The role of EXT and growth signalling pathways in osteochondroma and its progression towards secondary peripheral chondrosarcoma

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Multiple Osteochondromas: Clinocopathological and Genetic Spectrum and Suggestions for Clinical Management

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Abstract

Multiple Osteochondromas is an autosomal dominant disorder characterised by the presence of multiple osteochondromas and a variety of orthopaedic deformities. Two genes causative of Multiple Osteochondromas, *Exostosin-1* (*EXT1*) and *Exostosin-2* (*EXT2*), have been identified, which act as tumour suppressor genes. Osteochondroma can progress towards its malignant counterpart, secondary peripheral chondrosarcoma and therefore adequate follow-up of Multiple Osteochondromas patients is important in order to detect malignant transformation early.

This review summarizes the considerable recent basic scientific and clinical understanding resulting in a multistep genetic model for peripheral cartilaginous tumourigenesis. This enabled us to suggest guidelines for clinical management of Multiple Osteochondromas patients. When a patient is suspected to have Multiple Osteochondromas, the radiologic documentation, histology and patient history have to be carefully reviewed, preferably by experts and if indicated for Multiple Osteochondromas, peripheral blood of the patient can be screened for germ line mutations in either *EXT1* or *EXT2*. After the Multiple Osteochondromas diagnosis is established and all tumours are identified, a regular follow-up including plain radiographs and base-line bone scan are recommended.

Keywords: bone neoplasm, multiple osteochondromas, genetics, clinical management, chondrosarcoma, exostosis

Introduction

Osteochondroma is the most common benign bone tumour, which can occur sporadic (solitary) or multiple, usually in the context of the hereditary syndrome, Multiple Osteochondromas (MO) [1,2]. Considerable understanding obtained through research on the genetic, pathological and radiologic background of these tumours has provided insights into the tumorigenesis of Multiple Osteochondromas resulting in the optimisation of clinical management, including radiologic and mutational screening.

Incidence

Osteochondromas represent about 50% of all surgically treated primary benign bone tumours[1]. Approximately 15% of the osteochondroma patients have multiple lesions [1,3] of which 62% have a positive family history [4].

The incidence for Multiple Osteochondromas has been estimated at 1:50,000 in the general population [5], with a higher prevalence in males (male: female ratio of 1.5:1) [4,6], which is partly due to incomplete penetrance in females [4].

Osteochondroma

Osteochondroma (*osteocartilaginous exostosis*), according to the 2002 WHO definition, is a cartilage capped benign bony neoplasm on the outer surface of bones preformed by endochondral ossification [7-9]. They develop and increase in size in the first decade of life and cease to grow at skeletal maturation or shortly thereafter. The most common site of involvement is the metaphyseal region of the long bones of the limbs, like the distal femur, upper humerus, upper tibia and fibula [1,8]. However, osteochondromas also occur in flat bones, in particular the ilium and scapula. An important differential diagnostic feature as compared to e.g. metachondromatosis or parosteal and periosteal osteosarcoma, is the extension of the medullar cavity into the lesion and the continuity of the cortex with the underlying bone. The perichondrium, the outer layer of osteochondroma, is continuous with the periosteum of the underlying bone.

Many osteochondromas are cauliflower shaped and can be divided on macroscopical grounds to often long slender pendunculated osteochondromas and flat sessile ones (figure 2.1A-C).

In the cartilage cap the chondrocytes are arranged in a similar fashion as in the epiphyseal growth plate. As a typical benign tumour the chondrocytes have small single nuclei. Binucleated chondrocytes may be seen during active growth.

The stalk may fracture, which may result in reactive fibroblastic proliferation and new bone formation, erroneously leading to interpretation as formation of secondary sarcoma formation. Attached to the perichondrium a secondary bursa may develop and simulating growth of the underlying tumour. This bursa is lined by synovium and may show inflammatory changes [3].

Multiple Osteochondromas

Multiple Osteochondromas (hereditary multiple exostoses, diaphyseal aclasis) is characterised by the presence of multiple osteochondromas [2,4,6,10,11] the number of which can vary significantly between and within families. Most Multiple Osteochondromas patients also suffer from a variety of orthopaedic deformities like shortening of the ulna with secondary bowing of the

radius (39-60%; figure 2.1D), inequality of the limbs (10-50%), varus or valgus angulation of the knee (8-33%), deformity of the ankle (2-54%) and disproportionately short stature[2,4-6,12]. It has been a matter of debate whether these deformities are a result of skeletal dysplasia or a result of local effects on the adjacent growth plate caused by developing osteochondromas.

No well-documented association between Multiple Osteochondromas and other non-bone related disorders has been described so far.

