Int J Clin Exp Pathol 2017;10(3):3543-3550
www.ijcep.com /ISSN:1936-2625/IJCEP0040277

Case Report

Characterization of a rare case of a bone bridge formed by osteochondromas associated with a novel EXT2 mutation in a patient with hereditary multiple osteochondromas

Qing Bi[1*], Li Cao[3], Weiwei Ruan[2*], Youjia Xu[4]

[1]Soochow University, Suzhou, China; [2]Wenzhou Medical University, Wenzhou, China; [3]Zhejiang Provincial People's Hospital, Zhejiang, China; [4]Department of Orthopedics, The Second Affiliated Hospital of Soochow University, Suzhou, China. [*]Equal contributors.

Received September 19, 2016; Accepted September 27, 2016; Epub March 1, 2017; Published March 15, 2017

Abstract: Hereditary multiple osteochondromas (HMO) is an autosomal dominant bone disorder that presents as multiple benign cartilage-capped tumors. The major morbigenous genes *EXT1* and *EXT2* account for 90% of HMO cases. In HMO patients, osteochondromas appear adjacent to the physis and remain in the metaphyseal lesion of the long bones. Consequently, it is uncommon for osteochondromas to form a bone bridge in the inferior tibiofibular syndesmosis. We present a rare case of a 20-year-old female patient with HMO with limited flexing range in her left ankle joint. Based on plain radiographs, a bone bridge formed by osteochondromas was situated in the distal tibiofibular syndesmosis of her left ankle. A novel nonsense mutation, c.67C>T p.Arg23X in exon 2 of the *EXT2* gene, was discovered; we inferred that this mutation was the cause of HMO.

Keywords: Hereditary multiple osteochondromas, *EXT2*, bone bridge, nonsense mutation

Introduction

Osteochondromas, also called osteocartilaginous exostoses, are benign growths capped with hyaline cartilage; they represent the majority of bone tumors. Solitary osteochondromas are not inborn, but develop in a single bone. Hereditary multiple osteochondromas (HMO), is an autosomal dominant disorder characterized by the abundant duplication of a solitary exostosis [1]. Genetic studies have demonstrated associations between HMO and three loci, *EXT1* [2], which maps to 8q24.1, *EXT2* [3], which maps to 11p13, and *EXT3* [4], which is located on the short arm of chromosome 19 (the exact position is unknown). An estimated half of all HMO patients have *EXT1* mutations, and one-third have *EXT2* mutations [5].

The size and number of osteochondromas often increase during childhood and adolescence. In fact, these tumors can occur on almost every bone, including the short bones, flat bones, and irregular bones, though they are preferentially located at the juxta-epiphyseal region of the long bones [6]. Patients with HMO typically have no symptoms, unless the pressure exerted by the osteochondroma affects the adjacent muscles, tendons, nerves, or blood vessels [7]. The clinical manifestation is often related to this pressure and includes pain, angular deformities, short stature, restricted joint motion, fracture of the lesion itself, inflammatory changes of the bursa exostotica covering the cartilaginous cap, and even malignant transformation [8].

Osteochondromas generally develop in the growth plate of the long bones of children and subsequently grow toward the diaphysis [9]. Bone bridges formed by osteochondromas are a rare phenomenon. In these cases, patients can experience pain and discomfort as well as a restricted range-of-motion.

In this study, we performed clinical, imaging, histological, and genetic analyses of a patient with typical HMO with a bone bridge formed by

