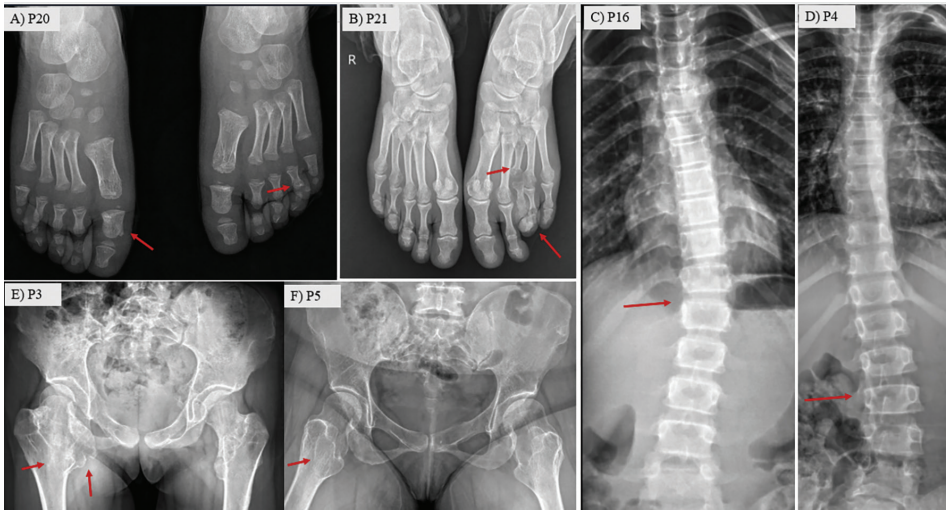

Figure 3. Findings observed in the feet, pelvis/proximal femur, and spine in patients with hereditary multiple exostoses. Red arrows indicate the relevant pathology. A) P20: Exostosis/osteochondroma foci in the foot at the metatarsal and phalangeal levels. B) P21: Multiple exostoses in the foot involving the metatarsals and phalanges. C) P16: Scoliosis on spine radiograph (arrows indicate the curvature). D) P4: Scoliosis on spine radiograph (arrows indicate the curvature). E) P3: Exostosis/osteochondroma foci around the proximal femur/hip on pelvic radiograph. F) P5: Exostosis/osteochondroma foci around the proximal femur/hip on pelvic radiograph

harbored variants within the first eight exons. *De novo* disease has been reported in the literature at a rate of approximately 10%; in our study, a higher frequency of 25% was observed [1]. This discrepancy may be related to the inability to perform genetic testing on the parents of all probands and the limited sample size.

Multilocus genomic variation is defined as the concurrent identification of pathogenic variants at more than one independent locus in patients presenting with complex clinical phenotypes [37]. In this context, in addition to the *EXT1* variant, other genomic variant were identified in our patients P1 and P3: a paternally inherited heterozygous variant of uncertain significance in *COL11A1* in P1, and a maternally inherited heterozygous, likely pathogenic variant in *NOG* in P3. These cases were published by Kablan et al. [37].

Follow-up of patients with HME should include documentation of growth parameters at each visit and a particularly thorough assessment of the musculoskeletal system. Given the variable clinical manifestations and potential complications, the management of HME requires a multidisciplinary approach. Optimal care, coordinated through a multidisciplinary team that includes specialists in pediatric oncology, orthopedic

Table 3. General characteristics of variants detected in the *EXT1* (NM_000127.3) and *EXT2* (NM_207122) genes in patients

