

Chondrosarcoma in a family with multiple hereditary exostoses

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Multiple hereditary exostoses is an autosomal dominant skeletal disorder in which there are numerous cartilage-capped excrescences in areas of actively growing bone. The condition is genetically heterogeneous, and at least three genes, *ext1*, *ext2* and *ext3* are involved. The reported risk for malignant transformation to chondrosarcoma has been from 0.6% to 2.8%. We have reviewed six generations of a family with 114 living adult members, 46 of them with multiple exostoses. Four have had operations for chondrosarcoma, giving the risk for malignant transformation as 8.3% in this family. Clinical and radiological examination revealed two additional patients with a suspicion of malignancy, but in whom the histological findings were benign. Reported elsewhere in detail, genetic linkage analysis mapped the causative gene to chromosome 11 and molecular studies revealed a guanine-to-thymine transversion in the *ext2* gene. Patients with multiple hereditary exostoses carry a relatively high risk of malignant transformation. They should be informed of this possibility and regularly reviewed.

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Multiple hereditary exostoses (MHE) is a heterogeneous, autosomal-dominant skeletal disorder in which the penetrance is from 96% to 100%.¹ There are numerous cartil-

age-capped bony protuberances at the juxtaepiphyseal areas of the axial skeleton which are usually detectable before the age of 12 years. The exostoses grow during childhood, and may cause symptoms as a result of compression of local tissues, deformities and discrepancies of length. Typically, they appear in the metaphyseal regions of the distal and proximal tibia, distal femur, proximal humerus, and in the pelvis and scapula.² The patients tend to be short. Relative shortening of the ulna is common with bowing of the forearm. Coxa valga and coxa magna may predispose to early degenerative osteoarthritis.^{3,4} Distal varus deformity of the femur and valgus deformity of the tibia may occur.⁵

A serious complication of MHE is the malignant transformation of an exostosis to chondrosarcoma and, rarely, to other malignancies.⁶

The prevalence of MHE is at least 1/50 000. The genetic heterogeneity has been shown by detection of at least three gene loci, at which mutations cause the same or similar clinical phenotypes. The *ext1* on chromosome 8q24.1 and the *ext2* on chromosome 11p11 have been identified by positional cloning.⁷⁻⁹ The *ext3* has been mapped to 19p by linkage analysis.¹⁰ In addition, several *ext*-like (*ext1*) genes have been found which have a similarity of sequence to other *ext*-genes, indicating that both *ext* and *ext1* genes are members of the same gene family.¹¹⁻¹³

Loss of heterozygosity has been observed with markers linked to the *ext1* and *ext2* genes in both sporadic and exostosis-derived tumours and with a marker linked to *ext3* in one sporadic tumour.¹⁴⁻¹⁷

Alarmed by the occurrence of four cases of chondrosarcoma in the same MHE family, we have reviewed six generations of the kindred clinically and radiologically in order to detect the risk of malignant transformation, to describe the clinical phenotype and to review the value of MRI as a technique for finding early stages of chondrosarcoma in exostoses of the pelvis. The gene mutation is a novel splice site mutation of the *ext2* gene, and it has been reported elsewhere in detail.¹⁸

Patients and Methods

The proband (case 4), a woman with familial multiple exostoses, was referred for treatment of a chondrosarcoma.