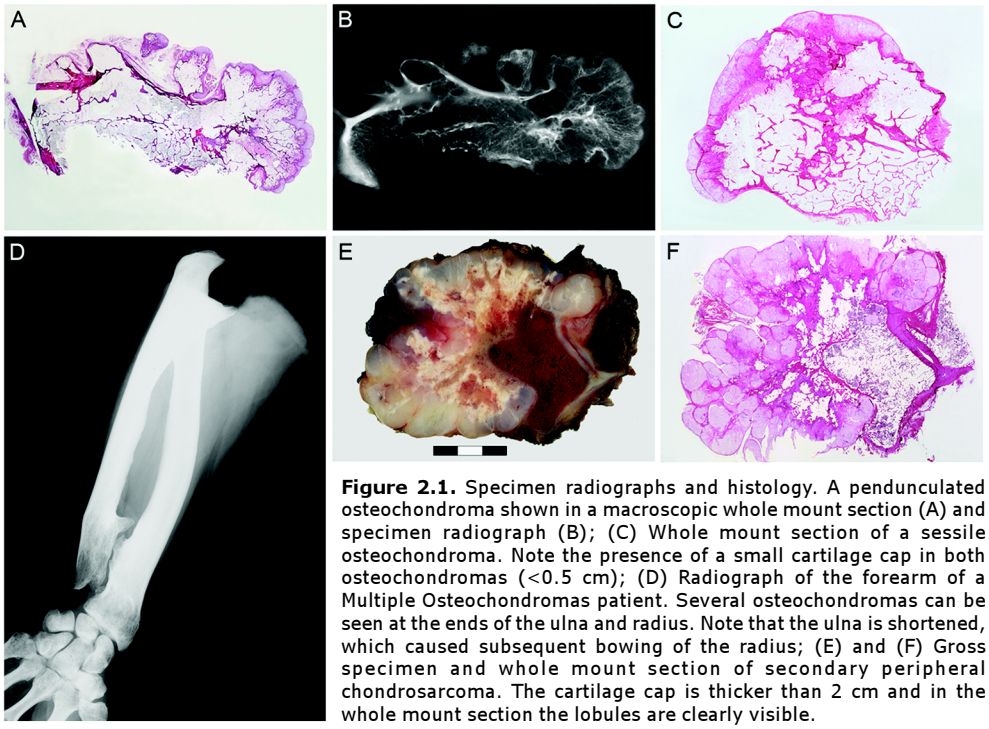

Figure 2.1. Specimen radiographs and histology. A pedunculated osteochondroma shown in a macroscopic whole mount section (A) and specimen radiograph (B); (C) Whole mount section of a sessile osteochondroma. Note the presence of a small cartilage cap in both osteochondromas (<0.5 cm); (D) Radiograph of the forearm of a Multiple Osteochondromas patient. Several osteochondromas can be seen at the ends of the ulna and radius. Note that the ulna is shortened, which caused subsequent bowing of the radius; (E) and (F) Gross specimen and whole mount section of secondary peripheral chondrosarcoma. The cartilage cap is thicker than 2 cm and in the whole mount section the lobules are clearly visible.

Malignant transformation

Malignant transformation of osteochondroma is estimated to be less than 1% in patients with solitary lesions and 0.5-3% in patients with Multiple Osteochondromas [2,7]. In 94% of the cases with malignant progression a secondary peripheral chondrosarcoma has developed within the cartilage cap of an osteochondroma [13] (figure 2.1E-F). Secondary peripheral chondrosarcoma is a hyaline cartilage producing tumour and constitutes approximately 15% of all chondrosarcomas [1,14], which is the third most frequent malignant bone tumour after myeloma and osteosarcoma [15]. Increasing pain, functional disability and/or a growing mass, specifically after maturation of the skeleton, may indicate malignant transformation. Radiological features show irregular mineralisation and increased thickness (over 2 cm) of the cartilage cap of an osteochondroma. The cap shows lobules of hyaline cartilage that are

separated by bands of fibrous tissue [15]. With (dynamic) contrast enhanced magnetic resonance (MR) imaging this can be seen as septal enhancement whereas osteochondromas only display peripheral enhancement. High-grade peripheral chondrosarcomas are characterised by inhomogeneous and homogeneous enhancement patterns on gadolinium-enhanced MR images[16,17].

The histological grading of chondrosarcoma is based on nuclear size and chromasia and cellularity [18] and is the most important predictor of clinical behaviour and thus prognosis of patients with chondrosarcomas [15]. Chondrosarcomas secondary to osteochondromas are usually low-grade tumours resulting in a reasonably fair prognosis for these patients [15].

In the remaining 6% of the cases with malignant progression tumours arise in the bony stalk of the osteochondroma, including osteosarcomas and spindle cell sarcomas [19-22].

Genetics

Multiple Osteochondromas is an autosomal dominant disorder for which two genes have been isolated, *Exostosin-1* (*EXT1*; OMIM 133700) located at 8q24 and *Exostosin-2* (*EXT2*; OMIM 133701) located at 11p11-p12 [23-25]. 44-66% of the Multiple Osteochondromas families show linkage at the *EXT1* region [26,27], compared to 27% for *EXT2* [27]. Germ line mutations of *EXT1* and *EXT2* have been described in Multiple Osteochondromas patients from Caucasian[23,25,28-31] and Asian populations [32-34].