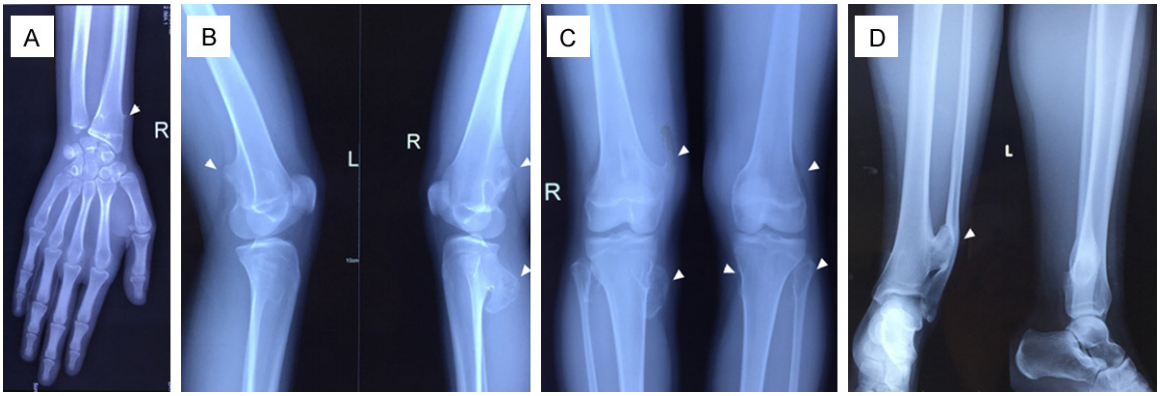

Figure 1. Radiographs of patient III1. A: Osteochondromas on the distal radius. B and C: Multiple osteochondromas were noted around the bilateral knee (white arrows). D: Osteochondromas in the distal tibiofibular syndesmosis of the left ankle.

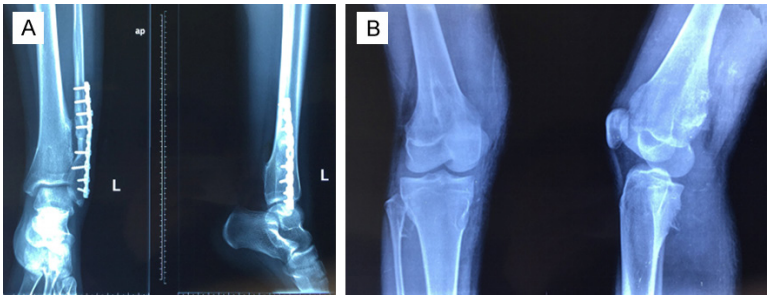

Figure 2. Radiographs after the first surgery.

osteochondromas located in the distal tibiofibular syndesmosis of her left ankle. To the best of our knowledge, this is the first reported incidence of a HMO patient with a bone bridge formed by osteochondromas. Based on a genetic analysis of the patient and her family members, we detected a novel nonsense mutation, c.67C>T p.Arg23X, near the *EXT2* exostosin domain that results in a protein truncation of 705 C-terminal amino acids.

Case report

Five and half years ago, a 20-year-old, short-statured female patient presented at our clinic with multiple elevated bony prominences and a limited ability to bend her left ankle for approximately 1 year. She had no history of trauma. The bony prominences and shape anomalies were asymptomatic and were initially observed when she was 4 years old. They progressively increased in size and extent. She first experienced pain when her left ankle was at its maximum bending angle seven years prior to visiting our clinic, and she experienced progressive limitation in vigorous activity. The patient was also uncomfortable with the appearance of the multiple osteochondromas.

The patient had a family history of HMO on the paternal side. Her father, aunt, and paternal grandfather also had short statures and multiple elevated exostoses in various locations, but they had no limitations in joint mobility and no notable symptoms. The pedigree of this Chinese family is shown in **Figure 7**.

A physical examination revealed multiple bony prominences around her right knee and wrist, with hard, clear boundaries, no activity, and no tenderness. However, there was significant pain in the left ankle joint during loaded flexion. Although the left ankle was capable of activity, the maximum dorsiflexion was 10° and the maximum plantar flexion was 30°. The circumference of the left ankle was 4.5 cm longer than that of the right ankle. The function of her left ankle was normal. Plain radiographs revealed exostoses in the right distal radius, bilateral distal femur, and bilateral proximal tibia, and a bone bridge in the distal tibiofibular syndesmosis of the left ankle (**Figure 1**).

Surgical excision was performed owing to the pain and limited motion experienced by the patient and the unknown nature of the lesion. Under general anesthesia, the patient was