Patient	Genomic Analysis	Variant (c./p.)	Exon	Molecular consequence	Classification ACMG Criteria	Parental segregation	ClinVar submission status (submitted/novel)
F1P1	CES, SS	*EXT1* c.325delT p.(Cys109Alafster27)	1/11	Frameshift	Pathogenic (PP1, PP4, PVS1, PM2)	Paternal	Novel
F1P2	SS	*EXT1* c.325delT p.(Cys109Alafster27)	1/11	Frameshift	Pathogenic	Paternal (no tested)	Novel
F2P3	CES, SS karyotyping	*EXT1* c.390_406del p.(Tyr131Glyfs*52)	1/11	Frameshift	Pathogenic (PP1, PP4, PVS1, PM2)	Maternal	Novel
F2P4	SS	*EXT1* c.390_406del p.(Tyr131Glyfs*52)	1/11	Frameshift	Pathogenic	Maternal	Novel
F2P5	SS	*EXT1* c.390_406del p.(Tyr131Glyfs*52)	1/11	Frameshift	Pathogenic	NA	Novel
F3P6	CES, SS	*EXT1* c.493C>T p.(Gln165*)	1/11	Nonsense	Pathogenic (PP1, PP4, PP5, PS4, PVS1, PM2)	Maternal	Submitted rs2130043213
F3P7	SS	*EXT1* c.493C>T p.(Gln165*)	1/11	Nonsense	Pathogenic	Maternal	Submitted rs2130043213
F3P8	SS	*EXT1* c.493C>T p.(Gln165*)	1/11	Nonsense	Pathogenic	Maternal (no tested)	Submitted rs2130043213
F4P9	CES, SS	*EXT1* c.1057-3C>G	3/11	Splice-site	Pathogenic (PP1, PP4, PP3, PP2)	Maternal	Submitted rs200927981
F4P10	SS	*EXT1* c.1057-3C>G	3/11	Splice-site	Pathogenic	NA	Submitted rs200927981
F5P11	CES, SS	*EXT1* c.1468del p.(Leu490Trpfs*9)	6/11	Frameshift	Pathogenic (PS4, PVS1, PM2, PP5, PM6, PP4)	*De novo*	Submitted rs886039355
F6P12	SS	***EXT2*** c.670C>T p.(Gln224*)	4/14	Nonsense	Pathogenic (PS4, PM2, PP1, PVS1, PP4, PP5)	Maternal	Submitted rs1565199251
F6P13	CES, SS	***EXT2*** c.670C>T p.(Gln224*)	4/14	Nonsense	Pathogenic	NA	Submitted rs1565199251
F7P14	CES, SS	***EXT2*** c.244dup p.(Asp82Glyfs*11)	2/14	Frameshift	Pathogenic (PS4, PVS1, PM2, PP5, PP4)	NA	Novel
F8P15	CES, SS	*EXT1* c.584T>G p.(Leu195*)	1/11	Nonsense	Pathogenic (PVS1, PM2, PP5)	NA	Submitted rs1586279621
F9P16	CES	***EXT2*** c.623del p.(Asp208Alafs*62)	3/14	Frameshift	Likely Pathogenic (PP4, PVS1, PM2)	Maternal (no tested)	Novel
F10P17	CES, SS karyotyping	*EXT1*.1469del p.(Leu490Argfs*9)	6/11	Frameshift	Pathogenic (PS4, PM2, PVS1, PP5)	Paternal	Submitted rs886039356
F10P18	SS	*EXT1* c.1469del p.(Leu490Argfs*9)	6/11	Frameshift	Pathogenic (PS4, PM2, PVS1, PP5)	NA	Submitted rs886039356
F11P19	CES	*EXT1* c.1019G>A p.(Arg340His)	2/11	Missense	Likely Pathogenic (PM1, PM5, PP3, PP4, PP5)	Paternal (no tested)	Submitted rs119103287
F12P20	CES, SS	***EXT2*** c.1187G>A p.(Trp396*)	8/14	Nonsense	Pathogenic (PVS1, PM2, PP5)	*De novo*	Submitted rs750542485
F13P21	SS	***EXT2*** c.1060del p.(Leu354PhefsTer11)	6/14	Frameshift	Likely Pathogenic (PM2, PVS1)	Paternal (no tested)	Novel

F: Family, P: Patient, NA: Not available, CES: Clinical exome sequencing, SS: Sanger sequencing, ACMG: American College of Medical Genetics and Genomics

surgery, pediatric genetics and medical genetics, pediatric neurology, pediatric radiology, and physiotherapy/rehabilitation, encompasses comprehensive clinical evaluation, the appropriate use of imaging modalities, an expanded differential diagnosis, and the integration of advanced molecular testing. This comprehensive collaboration facilitates early recognition of mild or atypical clinical features and complications and supports accurate genetic diagnosis. Diagnostic certainty can be enhanced through testing approaches such as *EXT1*/*EXT2*-focused NGS and deletion/duplication analyses. Management and follow-up are individualized according to parameters such as the number and location of lesions, the severity of the deformity, the symptom burden, and the age. Regarding the risk of secondary chondrosarcoma, warning signs such as new-onset or increasing pain, rapid growth, and thickening of the osteochondroma cartilage cap should be assessed meticulously. This approach enables effective management of HME-specific complications and improves quality of life; it also supports more accurate genetic counseling for families regarding prognosis and reproductive options in the context of autosomal dominant inheritance, penetrance, and variable expressivity.

Study Limitations

The main limitations of this study include its single-center design, limited sample size, and the inability to perform segregation analyses in some families. Nevertheless, our findings are expected to provide meaningful contributions to future research and patient management. Multicenter studies with larger cohorts will help clarify the pathogenesis of this syndrome more precisely and further expand its clinical spectrum.