Most mutations (80%) found in *EXT1* and *EXT2* (figure 2.2) are either non-sense, frame shift or splice-site mutations leading to premature terminations of the *EXT* proteins (reviewed by Zak et al. [36]). Mutations in *EXT1* occur in all parts of the gene, while mutations in *EXT2* concentrate towards the N-terminus of the gene, implying that this part of the protein may have special functions. This seems contradictive, since only the C-terminal region is highly conserved, implicating some functional importance for this part of the protein[24,25]. In the literature, only one somatic mutation in the *EXT1* gene has been described in a sporadic chondrosarcoma [29].

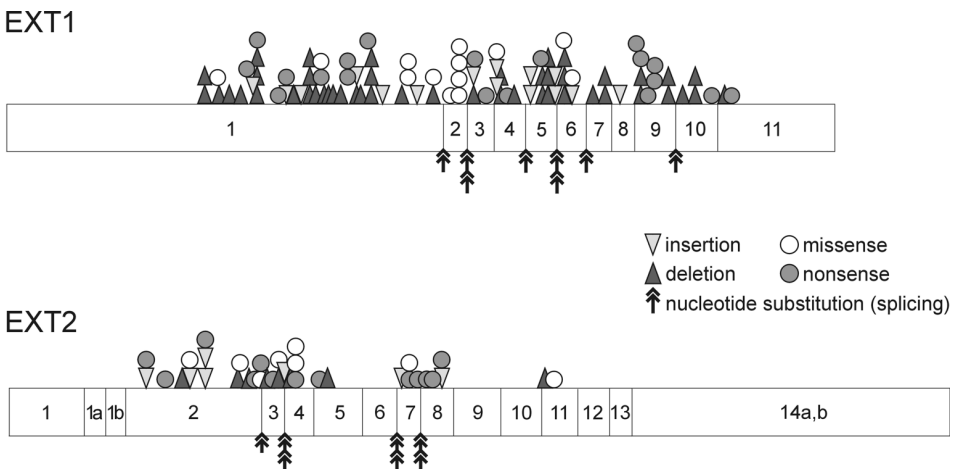

Figure 2.2. Mutation spectrum of the *EXT1* and *EXT2* genes in MO patients described so far [35].

Loss of the remaining wild type allele has been demonstrated in hereditary osteochondromas [31], indicating that the *EXT* genes act as tumour suppressor genes in Multiple Osteochondromas. This is consistent with Knudson's two-hit model for tumour suppressor genes [37].

Not many genotype-phenotype correlation studies have been described to draw definitive conclusions [38,39]. There seems to be a slightly higher risk of malignant transformation in patients with an *EXT1* mutation as compared to *EXT2* [39].

The existence of a third *EXT* gene on chromosome 19p, *EXT3* [40], has been suggested, however no gene has been identified, nor has this locus been implicated by other researchers. Based on their homology with *EXT1* and *EXT2*, three other members of the EXT-family of genes, the EXT-like genes (*EXTL1-3*), have been identified [41-43]. *EXTL1*, *EXTL2* and *EXTL3* are located at 1p36.1 [41], 1p11-p12 [42] and 8p12-p22 [43], respectively. No linkage with Multiple Osteochondromas or other bone diseases has been documented for these genes [44].

EXT1

Before linkage to Multiple Osteochondromas, osteochondromas were already known to be involved in a contiguous gene deletion syndrome, the Langer Gideon syndrome (LGS or trichorhinophalangeal syndrome type II; OMIM150230) [45], where patients carry a deletion of 8q24 [46]. Besides multiple osteochondromas the Langer Gideon Syndrome is characterised by craniofacial dysmorphism and mental retardation [45,46].

In the early nineties Cook et al. found linkage to the 8q24.11-q24.13 region in Multiple Osteochondromas families [47] and two years later the *EXT1* gene was identified by positional cloning [23].

The *EXT1* gene, composed of 11 exons, spans approximately 350kb of genomic DNA (figure 2.3) [48] with a promoter region that has the characteristics of a house keeping gene [48]. *EXT1* mRNA is ubiquitously expressed and has a coding sequence of 2238 bp [23]. In mouse embryos, high mRNA levels of the *EXT1* homologue were found in the developing limb buds[49,50]. *EXT1* homologues have also been identified in *Drosophila melanogaster* (*tout-velu, Ttv*) and *Caenorhabditis elegans* [51,52].

EXT2

In two large Multiple Osteochondromas pedigrees not linked to 8q24, linkage was found to a 3 cM region located at 11p11-p12, excluding the pericentrometric region [53,54]. In 1996, the *EXT2* gene was identified by positional cloning by two groups independently [24,25].