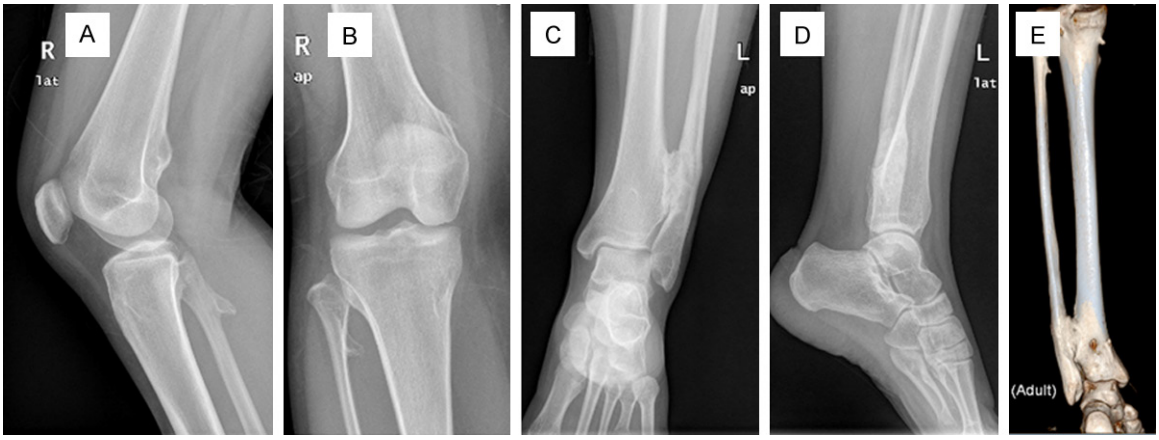

Figure 3. A and B: There were no new osteochondromas around the right knee. C-E: Bone fusion at the distal tibiofibular syndesmosis of the left ankle.

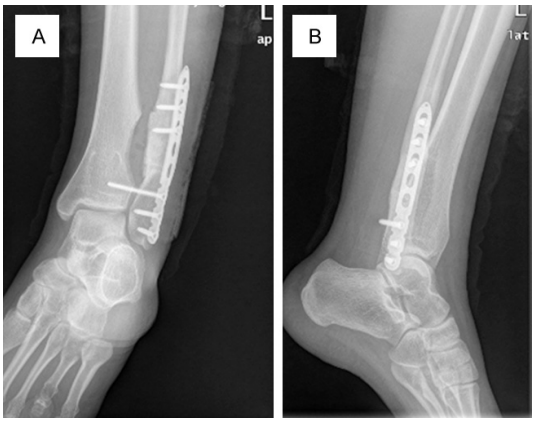

Figure 4. Radiographs after the third surgery.

placed in a supine position on the operating table. Sandbags were placed under the ipsilateral hip to easily reveal lateral and forward positions. We observed a decreased bending range, with a maximum dorsiflexion angle of 10°. We make a lateral fibular incision of approximately 10 cm to reveal the fibula. We stripped the periosteum of the leading edge of the fibula and exposed the bone tumors at the distal tibiofibular syndesmosis. We observed a bone tumor compressing the fibula at the distal tibiofibular syndesmosis, and cut the fibula at the distal tibiofibular syndesmosis. After the complete resection of the tumor, we reset the fibula using nickel clad and screws. During surgery, C-arm fluoroscopy revealed that the fibula was well-positioned on the line and the fixed position was good. A dramatic improvement was observed in the bending range, with a maximum dorsiflexion angle of 20°, which indicated that the bone bridge was preventing the right knee from bending fully. For aesthetic reasons, the protuberant extra-articular osteochondromas in the tibia and the femur around her right knee were resected via small incisions.

Pathological analyses of the bone tumors indicated typical HMO (**Figure 5B**). After surgery, the pain during loaded flexion in the left ankle was dramatically relieved. Two years after the removal, the knee was symptomless and no signs of recurrence were detected in a radiograph analysis. Two years later, the patient removed the internal fixation of fibula devices. Six months ago, the patient felt soreness, pain, and limited mobility in the left ankle. A physical examination revealed decreased activity of the ankle. Plain radiographs and CT showed that a bone was protruding in the left tibia near the ankle (**Figure 3**). Surgical excision was performed, using the original approach, owing to the pain and limited motion experienced by the patient and because the exact nature of the lesion was not known. We detected the bony fusion at the distal tibiofibular syndesmosis, which then we resected completely and sent to pathology (**Figure 5A**). We used a plate and screw at the outside of the fibula and fixed the distal tibiofibular syndesmosis by syndesmosis screw fixation.

