Hereditary Multiple Exostosis is an intriguing genetic condition with a clinical impact in the field of orthopaedics, paediatrics and oncology. In this review we highlight the current knowledge about this condition from a clinical and scientific point of view. This gives us more insight into the molecular mechanisms and current models on which therapeutic agents are based. It allows for a multidisciplinary approach to the management of this complex condition.

There is currently no exact pathological model that can accurately describe all the findings in the research on Hereditary Multiple Exostosis. Promising treatments with blocking agents are currently under investigation.

Keywords: Hereditary Multiple Exostosis; review.

INTRODUCTION

Hereditary Multiple Exostoses (HME) is an autosomal dominant inherited genetic condition with abnormal growth of bone, mainly affecting the epiphyses of long bones. The incidence in the Western population is 1.5%; a higher incidence is found in isolated groups. The abnormal chondro-osseous growths (exostoses) are a consequence of dysplasia in the peripheral part of the growth plate. Solitary exostoses are the major type of benign bone tumours, called “osteochondromas” and are generally diagnosed at a young age. They consist of a bony component with a cartilage cap on top.

Besides cosmetic complaints, patients with HME generally report pain and difficulty moving the affected joints. In rare cases, exostoses may undergo malignant transformation into chondrosarcomas. Subtle forms of HME may also be encountered by the orthopaedic surgeon.

CLINICAL PRESENTATION

Since most of the patients are asymptomatic at birth, early diagnosis can only be made by genetic screening, such as with registered affected families. Real symptoms will only manifest during growth and specifically during childhood. The exostoses start to grow, become visible and cause complaints. Because lesions on the scapula and tibia are easily noticed, these are the bones where the exostoses are primarily diagnosed. Fifty percent of all patients with HME will present with a clinical visible tumour by the age of 5, and 80% of all patients are...
diagnosed by the age of 10. Most patients present with an average of 6 exostoses, of which the extent, size and shape can vary largely (55). Radiographically we can define two different forms of exostoses: the broad based sessile osteochondroma and the small based stalked osteochondroma (45).

The distal femur (90%) and the proximal tibia (84%) present a high incidence of exostoses. Disease affecting the knee joint has been described in 94% of all cases (53).

Descriptions of affected proximal humerus (Fig. 3B), distal ulna and radius, scapula, ribs and pelvic girdle (Fig. 5B) are found in the literature, as well as rare cases of exostoses on the spine, the metacarpals, metatarsals and the sternum. Overall, almost any joint or bone in the body may be affected by HME. However, the facial bones are never affected. This is because facial bones grow by intra-membranous ossification, a different process from growth in the long bones.

If exostoses affect the long bones, the origin of the disease lies within the growth plate. As the patient grows, exostoses will move towards the diaphysis. Exostoses which continue to grow after closure of the growth plate and the cessation of growth, should be suspected of malignant degeneration (18).

Although exostoses are benign tumours, they can lead to a range of clinical problems and complications. Patients with HME generally have a lower height: 37% of male patients and 44% of female patients are lower than P5 (65). Severe HME may lead to major spinal deformities and scoliosis. The limitation of joint range of motion and articular deformities are the most frequent complaints reported by patients.

**Lower limb**

The lower limb is mainly affected by a valgus deformity which is caused by unbalanced shortening of the tibia and fibula (Fig. 1). Disease about the knee leads in 33% of patients to a valgus configuration and secondary patellar dislocation (50).

Coxa valga is associated with exostoses near the minor trochanter and is found in 25% of cases (53) (Fig. 3A). Acetabular exostoses and deformations at the medial femur are rarely found (15,34). Ischio-femoral impingement has been described due to proximal femoral widening in HME (64).

Valgus deformities at the ankle joint are found in 50% of patients and may exacerbate to medial subluxation of the talus (22) (Fig. 4). These axial deformities are sometimes mistakenly not regarded as an exostosis; subtle forms may only present as a deformed metaphysis with valgus/varus deformity of the extremity. These deformities are easily overlooked.

**Upper limb**

The upper limb is mainly affected at the elbow joint, with exostoses at the elbow described in 40 to 74% of all patients with HME (21,65,67). Unbalanced shortening of the ulna leads to a higher curved radius and disturbed proximal pronation. In 25% of all patients, shortening of the ulna causes subluxation or dislocation of the radial head (47) (Fig. 2). The deformities at the elbow are described in the Masada classification, with Masada I (incidence 55%) being an exostosis at the distal ulna with nor-
The hand is affected in 30-70% of cases and mainly ulnar metacarpals and proximal phalanges show abnormal growth (13,67). Rarely an exostosis on the distal phalanx can cause a pseudo-mallet finger (44).