The *EXT2* gene contains 16 exons (figure 2.3) and spans approximately 108 kb of genomic DNA [52]. The mRNA consists of approximately 3kb, with a single open reading frame of 2154 bp in which the C-terminal region shows high similarity with *EXT1* [24,25]. The mRNA shows alternative splicing in exon 1a and 1b and is ubiquitously expressed [24,25]. Homologues of *EXT2* have been found in mouse (chromosome 2) [52,55], *Drosophila melanogaster* (*sister of tout-velu*, *sotv*) [56] and *Caenorhabditis elegans* [52].

Like *EXT1*, *EXT2* has been implicated in a contiguous gene deletion syndrome, Potocki-Shaffer syndrome (DEFECT11; OMIM 601224), where patients carry a deletion of 11p11.2-p12 [57,58]. Patients with this syndrome demonstrate multiple osteochondromas, enlarged parietal foramina (FPP), craniofacial dysostosis and mental retardation [57,58].

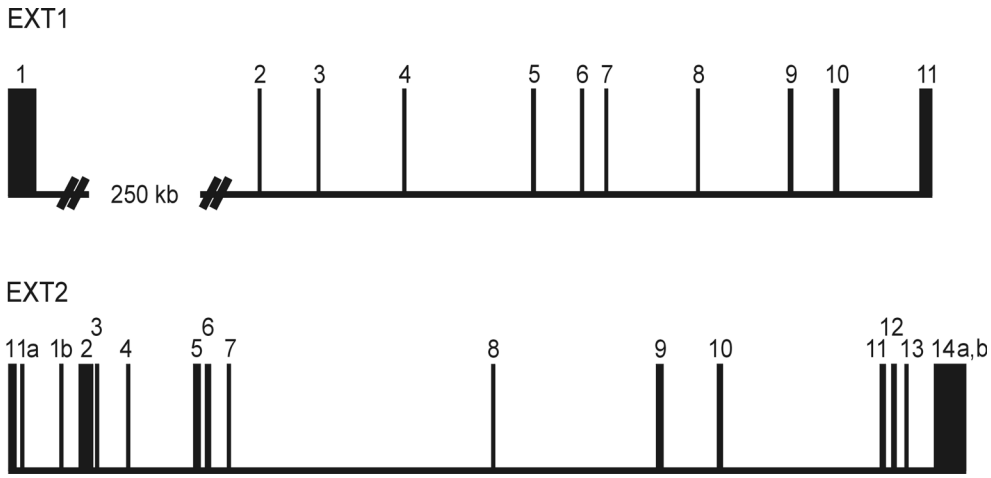

Figure 2.3. Genomic DNA structures of the *EXT1* and *EXT2* genes.

EXT function

The gene products of human *EXT1* and *EXT2* are endoplasmic reticulum localised type II transmembrane glycoproteins. *In vivo* they form a stable hetero-oligomeric complex that accumulates in the Golgi apparatus, where it is involved in heparan sulphate proteoglycan (HSPG) biosynthesis (reviewed by Esko et al. [59]; figure 2.4). The EXT1/EXT2 complex catalyses the elongation of the HS chain [60,62-64], which is subsequently deacetylated, sulphated and epimerised resulting in a large spectrum of structural heterogenic HS chains. The sulphation pattern of HS chains is critical for binding specific proteins [59]. Several growth factors have conserved patterns of basic amino acids for binding to HSPGs, which is crucial for proper signalling [68,69].

Heparan Sulphate Proteoglycans (HSPG)

HSPGs are large multifunctional macromolecules, involved in several growth signalling pathways, anchorage to the extracellular matrix and sequestering of growth factors (reviewed by Knudson [70]) Four HSPG families have been identified: syndecan, glypican, perlecan and CD44 isoforms.

The syndecan family consists of four members, encoding type I transmembrane polypeptides involved in the anchorage of cells to the extracellular matrix and binding of growth factors [71]. In mouse and chick, syndecan-2 and -3 have shown to be involved in signalling pathways in proliferating chondrocytes [72-75].

The six glypican family members encode proteins attached to the cell membrane with a glycosylphosphatidylinositol (GPI)-anchor. They predominantly function as co-receptors [71]. Expression of several glypicans has been found in the perichondrium, the developing limb and mesenchymal tissues of the developing mouse embryo [76].

The largest HSPG, perlecan, is the most common proteoglycan of the basement membrane. It is expressed in hyaline cartilage and in all zones of the rat growth plate during