Conclusion

HME is a clinically heterogeneous entity with variable expressivity. In the presence of a family history, patients should be monitored closely, given the high penetrance and risk of malignant transformation. Careful follow-up is warranted for restricted joint range of motion, cosmetic concerns, and associated skeletal abnormalities. In patients with these features, HME should routinely be considered in the differential diagnosis and comprehensive molecular testing should be prioritized to elucidate the underlying genetic etiology.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Clinical Research Ethics Committee of the University of Health Sciences, Ankara Etlik City Hospital (approval no: AEŞH-BADEK1-2025-349, date: 02.09.2025).

Informed Consent: This retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.K., M.A.K., T.D., F.D.B., A.Ka., G.Ş., Concept: A.K., M.A.K., T.D., S.D., G.Ş., Design: A.K., M.A.K., T.D., Ş.Y., Ş.Ye., Data Collection or Processing: A.K., M.A.K., F.D.B., A.Ka., Ş.Y., Ş.Ye., Analysis or Interpretation: A.K., M.A.K., F.D.B., A.Ka., A.D., Ş.Ye., G.Ş., Literature Search: A.K., T.D., G.Ş., Writing: A.K., T.D., F.D.B., A.Ka., Ş.Y., A.D., G.Ş.

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References

1. Sefcik R, Earl D. Hereditary multiple osteochondromas. 2000 [updated 2026]. In: Adam MP, Bick S, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2026.
2. Rueda-de-Eusebio A, Gomez-Pena S, Moreno-Casado MJ, Marquina G, Arrazola J, Crespo-Rodríguez AM. Hereditary multiple exostoses: an educational review. Insights Imaging. 2025;16:46.
3. Petersen RB, Buch CD, Faergemann C, Nymark T. Bone deformities with hereditary multiple osteochondromas. Dan Med J. 2025;72:A11230696.
4. Comisi F, Fusco C, Mura R, et al. Hereditary multiple osteochondromas and acute lymphoblastic leukemia: a possible role for EXT1 and EXT2 in hematopoietic malignancies. Am J Med Genet A. 2025;197:e64052.
5. Borovikov A, Marakhonov A, Murtazina A, et al. Cases report: mosaic structural variants of the *EXT1* gene in previously genetically unconfirmed multiple osteochondromas. Front Genet. 2024;15:1435493.
6. Neyzi O, Bundak R, Gökçay G, et al. Reference values for weight, height, head circumference, and body mass index in Turkish children. J Clin Res Pediatr Endocrinol. 2015;7:280-293.
7. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-424.
8. Pacifici M. Hereditary multiple exostoses: new insights into pathogenesis, clinical complications, and potential treatments. Curr Osteoporos Rep. 2017;15:142-152.
9. D'Arienzo A, Andreani L, Sacchetti F, Colangeli S, Capanna R. Hereditary multiple exostoses: current insights. Orthop Res Rev. 2019;11:199-211.
10. Bukowska-Olech E, Trzebiatowska W, Czech W, et al. Hereditary multiple exostoses-a review of the molecular background, diagnostics, and potential therapeutic strategies. Front Genet. 2021;12:759129.
11. Fusco C, Nardella G, Fischetto R, et al. Mutational spectrum and clinical signatures in 114 families with hereditary multiple osteochondromas: insights into molecular properties of selected exostosin variants. Hum Mol Genet. 2019;28:2133-2142.
12. Chilvers R, Gallagher JA, Jeffery N, Bond AP. An unusual example of hereditary multiple exostoses: a case report and review of the literature. BMC Musculoskelet Disord. 2021;22:96.
13. Grelat M, Gimenez C, Madkouri R. Cervical cord compression by exostosis. J Orthop Sports Phys Ther. 2019;49:112.
14. Jemel N, Gader G, Bedioui A, Zammel I, Badri M. C1 C2 spinal cord compression in hereditary multiple exostoses: case report and review of the literature. Int J Surg Case Rep. 2021;89:106576.
15. Bukowska-Olech E, Trzebiatowska W, Czech W, et al. Hereditary multiple exostoses-a review of the molecular background, diagnostics, and potential therapeutic strategies. Front Genet. 2021;12:759129.
16. Shu C, Smith SS, Little CB, Melrose J. Comparative immunolocalisation of perlecan, heparan sulphate, fibroblast growth factor-18, and fibroblast growth factor receptor-3 and their prospective roles in chondrogenic and osteogenic development of the human foetal spine. Eur Spine J. 2013;22:1774-1784.
17. Furtado Freitas L, Schaefer Abu Hana L, Alves Benjamin M, Dias Junior M, Duarte ML. Hereditary multiple exostoses with spinal canal involvement. Medicina (B Aires). 2023;83:493.