Spinal involvement is described in 7% of all cases with rarely life threatening spinal cord compression and neurologic conditions (23) (Fig. 5A).

**Complications**

Spontaneous haemothorax may be caused by exostoses of the ribs (61). Chronic irritation of tendons and muscles over a bony prominence may lead to impingement, entrapment and tendon ruptures. When exostoses are located at the medial site of the extremity, vascular and neurological complications are common. Up to 22% of patients have compression of peripheral nerves (65). Compression of the superficial peroneal nerve at the fibular head is a known entity in children with HME. These children will present with disturbed dorsiflexion and sometimes a foot drop with a positive heel walking test (11).

Vascular complications are mostly seen at the lower extremity (83%). Less frequent (10%), but the most urgent, are vascular compressions, pseudo-

**Fig. 2.** — Radiographs of right forearm taken at the age of 14 years. Note shortening of the ulna and deformity of the wrist. Same MHE patient as in fig 1. Radial head can be dislocated on examination. The patient presented after a traumatic incident to the elbow with persistent pain. During this visit in outpatient clinic diagnosis of HME was made for the first time.

**Fig. 3.** — Silent forms of HME at age 14 yrs. Fig 3A shows valgus hip with exostosis mimicking gross lesser tuberosity. Asymptomatic patient. Fig 3B shows deformity in proximal humerus which is asymptomatic. Note the deformed aspect of the coraco-clavicular connection and scapular wing, and the prominent distal clavicle. These are clinically detectable, but totally asymptomatic to the patient.

**Fig. 4.** — Radiograph of left and right ankle joint in patient with HME. Fig. 4A shows ankle joints at age 11 yrs, when patient was seen in out-patient clinic for mild pain in heel region. Diagnosis of Weber disease was made. No diagnosis of HME was made until the age of 14. Fig. 4B shows same right ankle at age 14, which now clearly shows the valgus deformity due to HME.
and real aneurysms, and arterial and venous thrombosis (63). These severe complications, with mainly the popliteal artery as the involved vessel, should always be suspected in HME.

GENETICS

1. Ext genes

HME is an autosomal dominant condition with an almost complete penetrance (95%) (65). The risk that a six-year-old asymptomatic child with an affected parent will develop HME is about 20%. At birth, this risk is 50% (53). Different genetic loci are associated with HME. A first EXT1 locus on chromosome 8 (8q24.1) was discovered by Cook in 1993 (25). Chromosome 8 was suspected as a potential locus for HME since it was already linked to the Langer-Giedion syndrome. On the distal end of 8q a locus responsible for the formation of exostoses in both genetic conditions was identified as the EXT1, or exostosis gene 1 (33,70). Later on a new gene on chromosome 11 (11p11-13) was identified as a locus for HME and named EXT2, exostosis gene 2 (57). A third locus on chromosome 19p, suspected of causing HME was named EXT3, exostosis gene 3, but it is considered to be a minor contributor to the actual formation of exostoses (31).

EXT1 and EXT2 are very similar genes which code for proteins of 80kD which can be modified after translation. These genetic and molecular similarities suggest a similar biological function of both EXT genes. By researching homologous sequences of EXT genes, three EXTL or EXT-like genes were identified. EXT genes and EXTL genes are considered as one family of EXT/EXTL genes with very similar genetic and molecular function (62,66,71). This function however remained unknown until Loss-Of-Heterozygosity studies (LOH) of chondrosarcomas showed that EXT1/2 were related to primary chondrosarcomas and malignant degeneration of osteochondromas. The researchers concluded that the EXT/EXTL genes functioned as tumour suppressor genes (17,40).

2. EXT genes and heparansulfate

By screening a DNA-library Mc Cormick et al discovered a gene that could restore heparansulfate (HS) synthesis in mice. This gene was the already identified EXT1 gene (38). Other research in mice showed that heparin sulfate polymerase (HS-POL) was a key molecule in the synthesis of HS. The gene coding for HS-POL was surprisingly the EXT2 gene (32). Both EXT genes are components of the synthesis of HS and are transmembrane glycoproteins with glycosyltransferase activity. These proteins would have to interact and be intact in order to make it possible to produce HS. EXT1 and EXT2 therefore form a complex at the Golgi apparatus, and with the formation of this complex there is a significantly higher enzymatic activity leading ultimately to a higher production of HS (37). The EXTL genes were also found to be associated with HS biosynthesis (27,28). All of these genes may have mutations, chain elongations and non-
sense coding, all leading to structural changes in the EXT/EXTL associated proteins (69). Structural changes in these proteins then lead to disturbed interactions and lower enzymatic activity, which causes a lower production of HS. This process and a significantly lower amount of glucosyltransferase activity was detected in HME patients (6). So a disturbance in the HS synthesis is the cause of the formation of exostoses. Heparansulfate chains are found on a wide range of proteoglycans and perform a broad range of cellular functions. Expression of these proteoglycans was detected in the perichondrium as well as in the mesenchyme and developing limbs of mice embryos. CD44 controls the binding of Growth Factor via HS chains and regulates cell growth and cell motility. Heparansulfate proteoglycans (HSPG) can mainly be found at the cell membrane or in the extracellular matrix. Here they function as ligands or co-receptors, with HS chains as the main interacting and binding components (12,16).