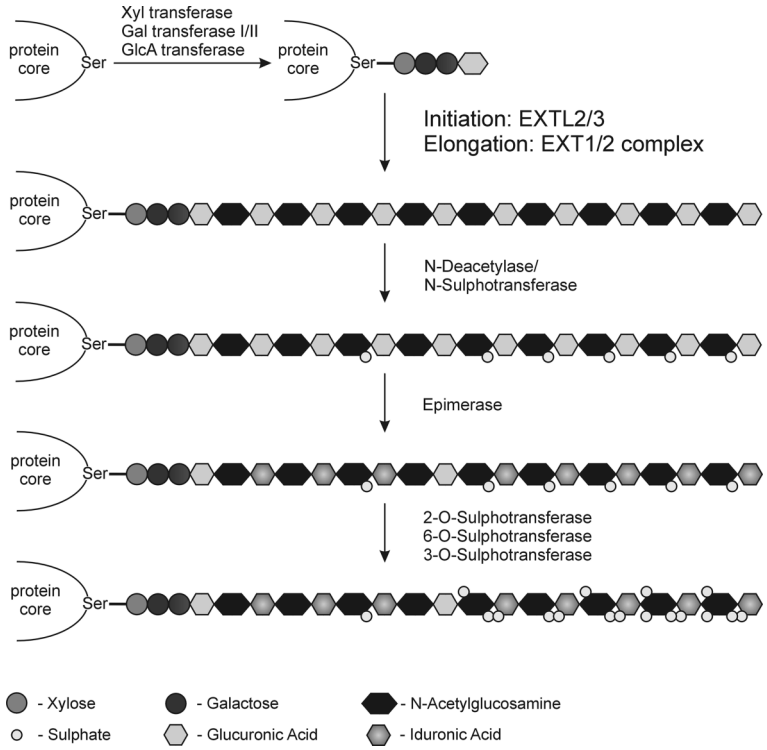

Figure 2.4. The mode of action of the EXT-proteins in heparan sulphate biosynthesis. After a tetrasaccharide linker is synthesised on conserved serine residues of the core protein, EXTL2 and/or EXTL3 initiate the polymerisation of the heparan sulphate chain by the addition of N-acetylglucosamine [60,61]. The EXT1/EXT2 complex subsequently catalyses further elongation of the heparan sulphate chain by adding alternating units of N-acetylglucosamine and glucuronic acid [60,62-64]. Subsequent deacetylation and sulphation of most N-acetylglucosamines, epimerisation of the glucoronic into iduronic acid and further sulphation result in a large spectrum of structural heterogenic heparan sulphate chains [59,65]. Adapted from Couchman et al. [66] and Nybakken et al. [67].

endochondral ossification [77]. Perlecan, syndecan and glypican are reported to be involved in Fibroblast growth factor (FGF)-signalling [70,71].

The fourth HSPG family is specific isoforms of the type I transmembrane glycoproteins CD44. The CD44 gene consists of 20 exons of which 10 (so-called variable exons) can be alternatively spliced (reviewed by Ponta et al. [78]). CD44 isoforms containing variable exon 3 (v3) have been shown to bind growth factors through HS side chains, thereby regulating cell growth and motility [79].

In *Drosophila*, the *EXT1* homologue *ttv* (*tout-velu*), also involved in HS synthesis, is required for the diffusion of Hedgehog (Hh), an important segment polarity protein (homologue of mammalian Indian Hedgehog (IHH)) [51]. Remarkably, in *ttv* mutants only the IHH signalling is affected, while other HSPG-dependent pathways, like FGF and WNT signalling, are not. This indicates a specificity in the regulation of the distribution of extracellular signals by HSPGs in *Drosophila* [80,81].

Growth Signalling

IHH/PTHLH signalling in the growth plate

In the growth plate EXT1 and EXT2 are expressed in the proliferative and transition zone [82] (figure 2.5). The HSPGs, expressed in all zones of the growth plate [72-77], are presumed to be involved in the diffusion of IHH to its receptor in the perichondrium. During normal embryonic growth IHH, expressed in the transition zone, is involved in a paracrine feedback loop regulating proliferation and differentiation of chondrocytes and bony collar formation in the growth plate (figure 2.5A). In this feedback loop parathyroid hormone-like hormone (PTHLH, PTHrP) regulates chondrocyte differentiation by delaying progression of chondrocytes towards the hypertrophic zone, allowing longitudinal bone growth [84]. In the rat post-natal growth plate the feedback loop is confined to the growth plate itself (figure 2.5B), in particular to the transition zone [85].

Fibroblast Growth Factor (FGF) signalling in the growth plate

The FGF signalling pathway is dependent on HSPGs for the high affinity binding capacity of the FGF receptor (FGFR), allowing receptor dimerisation and subsequent cell signalling [83,86]. The most potent mitogen for chondrocytes, FGF-2 (basic FGF), inhibits differentiation of