18. van den Hurk L, van den Besselaar M, Scheltinga M. Exercise induced neuropathic lower leg pain due to a tibial bone exostosis. Phys Sportsmed. 2021;49:363-366.
19. Huang H, Zhang X, Wang Y, Tang H, Huang X, Zhang H, Li D. Popliteal artery pseudoaneurysm and secondary ipsilateral deep vein thrombosis caused by an exostosis in a mature adult. J Vasc Surg Cases Innov Tech. 2023;10:101375.
20. Kawashima K, Ogawa H, Komura S, et al. Heparan sulfate deficiency leads to hypertrophic chondrocytes by increasing bone morphogenetic protein signaling. Osteoarthritis Cartilage. 2020;28:1459-1470.
21. Clement ND, Porter DE. Can deformity of the knee and longitudinal growth of the leg be predicted in patients with hereditary multiple exostoses? A cross-sectional study. Knee. 2014;21:299-303.
22. Noonan KJ, Feinberg JR, Levenda A, Snead J, Wurtz LD. Natural history of multiple hereditary osteochondromatosis of the lower extremity and ankle. J Pediatr Orthop. 2002;22:120-124.
23. Wang YZ, Park KW, Oh CS, et al. Developmental pattern of the hip in patients with hereditary multiple exostoses. BMC Musculoskelet Disord. 2015;16:54.
24. Fei L, Ngoh C, Porter DE. Chondrosarcoma transformation in hereditary multiple exostoses: a systematic review and clinical and cost-effectiveness of a proposed screening model. J Bone Oncol. 2018;13:114-122.
25. Beltrami G, Ristori G, Scoccianti G, Tamburini A, Capanna R. Hereditary multiple exostoses: a review of clinical appearance and metabolic pattern. Clin Cases Miner Bone Metab. 2016;13:110-118.
26. Tepelenis K, Papathanakos G, Kitsouli A, et al. Osteochondromas: an updated review of epidemiology, pathogenesis, clinical presentation, radiological features and treatment options. In Vivo. 2021;35:681-691.
27. Comisi FF, Comisi AM, Esposito E, Savasta S. Malignancy ratio in pediatric patients with hereditary multiple exostoses: true association or reporting bias? Pediatr Rep. 2025;17:132.
28. Wu Q, Xiao BO, Li LI, Feng LI. Atypical teratoid/rhabdoid tumor with hereditary multiple exostoses in an 18-year-old male: a case report. Oncol Lett. 2015;10:1561-1564.
29. Ramírez Calas RA, González Millán T, Mohammed S, Azahares Leal G, Amadu M, Sadat Seidu A. Advanced colon cancer coexisting with multiple osteochondromatosis in a child; coincidence or causality? - A case report. Int J Surg Case Rep. 2023;108:108427.
30. Pata G, Nascimbeni R, Di Lorenzo D, Gervasi M, Villanacci V, Salerni B. Hereditary multiple exostoses and juvenile colon carcinoma: a case with a common genetic background? J Surg Oncol. 2009;100:520-522.
31. Chudina AP, Akulenko LV, Prokopenko VD. Sochetanie mnozhestvennyk ékzostozov i raka legkikh v odnoĭ sem'e [Combination of multiple exostoses and lung cancer in 1 family]. Vopr Onkol. 1981;27:81-83. Russian.
32. Nakane T, Goi K, Oshiro H, Kobayashi C, Sato H, Kubota T, Sugita K. Pre-B-cell acute lymphoblastic leukemia in a boy with hereditary multiple exostoses caused by EXT1 deletion. Pediatr Hematol Oncol. 2014;31:667-669.
33. Caino S, Cubilla MA, Alba R, et al. Clinical and genetic analysis of multiple osteochondromas in a cohort of argentine patients. Genes (Basel). 2022 ;13:2063.
34. Delgado MA, Martinez-Domenech G, Sarrión P, et al. A broad spectrum of genomic changes in latinamerican patients with EXT1/EXT2-CDG. Sci Rep. 2014;4:6407.
35. Pacifici M. The pathogenic roles of heparan sulfate deficiency in hereditary multiple exostoses. Matrix Biol. 2018;71-72:28-39.
36. Kim S, Lee CH, Choi SY, Kim MK, Jung ST. A genotype-phenotype study of multiple hereditary exostoses in forty-three patients. J Clin Med. 2022;11:3703.
37. Kablan A, Sezer A, Bakır A, et al. Multilocus disease-causing genomic variations for genetic disorders: single tertiary centre experience from Türkiye. Clin Genet. 2025;108:240-258.