To identify the genetic basis of HMO in our patient, each exon of *EXT1* and *EXT2* was sequenced in the patient and three affected family members (I1, II2, II3, and III1) as well as four unaffected family members (I2, II1, II4, and III2). After data filtering procedures, we discov-

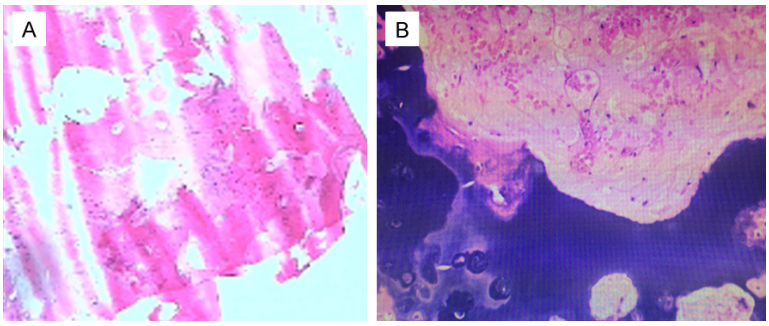

Figure 5. A: Pathological analyses revealed mostly mature bone tissue and local cartilage ossification. B: Pathology revealed hereditary multiple osteochondromas with three layers (i.e., fibrous perichondrium, cartilage cap, and bone).

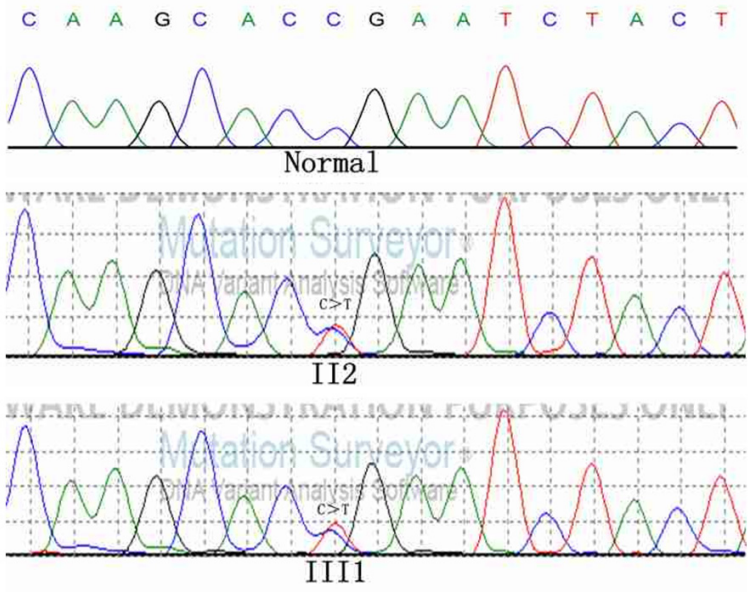

Figure 6. The heterozygous nonsense mutation c.67C>T (p.Arg23X) was detected in the *EXT2* gene of HMO patients, but not in the healthy controls.

ered a novel nonsense mutation in *EXT2*, c.67C>C/T (amino acid 23R>X), in all 4 HMO patients (**Figure 6**).

Discussion

Most osteochondromas are not hereditary and occur singly [10, 11]. However, approximately 15% of patients have two or more osteochondromas [12, 13], and the vast majority of these patients (over 70%) have a family history indicating HMO. Although they are benign tumors, there are common complications in patients with HMO, including abnormal skeletal growth, bone deformities, and short stature (37%), limited joint mobility and early-onset osteoarthritis (14%) [13], pain due to nerve compression (22.6%), blood circulation disorders caused by vascular compression (11.3%), and so on. Hand deformities caused by short metacarpals are also common [5, 14]. There are also more serious complications; osteochondroma can become chondrosarcoma or osteosarcoma, and the rate of malignant transformation is approximately 0.5% to 2% [12, 15, 16].

Bone bridges formed by osteochondromas are rare in patients with HMO and have not been described previously. The bone bridge not only made the fibula diastrophic, but also injured the distal tibiofibular syndesmosis, affecting ankle function. The syndesmosis maintains the structural stability of the ankle joint. Ankle fractures are often combined with varying degrees of tibiofibular joint damage, resulting in chronic ankle instability and traumatic arthritis.