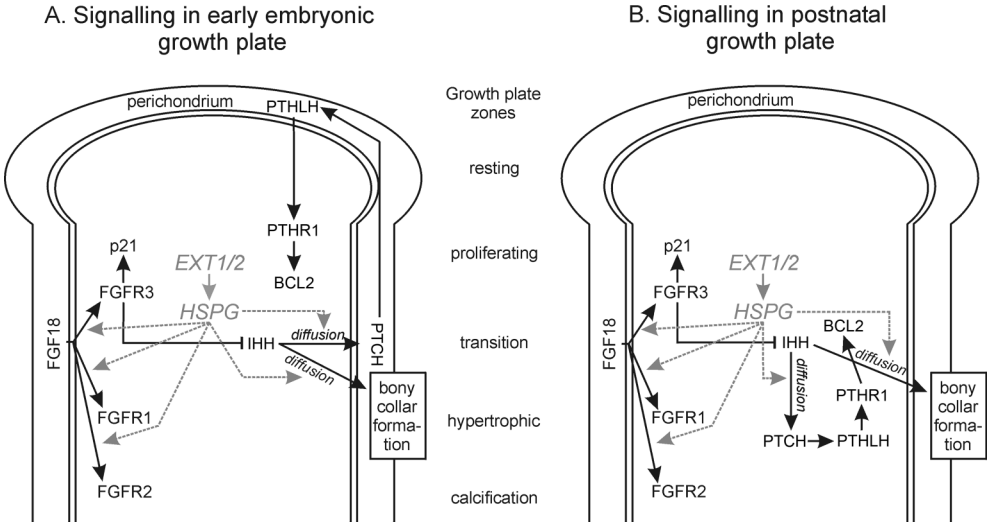

Figure 2.5. Growth plate signalling. EXT1 and EXT2 are expressed in the proliferative and transition zone[82]. The HSPGs, expressed in all zones of the growth plate [72-77]. (A) In the embryonic growth plate chondrocytes in the transition zone secrete IHH protein, which diffuses to its receptor Patched (PTCH) in the lateral perichondrium. Subsequently, via a yet incompletely understood mechanism, increased secretion of parathyroid hormone-like hormone (PTHLH) is induced at the apical perichondrium, which diffuses to its receptor (PTHR1) expressed in the late proliferating chondrocytes [83]. Terminal differentiation is inhibited by direct or indirect upregulation of BCL2, prolonging cell survival [84]. In this way, PTHLH regulates chondrocyte differentiation by delaying the progression of chondrocytes towards the hypertrophic zone and allowing longitudinal bone growth. (B) In the post-natal growth plate the signalling is confined to the growth plate [85].

chondrocytes via stimulation of extracellular matrix synthesis [87,88]. In contrast, activation of FGFR3 in the proliferative zone (figure 2.5), by FGF18 [89] inhibits chondrocyte proliferation via phosphorylation of STAT-1 and subsequent upregulation of $p21^{WAF/CIP1}$, which can inhibit the cell cycle [90]. FGFR3 activation also leads to repression of IHH signalling [83,86,91].

Histogenesis and secondary sarcoma formation

In the past, many have considered the histogenesis of osteochondroma as a perversion in the direction of normal bone growth resulting from aberrant epiphyseal development with displacement of epiphyseal cartilage. However, several research groups have demonstrated using different techniques that both sporadic and hereditary osteochondromas are true neoplasms [31,92,93], resulting in a multi-step genetic model for peripheral cartilaginous tumourigenesis (figure 2.6) [94].

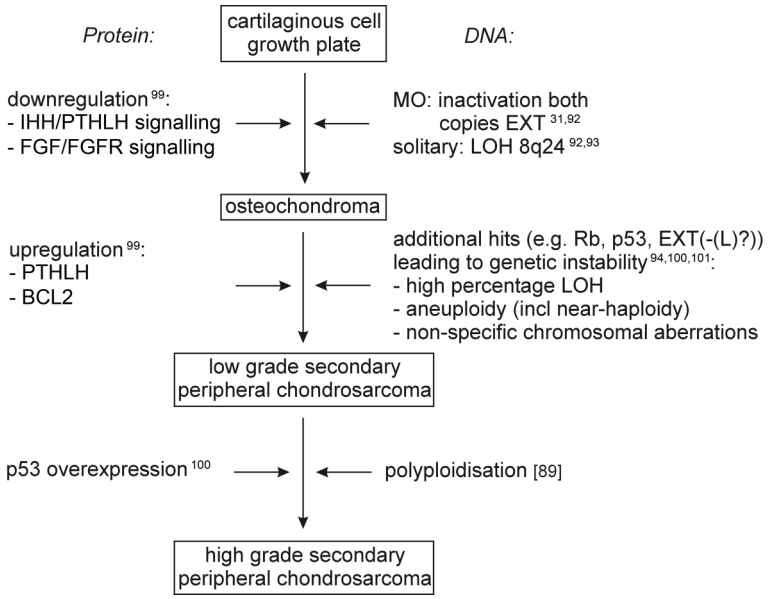

Figure 2.6. Peripheral Cartilaginous Tumourigenesis.

Although some believe that the severity of the angular deformity is correlated with the number of sessile osteochondromas [38], several studies in mice have shown that haploinsufficiency of *EXT1* or *EXT2* causes severe skeletal deformities [95,96]. Loss of the remaining wild type allele of *EXT1* in hereditary osteochondromas [31] indicated that inactivation of both copies of the *EXT1*-gene in cartilaginous cells of the growth plate is required for osteochondroma formation, thereby acting as a tumour suppressor gene [31]. Two studies have shown diminished HSPG expression in either osteochondromas or cultured $EXT1^{-/-}$ cells[97,98]. This is hypothesised to affect the negative feedback loop by disturbing IHH diffusion to Patched (PTCH) and by preventing high-affinity binding of FGF to its receptor (figure 2.5).