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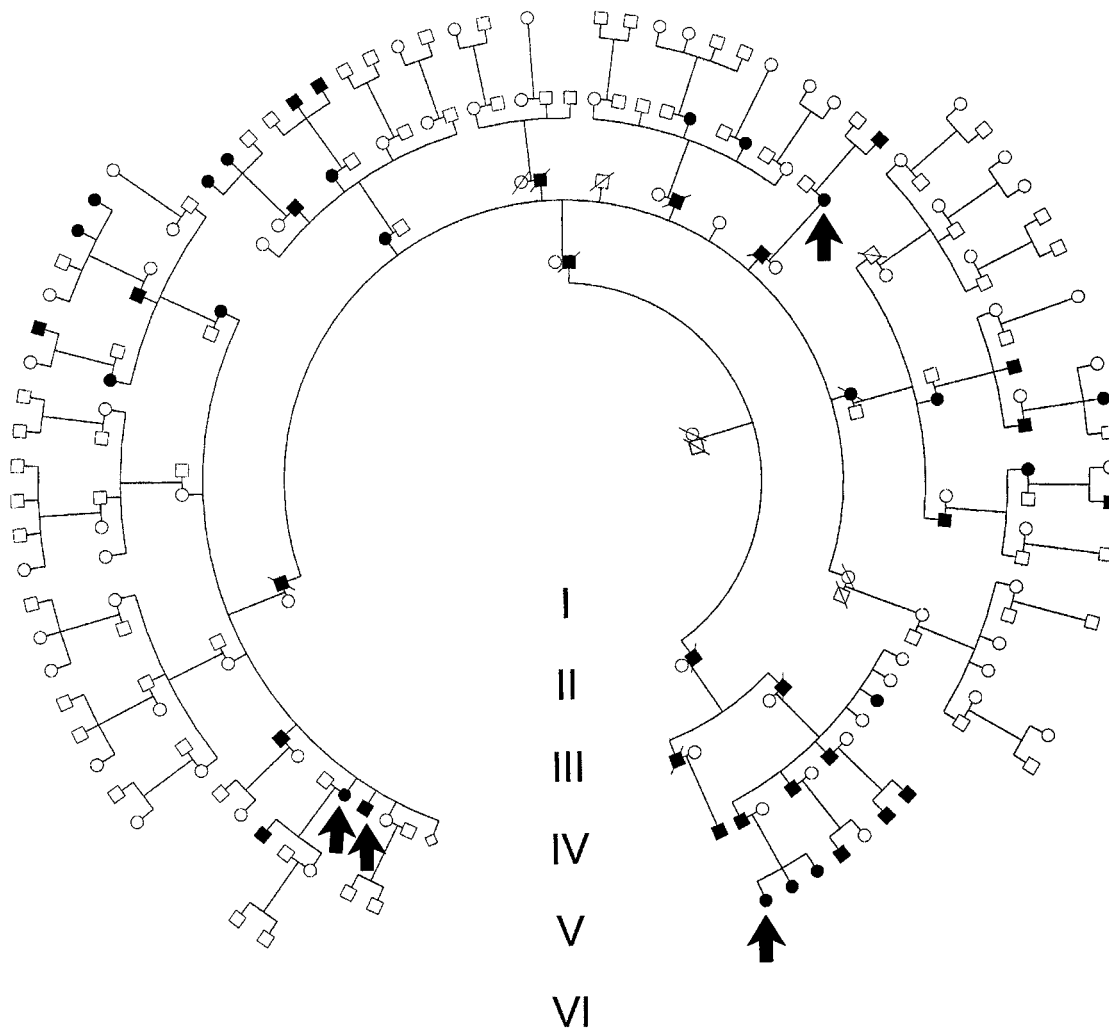


Fig. 1

The pedigree of the family. The affected men are shown as dark boxes and the affected women as dark circles. The individuals with chondrosarcoma are shown with arrows.

Further study revealed three additional family members with this tumour. The family history of multiple exostoses was reviewed, and through an affected member of the family, the individuals over 13 years of age were informed about the purpose of the study. The pedigree consisted of 144 members in six generations from which 28 men and 20 women had a history of or had been troubled by multiple exostoses (Fig. 1). There were 18 children in the pedigree. All 114 living members of the family, aged from 18 to 70 years, were invited to participate in the study; 37 individuals agreed to collaborate with the clinical part of the investigation.

The assessment included the clinical history, age at detection, the number and distribution of and any difficulties caused by the exostoses. Surgical interventions were recorded. The physical examination consisted of inspection, palpation, and detailed measurements of the patient, and

radiological studies of plain films of the bony prominences with symptoms.

The radiological protocol included taking plain films of the symptomatic bony prominences. MRI with conventional T1 and T2 sequences without contrast enhancement, was used to screen the pelvis, proximal femora and proximal humeri of all affected individuals. If any irregularities were observed on the plain films around the margins of the exostoses, MRI with intravenous contrast enhancement was undertaken. The equipment was an open 0.23 T MRI unit (Outlook; Picker Nordstar, Helsinki, Finland). The aim was to find a cartilage cap, to assess its size, and to detect possible neoplastic contrast enhancement.

The histological diagnoses of the chondrosarcomas were reconfirmed and graded from I to III according to cellularity, number of double-nucleated cells, and nuclear pleomorphism.¹⁹ Grade-I tumours were the most differentiated.