For orthopedic or functional reasons, approximately 75% of patients with HME accept one or more osteochondroma surgical procedures [15]. The patient in our case study accepted surgery to resect the osteochondroma and correct the force line of the fibula. Injury of the distal tibiofibular syndesmosis without fracture is uncommon [17-22]. Our understanding of the disruption of the distal tibiofibular syndesmosis is insufficient, and it was not resolved during the first operation. After removing the fixation, instability of the ankle may have caused hyperostosis at the distal tibiofibular syndesmosis. There is still no gold standard for the treatment of chronic disruption of the distal tibiofibular syndesmosis, although several relevant techniques have

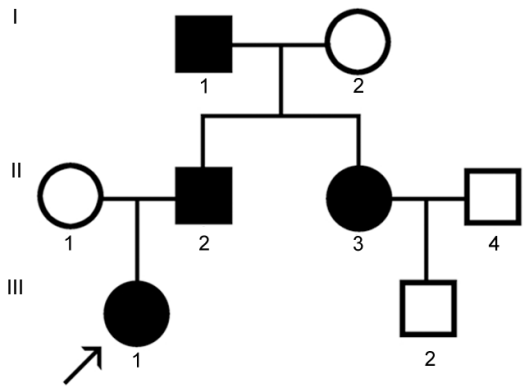

Figure 7. Pedigree of the Chinese family with hereditary multiple osteochondromas. The filled symbols indicate affected individuals and empty symbols indicate unaffected family members. The proband (III1) is noted with an arrow. There was no consanguinity in this family. HMO, hereditary multiple osteochondroma.

been reported [23-32]. Harper used a similar surgical technique to ours for an external rotation stage 4 fracture and evaluated the performance of syndesmosis screw fixation with or without syndesmosis debridement in 6 patients with chronic disruption after pronation [24]. The efficacy of arthroscopic debridement of the distal tibiofibular syndesmosis and medial gutter with percutaneous fixation of the syndesmosis using screws, which is a less invasive technique, has also been described [25]. Some researchers have recommended arthrodesis of the distal tibiofibular joint for chronic cases [30-32]. Katznelson et al. [30] performed arthrodesis of the distal tibiofibular joint in 5 patients, among whom 4 had no pain and full range of motion of the ankle joint at one year after surgery. We fixed the distal tibiofibular syndesmosis by syndesmosis screw fixation. After 6 months, pain in the left ankle was dramatically relieved and we observed a notable improvement in the bending range. Usually, osteochondroma growth occurs over time and eventually stops, then the likelihood of its new small osteoma body [1]. **Figures 2B**, **3A**, **3B** and **4** show images of our patient with no evidence of recurrence. After 20 years, patients have no new osteochondroma, and existing osteochondromas do not increase.

The osteochondroma system is composed of three different tissue types: the substrate and tumor made of bone, fibrous cap made of hyaline cartilage, and envelope made of fibers. The deep envelope is cartilage tissue that produces hyaline cartilage. Disordered cartilage growth plates shift to the outside and proliferates along the long diagonal axis, away from the adjacent joint bone, forming cartilaginous, fibrous cartilage or bony cartilaginous bodies. Osteochondroma occurs by calcification or ossification to form bone-like bodies [9, 33].

EXT1 is approximately 250 kb, containing 11 exons and encoding 746 amino acids [34], and *EXT2* is approximately 110 kb, containing 14 exons and encoding 718 amino acids [35]. They have an amino acid similarity of 30.9% [36]. Both EXT1 and EXT2 are widely expressed, and the proteins encoded by *EXT1* and *EXT2* are localized to the endoplasmic reticulum. EXTI and EXT2 can form a heterodimer. Glycosyltransferase activity of heterologous oligomeric complexes is much higher than that of EXT1 or EXT2 alone [37]. The heterodimer is a biological form of heparan sulfate polymerase, which explains why different *EXT* mutations can lead to very similar clinical phenotypes. Mutations in either EXT1 or EXT2 can lead to the insufficient synthesis of heparan sulfate and HSPG [39-41], and disrupt signaling of growth plate IHH and FGF [42-44]. Accordingly, signaling involved in normal bone development is interrupted, promoting early cartilage differentiation and increased chondrocyte proliferation. The bone in adjacent regions grows abnormally [45], leading to the occurrence of HME.