The main pathways directed by HSPG’s are Fibroblast Growth Factors (FGFs), Vascular Endothelial Growth Factors (VEGFs), and Tumour Growth Factor-beta (TGF-β). These pathways ultimately lead to the graduated formation of morphogens such as Hedgehog (Hh) or Bone Morphogenic Proteins (BMPs) (46).

3. Hedgehog

Mutation studies in Drosophila using EXT analogue genes showed that elimination of EXT genes leads to drastic lowering of expression of Hedgehog, BMP and Wingless (Wnt). These three proteins are major determinants of embryonic bone development (7). The Hh pathway plays a crucial role in the differentiation of chondrocytes during endochondral bone formation at the growth plate. The process of endochondral bone formation starts with the change of mesenchymal cells to chondrocytes. These chondrocytes then undergo a differentiation out of rest to proliferation, via prehypertrophic and hypertrophic stages, until eventually they undergo apoptosis. Prehypertrophic chondrocytes express the Hh ligand Indian hedgehog (Ihh). This Ihh is a major regulating factor for endochondral bone formation which is controlled by paracrine signals. Formation is controlled by a negative feedback loop between Ihh and Parathormone related Protein (PTHrP). This loop creates a regulated micro-environment in which chondrocytes can proliferate, migrate and die. This maturation process needs strict control by Ihh to maintain the balance between longitudinal growth of cartilage and consequent ossification. Ihh regulates the start of the hypertrophic differentiation of prehypertrophic chondrocytes. Furthermore a fraction of Ihh will disperse through the perichondrium to periarticular chondrocytes and lead to a production of PTHrP. This PTHrP will then slow the further differentiation of proliferating chondrocytes. When chondrocytes are fully differentiated and hypertrophic, the expression of Ihh stops.

This allows new chondrocytes to differentiate further. Ihh also plays a major role in perichondrial ossification, forming a bony collar on the side of the bone. The interactions between PTHrP and Ihh, controlling phased growth and perichondrial ossification are mediated by BMPs (41,42).

4. One unifying theory

Stickens et al proposed in 2000 that exostoses are caused by a disturbed coordination of chondrocyte maturation and perichondrial bone formation. A localised defect in Hh signalisation leads to a localised defect in perichondrial bone formation. Patients with HME have a heterozygous mutation in EXT1 or EXT2. For the formation of an enchondroma a second mutation in either the chondrocytes or the perichondrial osteogenic cell is necessary. This second mutation would then lead to a complete loss of expression of EXT1/EXT2 and this disturbs the crosstalk via Ihh and PTHrP between chondrocytes and perichondrial osteogenic cells. This local defect of regulation leads to a hiatus in the forming of the bony collar. This hiatus is a place where chondrocytes can escape growth depressing factors (56).

Mice studies with deletion of EXT1 showed disturbed signalisation of Ihh, TGF-β, FGF and BMP and a secondary increased production of Ihh. This disturbance leads to an elevation of proliferating chondrocytes and a slowdown in terminal
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Chondrosarcomas develop in the cartilage cap of an existing osteochondroma. The lifelong risk for degeneration is estimated to be between 1 and 5%. The average age at which patients present with secondary chondrosarcoma is 34 years. This is younger compared to patients with primary chondrosarcoma. The risk of malignant degeneration is twice as high in male patients as in female patients. Secondary chondrosarcomas frequently arise at the pelvis and femur, less frequently at the scapula and humerus. One needs to consider the possibility of secondary chondrosarcoma in patients presenting with pain, swelling and a palpable mass. These symptoms are mainly caused by growth of the cartilage cap (56). Rarely these tumours of the pelvic bone may cause urologic or enterologic problems (39,68). Secondary chondrosarcoma is also associated with Ollier disease and Maffucci syndrome.