Immunohistochemical studies have already shown that molecules involved in the IHH/PTHLH and FGF signalling (PTHLH, PTHR1, BCL2, FGF2, FGFR1, FGFR3 and p21) are absent in osteochondromas [99] suggesting that growth signalling is indeed disturbed in osteochondroma.

At the protein level, re-expression of several of these signalling molecules (FGF2, FGFR1, p21, PTHLH and BCL2) was found in secondary peripheral chondrosarcoma and the expression increased with increasing histological grade [99]. Upregulation of BCL2 characterised malignant transformation of osteochondroma towards grade I secondary peripheral chondrosarcoma [99]. Signalling may now occur in an autocrine fashion or in a paracrine one in which IHH acts on cells in its near vicinity, having to diffuse over only a few cell diameters and thereby avoiding HSPG-dependent diffusion [99].

The process of malignant transformation is genetically represented by chromosomal instability [100], probably caused by defects in spindle formation. The LOH found in osteochondroma was restricted to 8q24 [31], whereas in secondary peripheral chondrosarcomas LOH was found in virtually all loci tested [100]. Also a broad range in DNA ploidy including near-haploidy and non-specific chromosomal alterations were found [100,101]. DNA-flow cytometry of the cartilaginous cap of osteochondromas showed mild aneuploidy [31], whereas more severe aneuploidy [102-104], including near-haploidy [100], was seen in grade I secondary peripheral chondrosarcomas.

Further progression towards high-grade secondary peripheral chondrosarcomas is characterised by polyploidisation, which is thought to be evolved from near-haploid precursor clones [94], and overexpression of p53 [100].

Near-haploidy was not found in osteochondromas [92,93] or in high grade peripheral chondrosarcomas [100] and can be considered a progression marker towards a low malignant phenotype [94].

Patient management

Diagnosis

With the identification of *EXT1* and *EXT2* as the genes causative of Multiple Osteochondromas, it has become possible to screen patients with multiple lesions for germline mutations in either *EXT* gene in a diagnostic setting. However this procedure is time consuming and costly and therefore it is important to select patients carefully on basis of family history, radiologic documentation and, if available, review of histology of resected lesions.

The diagnosis of Multiple Osteochondromas is based on the combination of two or more radiologically documented osteochondromas originating from the juxta-metaphyseal region of the long bones [2,4], with or without a positive family history. Radiologically, Multiple Osteochondromas patients have a typical phenotype, easy to recognise by the expert eye. This can exclude the differential diagnoses of other skeletal disorders like metachondromatosis[105,106], dysplasia epiphysealis hemimelica [107,108] or non-hereditary syndromes that occur in multiple bones such as enchondromatosis (Ollier's disease) [107,109]. Given the specific radiologic and histological expertise needed, it is recommended to seek for expert opinion from a bone tumour specialist or from a national bone tumour registry consisting of clinicians, radiologists and pathologists, before screening for germline mutations.

If the typical Multiple Osteochondromas radiologic phenotype is present, it is important to evaluate the patient's family history to see if other relatives are (possibly) affected. From

these family members radiologic studies and, if available, histology of resected lesions can be examined. If there are other affected family members, Multiple Osteochondromas can be clinically established.

Then subsequent *EXT* mutation analysis is optional. However it can be useful to screen for germline mutations in family members presenting a mild or no phenotype and this will also give insight into the inheritance pattern (penetrance) of the specific mutation. A known *EXT* mutation can also be used for prenatal diagnostics. If there is no positive family history, Multiple Osteochondromas cannot be excluded, since it is possible that the patient is the founder of a new Multiple Osteochondromas family and these index patients should be screened for *EXT* mutations.

Mutation analysis for *EXT1* and *EXT2* can be performed on peripheral blood of the patient. This can be established through PCR and subsequent sequencing of all exons of *EXT1* and *EXT2* [30] and/or two-colour multiplex ligation-dependent probe amplification (MLPA)[110]. When a mutation in either gene is found, the Multiple Osteochondromas diagnosis can be confirmed. If there is no mutation, the diagnosis Multiple Osteochondromas cannot be excluded, since there is the small possibility that the mutation could not be detected due to technical limitations. With the currently used methods it is possible to detect point mutations or gross deletions in 75-88% of the Multiple Osteochondromas patients [110]. These methods cannot detect positional changes, like translocations, inversions, insertions or transpositions. These changes affect the structure of the gene without changing the sequence or dosage of exons.