In China, *EXT2* mutations are more common than *EXTI* mutations [46]. Nonsense mutations, frameshift mutations, and splice site mutations, which result in truncated proteins, explain HME in 80% of patients [47]. *EXTI* mutations are broadly distributed and have been detected in each exon [48, 49]. *EXT2* mutations are rare in the final third of the coding region [47].

The 23R>X nonsense mutation resulted in a truncated EXT2 protein lacking 705 amino acids at the C-terminus (**Figure 3B**). Although the glycosyltransferase and exostosin domains play significant roles in HS biosynthesis, the loss of the C-terminus may have an important impact on EXT2 function, especially with respect to HS biosynthesis.

Acknowledgements

We thank the patient and her family members for their interest and cooperation. The study was supported by a grant from the Science and Technology Department of Zhejiang Province (2016C37123) and Medicine & Health Platform Key Project of Zhejiang Province (2012ZDA003) to Q.B.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Youjia Xu, Department of Orthopedics, The Second Affiliated Hospital of Soochow University, 1055 Sanxiang Road, Gusu District, Suzhou 215006, China. Tel: +86-512-68282030; Fax: +86-512-68284303; E-mail: youjiaxu_1@126.com

References

[1] Solomon L. Hereditary Multiple Exostosis. Am J Hum Genet 1964; 16: 351-63.
[2] Cook A, Raskind W, Blanton SH, Pauli RM, Gregg RG, Francomano CA, Puffenberger E, Conrad EU, Schmale G, Schellenberg G, et al. Genetic heterogeneity in families with hereditary multiple exostoses. Am J Hum Genet 1993; 53: 71-79.
[3] Wu YQ, Heutink P, de Vries BB, Sandkuijl LA, van den Ouweland AM, Niermeijer MF, Galjaard H, Reyniers E, Willems PJ, Halley DJ. Assignment of a second locus for multiple exostoses to the pericentromeric region of chromosome 11. Hum Mol Genet 1994; 3: 167-171.
[4] Le Merrer M, Legeai-Mallet L, Jeannin PM, Horsthemke B, Schinzel A, Plauchu H, Toutain A, Achard F, Munnich A, Maroteaux P. A gene for hereditary multiple exostoses maps to chromosome 19p. Hum Mol Genet 1994; 3: 717-722.
[5] Porter DE, Lonie L, Fraser M, Dobson-Stone C, Porter JR, Monaco AP, Simpson AH. Severity of disease and risk of malignant change in hereditary multiple exostoses. A genotype-phenotype stuay. J Bone Joint Surg Br 2004; 86: 1041-6.
[6] Cao L, Liu F, Kong M, Fang Y, Gu H, Chen Y, Zhao C, Zhang S, Bi Q. Novel EXT1 mutation identified in a pedigree with hereditary multiple exostoses. Oncol Rep 2014; 31: 713-718.
[7] Takahashi M, Nishihara A, Ohishi T, Shiga K, Yamamoto K and Nagano A. Arthroscopic resection of an intra-articular osteochondroma of the knee in the patient with multiple osteochondromatosis. Arthroscopy 2004; 20 Suppl 2: 28-31.
[8] Vanhoenacker FM, Van Hul W, Wuyts W, Willems PJ and De Schepper AM. Hereditary multiple exostoses: from genetics to clinical syndrome and complications. Eur J Radiol 2001; 40: 208-217.
[9] Wicklund CL, Pauli RM, Johnston D, Hecht JT. Natural history study of hereditary multiple exostoses. Am J Med Genet 1995; 55: 43-6.
[10] Volpi N, Dotti MT, Giannini F, Cappelli B, Terrosi Vagnoli P, Federico A. Familial multiple exostoses syndrome: 4 phacomatosis of bone Tissue. Acta Neural (Napoli) 1986; 8: 516-27.
[11] Koehl GL and Tilson HB. Osteochondromas associated with facial asymmetry and masticatory dysfunction: report of two cases. J Oral Surg 1977; 35: 934-9.
[12] Hennekam RC. Hereditary multiple exostoses. J Med Genet 1991; 28: 262-6.
[13] Paik NJ, Han TR, Lim SJ. Multiple peripheral nerve compressions related to malignantly transformed hereditary multiple exostoses. Muscle Nerve 2000; 23: 1290-4.
[14] Shapiro F, Simon S and Glimcher MJ. Hereditary multiple exostoses Anthropometric, roentgenographic, and clinical aspects. J Bone Joint Surg Am 1979; 61: 815-24.
[15] Schmale GA, Conrad EU 3rd, Raskind WH. The natural history of hereditary multiple exostoses. J Bone Joint Surg Am 1994; 76: 986-92.
[16] Nawata K, Teshima R, Minamizaki T, Yamamoto K. Knee deformities in multiple hereditary exostoses. A longitudinal radiographic stuay. Clin Orthop Relat Res 1995; 194-9.
[17] Edwards GS Jr, DeLee JC. Ankle diastasis without fracture. Foot Ankle 1984; 4: 305-312.
[18] Marymont JV, Lynch MA, Henning CE. Acute ligamentous diastasis of the ankle without fracture. Evaluation by radionuclide imaging. Am J Sports Med 1986; 14: 407-409.
[19] Boytim MJ, Fischer DA, Neumann L. Syndesmotic ankle sprains. Am J Sports Med 1991; 19: 294-298.
[20] Hopkinson WJ, St Pierre P, Ryan JB, Wheeler JH. Syndesmosis sprains of the ankle. Foot Ankle 1990; 10: 325-330.
[21] Taylor DC, Englehardt DL, Bassett FH 3rd. Syndesmosis sprains of the ankle. The influence of heterotopic ossification. Am J Sports Med 1992; 20: 146-150.
[22] Miller CD, Shelton WR, Barrett GR, Savoie FH, Dukes AD. Deltoid and syndesmosis ligament injury of the ankle without fracture. Am J Sports Med 1995; 23: 746-750.
[23] Beals TC, Manoli A 2nd. Late syndesmosis reconstruction: a case report. Foot Ankle Int 1998; 19: 485-488.
[24] Harper MC. Delayed reduction and stabilization of the tibiofibular syndesmosis. Foot Ankle Int 2001; 22: 15-18.