Fig. 2

A suspicious left posterior pelvic lesion (arrow) seen on screening MRI. Biopsy indicated a benign exostosis.

The members of the family were given genetic counseling after the clinical review and search for the gene mutation had been completed.

The study protocol was assessed and accepted by the Ethics Committee of the hospital.

Results

From the 37 patients in the clinical study, 23 (9 men and 14 women) had multiple exostoses. Their mean age was 42 years (13 to 70). Of the 23 affected individuals, 16 had undergone operations for exostoses in the extremities and pelvis, and 16 had bony deformities, either ulnar bowing or limb-length discrepancies exceeding 2 cm. The mean adult height was 179 cm for affected men and 159 cm for women compared with 182 cm for unaffected men and 165 cm for unaffected women in the family.



Fig. 3

MRI revealed an exostosis with irregular suspicious margins (marked with arrow) in the upper humerus. The exostosis had been partially resected years earlier.

MRI was performed on the 23 patients and showed one suspicious lesion in the posterior pelvis. Histological examination showed it to be definitively benign (Fig. 2). One large exostosis of the proximal humerus, which had been partially resected years before, was totally excised because of a suspicious MRI appearance with an irregular, although small, cartilage cap (Fig. 3). Again, histological examination showed a benign lesion. No other MRI studies showed any potential for malignant transformation of exostoses in the pelvis or extremities. The clinical history of the four patients with chondrosarcoma was studied.

Case 1. A 32-year-old woman was referred to the hospital for review of a bony prominence of her left tibia which had



Fig. 4

Case 2. CT of a chondrosarcoma (grade I) in the wing of the ilium.



Fig. 5

Case 3. Radiograph of a chondrosarcoma (grade I) in the distal ulna.

been growing for 18 months. Since the radiological appearances strongly suggested malignancy a below-knee amputation was carried out. Histological examination diagnosed the tumour as a chondrosarcoma. The patient is still alive and free from disease 22 years later.

Case 2. A 43-year-old man sought advice about a mass in the wing of the right ilium during a routine clinical visit for diabetes (Fig. 4). The bony prominence had been growing during the past year and measured 10 × 15 cm before resection. The histological diagnosis was a chondrosarcoma (grade I) and the resection was assessed as marginal. After a follow-up of nine years no recurrence has been observed. He has had no disability since the operation.

Case 3. A 24-year-old woman complained of a mass in her right forearm which was enlarging. The tumour had been growing steadily during her pregnancy, and at the time of the examination it measured 7 × 9 cm. The radiological appearance was of chondrosarcoma in the ulna and the already hypoplastic distal ulna was resected (Fig. 5). Histological examination confirmed that the tumour was a chondrosarcoma (grade I). The patient is free from disease ten years later, and the functional level of the wrist and of the forearm is unchanged.

Case 4. A 52-year-old woman had had a mass on the posterior iliac crest for a year. Biopsy gave a diagnosis of chondrosarcoma (grade II). The tumour was lying behind the left sacroiliac joint covering it over an area of 10 cm in diameter (Fig. 6). It was resected intralesionally and post-

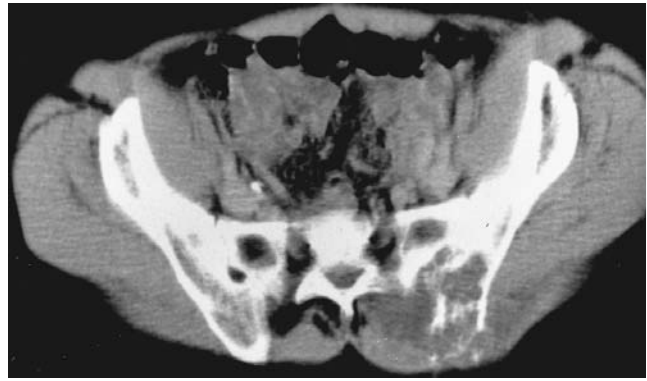


Fig. 6

Case 4. CT of a chondrosarcoma (grade II) overlying the left posterior sacroiliac joint.

operative radiotherapy was given. After a follow-up of four years there are no signs of recurrence.