Follow-up

When the diagnosis of Multiple Osteochondromas is established, patients should have a regular follow-up to discover potential malignant transformation at an early stage and enable adequate treatment to be implemented. To our knowledge, the literature does not mention a specific clinical and/or radiologic consensus about the most proper method for the follow-up of patients with proven Multiple Osteochondromas. The following pathways for both clinical and radiologic follow-up can be followed. Localisation of all, relatively larger, osteochondromas can be established with a base-line bone scan, which shows increased bone activity within the skeleton at sites of increased bone turnover, like at the sites of osteochondromas, but also at the epiphysis and apophyses of growing bones. Since secondary peripheral chondrosarcomas are extremely rare before puberty, this is, therefore, only recommended for patients who have reached skeletal maturation. Regular follow-up before that time is not necessary unless the patient presents with clinical complaints. A number of osteochondromas will demonstrate a normal uptake of the radiopharmacon, demonstrating complete maturation, while others may still show an increased activity of the radiopharmacon. This finding, at the base-line, does not immediately and specifically imply malignant transformation, but can well be explained by, as yet, incomplete maturation of the osteochondroma or just by its distinct size. Furthermore, base-line plain radiographic examinations of areas that are not accessible to palpation, like the chest, pelvis and scapula are recommended, because in these areas of the body late detection of malignant transformation of an osteochondroma towards peripheral chondrosarcoma is most common.

After these base-line examinations, patients with Multiple Osteochondromas could routinely be seen, each year or every two years, in the outpatient clinic for clinical and

radiologic follow-up. It should be emphasised to the patients to come at an earlier time if changes in their clinical condition occurs, such as pain or growth of a known lesion. It is also important to realise that no new osteochondromas develop after skeletal maturation.

Radiologic follow-up could consist of both plain radiographs of the pelvis, chest and scapulae in combination with follow-up bone scans. Changes in the clinical history and findings, in combination with changes on the plain radiographs or bone scans, should be regarded with suspicion. As to changes in the uptake of the radiopharmacon on bone scans however, it should be considered that increase of the uptake does not always indicate malignant transformation. It can also be the result of trauma or the formation of an overlying bursa or inflammatory reaction. Nevertheless, these changes warrant further examination through plain radiographs and dedicated magnetic resonance (MR) imaging, including contrast-enhanced MR sequences. Also the thickness of the cartilage cap can be monitored with MR imaging.

Radiologic skeletal surveys, as a means of follow-up, do not seem to be of additional value. The role of ultrasound, in the follow-up of lesions, is still controversial and needs further studies.

The entire purpose of adequate follow-up is aimed at the early detection of malignant transformation, which enables adequate surgical treatment consisting of en-bloc resection of the lesion and its pseudo-capsule with tumour-free margins, preferably in an oncology centre with experience in treating bone sarcomas. Inadequate primary surgery of a secondary peripheral chondrosarcoma will inevitably result in recurrences and can eventually result in

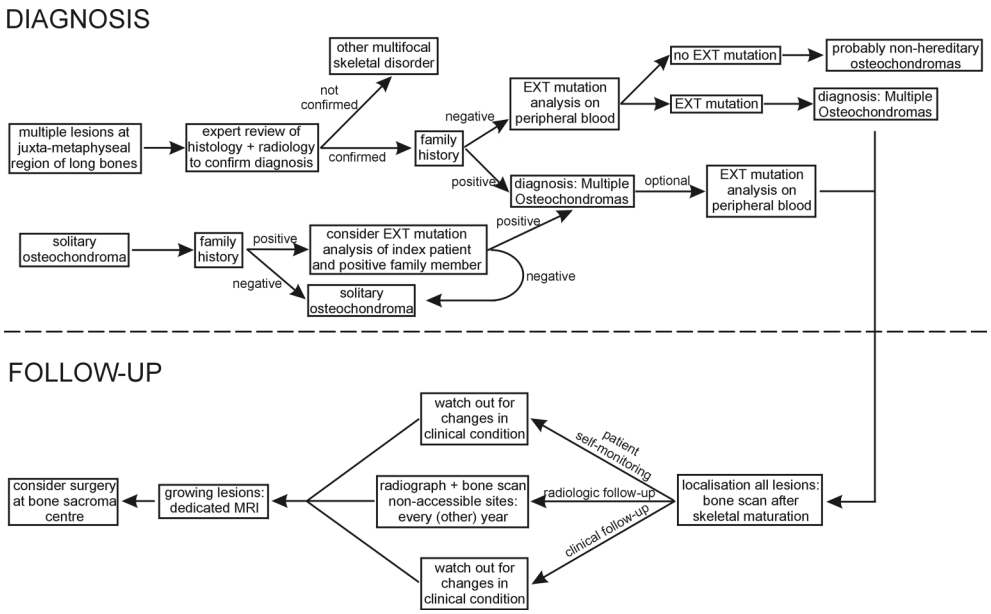

Figure 2.7. Overview of systematic steps to screen and follow-up (suspected) Multiple Osteochondromas patients.

death caused by local problems or even metastases.

The process of making a Multiple Osteochondromas diagnosis and patient follow-up is summarized in a flowchart (figure 2.7).

Conclusion

With all new developments and discoveries in the genetic, pathological and radiologic behaviour of osteochondromas and secondary peripheral chondrosarcomas, it has become possible to screen and carefully monitor Multiple Osteochondromas patients and their families. This will enable us to provide patients with more adequate care and treatment strategies.

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