[25] Schuberth JM, Jennings MM, Lau AC. Arthroscopy-assisted repair of latent syndesmotic instability of the ankle. Arthroscopy 2008; 24: 868-874.
[26] Beumer A, Heijboer RP, Fontijne WP, Swierstra BA. Late reconstruction of the anterior distal tibiofibular syndesmosis: good outcome in 9 patients. Acta Orthop Scand 2000; 71: 519-521.
[27] Mosier-LaClair S, Pike H, Pomeroy G. Syndesmosis injuries: acute, chronic, new techniques for failed management. Foot Ankle Clin 2002; 7: 551-565, ix.
[28] Grass R, Rammelt S, Biewener A, Zwipp H. Peroneus longus ligamentoplasty for chronic instability of the distal tibiofibular syndesmosis. Foot Ankle Int 2003; 24: 392-397.
[29] Morris MW, Rice P, Schneider TE. Distal tibiofibular syndesmosis reconstruction using a free hamstring autograft. Foot Ankle Int 2009; 30: 506-511.
[30] Katznelson A, Lin E, Militiano J. Ruptures of the ligaments about the tibio-fibular syndesmosis. Injury 1983; 15: 170-172.
[31] Espinosa N, Smerek JP, Myerson MS. Acute and chronic syndesmosis injuries: pathomechanisms, diagnosis and management. Foot Ankle Clin 2006; 11: 639-657.
[32] Peña FA, Coetzee JC. Ankle syndesmosis injuries. Foot Ankle Clin 2006; 11: 35-50, viii.
[33] Gigante M, Matera MG, Seripa D, Izzo AM, Venanzi R, Giannotti A, Digilio MC, Gravina C, Lazzari M, Monteleone G, Monteleone M, Dallapiccola B, Fazio VM. Ext-mutation analysis in Italian sporadic and hereditary osteochondromas. Int J Caneer 2001; 95: 378-83.
[34] Stickens D, Clines G, Burbee D, Ramos P, Thomas S, Hogue D, Hecht JT, Lovett M, Evans GA. The EXT2 multiple exostoses gene defines a family of putative tumour suppressor genes. Nat Genet 1996; 14: 25-32.
[35] Wuyts W, Van Hul W, Wauters J, Nemtsova M, Reyniers E, Van Hul EV, De Boulle K, de Vries BB, Hendrickx J, Herrygers I, Bossuyt P, Balemans W, Fransen E, Vits L, Coucke P, Nowak NJ, Shows TB, Mallet L, van den Ouweland AM, McGaughran J, Halley DJ, Willems PJ. Positional cloning of a gene involved in hereditary multiple exostoses. Hum Mol Genet 1996; 5: 1547-57.
[36] Van Hul W, Wuyts W, Hendrickx J, Speleman F, Wauters J, De Boulle K, Van Roy N, Bossuyt P, Willems PJ. Identification of a third EXT-like gene (EXTL3) belonging to the EXT gene family. Genomics 1998; 47: 230-7.
[37] McCormick C, Duncan G, Goutsos KT, Tufaro F. The putative tumor suppressors EXT1 and EXT2 form a stable complex that acumulates in the Golgi apparatus and catalyzes the synthesis of heparan sulfate. Proc Natl Acad Sci U S A 2000; 97: 668-73.