Discussion

The clinical and radiological phenotype of MHE is usually uniform, but the evolving molecular heterogeneity has not given rise to reports on critical genotype-phenotype analyses. The skeletal prominences, deformations, discrepancies of limb length, limitation of movement, and complications of compression on the soft tissues develop during childhood and early adolescence. This often occurs during the first two years of life and always during the first 12, after which the exostoses appear to cease growing.^{1,20,21} The ratio of solitary, non-familial exostoses to MHE is at least 10:1.⁴

The ratio of affected men to women varies between 0.5 and 1.5 in family reports which, in general, suggest that men are more often affected.^{2,3,20,22,23} Wicklund et al²³ found the mean height of men to be 170 ± 7.9 cm, and that of women 155 ± 6.9 cm. In the present family the affected adult female-to-male ratio was 0.70, and the mean height of the affected women was shorter than that of the unaffected. The men were well within the limits of ordinary Finnish stature.

The malignant transformation of an individual exostosis may occur at any age but rarely in childhood, and it results in a steady growth which is often painless. The prognosis of chondrosarcoma is, in general, favourable if detected early. Therefore patients with MHE should be carefully followed for inappropriate growth of an individual exostosis and treated operatively if malignancy is suspected. The malignant transformation of osteochondromas can be poorly differentiated as evidenced by unique cases.^{24,25}

Garrison et al²² showed that 64 out of 75 patients with secondary chondrosarcoma had grade-I tumours, the rest being grade II and III. There was also a local recurrence rate of 52%. In our family, with four chondrosarcomas,

there has been no recurrence so far. The reported risk of malignant transformation of exostoses in patients with MHE is up to 27.3% in older reports and this may be because of the selection of the patients.^{5,22} In more recent analyses, the risk of malignant transformation has been from 0.6% to 2.8% with the lowest number of 0.57% reported in a French study of 175 MHE patients by Legeai-Mallet et al²⁶ and others.^{1,23,27,28} Ozaki et al²⁹ described the first patient with synchronous malignant transformation, in the left pubic bone and the left greater trochanter.

Families and study populations without sarcomatous changes have been described.^{3,20} The risk of malignant transformation in a solitary osteochondroma is estimated to be around 1%.²²

In our patients, 114 adult members of six generations of a family, there were 46 members affected with MHE. The two men in the second generation who both had exostoses are to our knowledge the first representatives of this phenotype, and they both died in 1920. Most likely, one of their parents was affected, possibly being a *de novo* carrier of a mutation. Of the four patients with chondrosarcoma, three have occurred in generation IV and one in generation V giving an overall frequency of malignant transformation of 8.7% for adult patients, representing the highest reported number in recent literature.

A bone scan is unable to differentiate between benign and malignant lesions, although a negative bone scan seems to exclude the possibility of malignant transformation in an exostosis.³⁰ Since it is difficult to detect malignancy in the pelvis from symptoms and examination it has been suggested that this should be followed up by biannual radiographs. In our study, we used MRI as a screening technique on the pelvis, proximal femora and upper humerus. Two suspicious lesions were observed. Both were shown to be benign on histological examination. Experience with MRI in the early detection of chondrosarcomas and in the follow-up of patients with MHE is still too limited to assess the value of this technique.

Operations in children include the removal of exostoses which result in mechanical compression, corrections of deformities by osteotomies, excisions of the radial head and epiphyseodeses for discrepancies of growth.⁵ In the study family the operations in childhood had been for excision of exostoses producing mechanical symptoms. All the chondrosarcomas occurred in adults.

Three gene loci have been demonstrated to be involved in MHE. In addition, several homologous sequences have been found which have not yet been associated with the MHE phenotype.¹² It has been suggested that the *ext* genes are tumour-suppressor genes.⁷⁻⁹ We found the causative mutation in the *ext2* gene on chromosome 11p12-p11. The molecular studies revealed a guanine-to-thymine transversion within a 5-prime splice donor site after exon 6 resulting in skipping of exon 6.¹⁸ Seven other MHE-causing mutations have been described for the *ext2*-gene. All but one of these mutations lead to truncated gene products.

Patients with MHE and their affected family should be informed about the significant risk of chondrosarcoma at the time of genetic counselling and orthopaedic assessment. They should be advised about the importance of personal review of accelerated growth and/or pain at sites of exostoses. They should be asked to attend for annual clinical follow-up and radiological screening and possibly for MRI of suspicious protuberances. Based on our limited family material the prognosis is favourable after excision of the chondrosarcoma.

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