[38] Kitagawa H, Shimakawa H, Sugahara K. The tumor suppressor EXT-like gene EXTL2 encodes an alpha1, 4-N-acetylhexosaminyltransferase that transfers N-acetylgalactosamine and N-acetylglucosamine to the common glycosaminoglycan-protein linkage region. The key enzyme for the chain initiation of heparan sulfate. J Biol Chem 1999; 274: 13933-7.
[39] Hameetman L, Szuhai K, Yavas A, Knijnenburg J, van Duin M, van Dekken H, Taminiau AH, Cleton-Jansen AM, Bovée JV, Hogendoorn PC. The role of EXT1 in nonhereditary osteochondroma: identification of homozygous deletions. J Natl Cancer Inst 2007; 99: 396-406.
[40] Hameetman L, David G, Yavas A, White SJ, Taminiau AH, Cleton-Jansen AM, Hogendoorn PC, Bovée JV. Decreased EXT expression and intracellular accumulation of heparan sulphate proteoglycan in osteochondromas and peripheral chondrosarcomas. J Pathol 2007; 211: 399-409.
[41] Romeo S, Oosting J, Rozeman LB, Hameetman L, Taminiau AH, Cleton-Jansen AM, Bovée JV, Hogendoorn PC. The role of noncartilage-specific molecules in differentiation of cartilaginous tumors: lessons from chondroblastoma and chondromyxoid fibroma. Cancer 2007; 110: 385-94.
[42] Bornemann DJ, Duncan JE, Staatz W, Selleck S, Warrior R. Abrogation of heparan sulfate synthesis in Drosophila disrupts the wingless, Hedgehog and Decapentaplegic signaling pathways. Development 2004; 131: 1927-38.
[43] Bellaiche Y, The I, Perrimon N. Tout-velu is a Drosophila homologue of the putative tumour suppressor EXT-1 and is needed for Hh diffusion. Nature 1998; 394: 85-8.
[44] Lai LP, Mitchell J. Indian hedgehog: its roles and regulation in endochondral bone development. J Cell Biochem 2005; 96: 1163-73.
[45] Duncan G, McCormick C, Tufaro F. The link between heparan sulfate and hereditary bone disease: finding a function for the EXT family of putative tumor suppressor proteins. J Clin Invest 2001; 108: 511-6.
[46] Xu L, Xia J, Jiang H, Zhou J, Li H, Wang D, Pan Q, Long Z, Fan C, Deng HX. Mutation analysis of hereditary multiple exostoses in the Chinese. Hum Genet 1999; 105: 45-50.
[47] Wuyts W and Van Hul W. Molecular basis of multiple exostoses: mutations in the EXT1 and EXT2 genes. Hum Mutat 2000; 15: 220-7.
[48] Lonie L, Porter DE, Fraser M, Cole T, Wise C, Yates L, Wakeling E, Blair E, Morava E, Monaco AP, Ragoussis J. Determination of the mutation spectrum of the EXTI/EXT2 genes in British Caucasian patients with multiple osteochon-

dromas, and exclusion of six candidate genes in EXT negative cases. Hum Murat 2006; 27: 1160.

[49] Raskind WH, Conrad EU 3rd, Matsushita M, Wijsman EM, Wells DE, Chapman N, Sandell LJ, Wagner M, Houck J. Evaluation of locus heterogeneity and EXT1 mutations in 34 families with hereditary multiple exostoses. Hum Mutat 1998; 11: 231-9.