Imaging of the osteochondroma is essential in the further work-up of the patient. Radiological follow-up can detect malignant degeneration at an early stage and should be performed yearly. Degeneration manifests as a gradual change in a well circumscribed mass with bony edges and a cartilage cap towards an irregular border and a blurry mass. CT and MRI will detect a cartilage cap of more than 1.5 cm. At the moment, exact thickness of cartilage cap and diagnosis of malignancy is still under consideration, but a cap thickness of more than 1.5 cm is highly suspicious of malignancy (45).

In 2005 however another new model by Stickens et al was introduced. There were suggestions that besides the Ihh-PTHrP pathway, the major defects in HME would be located in the FGF and BMP-TGF β pathway. In normal conditions FGF leads to depression of proliferation in long bones by slowing chondrocyte differentiation and lowering expression of Ihh. BMPs antagonise FGF and stimulate the differentiation of chondrocytes. In this model disturbed HS synthesis leads to lower FGF and disturbed differentiation of cartilage (58). A new recent theory unites previous models in one unifying theory. Wrong signaling pathways (Ihh, FGF, BMP) lead to differentiation of some perichondrial chondrocytes to hypertrophic chondrocytes. With further growth and expansion of the growth plate these chondrocytes are stimulated to form bone.

These angled chondrocytes start to grow in a 90 degree angle as seen with exostoses. This latest model can explain the incomplete penetrance and variable distribution of exostoses in HME.

MALIGNANT DEGENERATION

The most feared complication of HME is malignant transformation of an existing osteochondroma into a secondary peripheral chondrosarcoma. These chondrosarcomas develop in the cartilage cap of an existing osteochondroma. The lifelong risk for degeneration is estimated to be between 1 and 5%. The average age at which patients present with secondary chondrosarcoma is 34 years. This is younger compared to patients with primary chondrosarcoma. The risk of malignant degeneration is twice as high in male patients as in female patients. Secondary chondrosarcomas frequently arise at the pelvis and femur, less frequently at the scapula and humerus. One needs to consider the possibility of secondary chondrosarcoma in patients presenting with pain, swelling and a palpable mass. These symptoms are mainly caused by growth of the cartilage cap (56). Rarely these tumours of the pelvic bone may cause urologic or enterologic problems (39,68). Secondary chondrosarcoma is also associated with Ollier disease and Maffucci syndrome.

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A biopsy of the cartilage cap will show hypercellularity and binuclear cells, multiple cells arranged in lacunes and myxoid changes. When invasion of surrounding tissue and scattered cartilage nodules are present, a more malignant type should be considered (2).

A genetic double hit hypothesis for tumour genesis in HME describes a primary inactivating mutation of both EXT1 genes and a consequent secondary mutation in other genes, which leads to malignant degeneration. When only the primary mutation is present, benign osteochondromas develop, with other mutations these will degenerate to malignant chondrosarcomas (9). The most degenerative mutations lead to constant activation of Hh, with no down regulation by PTHrP (60).
We advocate to screen the patient on a yearly basis with radiographs of affected areas and a paediatric/orthopaedic clinical examination. Always consider the risk of cumulative radiation. The prognosis of secondary chondrosarcomas is good, since these tumours rarely metastasise. The 5-year survival is estimated to be 90%. Patients with a solitary osteochondroma have a better prognosis (6% 5-year mortality) compared to HME patients (19.6% 5-year mortality). High-grade tumours have a higher rate of metastases. A wide surgical excision is the treatment of choice.

Ten percent of secondary chondrosarcomas are classified as dedifferentiated chondrosarcomas, a very aggressive type of tumour consisting of two components. A low grade, well differentiated chondrosarcoma, and a high grade (non-cartilage) sarcoma. They are peripherally located in 4-5% of all cases and have high metastatic risk and a bad prognosis. Two and five year survival rates are 38% and 24% respectively. To make matters worse, these tumours tend to be resistant to radiotherapy and chemotherapy, caused by poor vascularisation, low pH and high interstitial pressure. EXT gene mutations have been found in these tumours, and defects in TGF-β and FGF are described. Chemotherapeutic agents affecting upstream Her-1 show promising results.

Medical treatment

Promising treatments with blocking agents are currently under investigation. Hedgehog signalisation inhibits terminal differentiation of chondrocytes and regulates the differentiation status of chondrocytes in cartilage caps of osteochondromas. Defects in regulation of Hh are present in the pathogenesis of the whole spectrum of benign and malignant cartilage tumours.

Considering previous findings, researchers thought that the Hh pathway was a major therapeutic target for treating cartilage tumours. In a study of chondrosarcoma on mice, triparanol, a hedgehog blocking agent was able to reduce tumour volume, cellularity and proliferation. These effects are achieved by lowering diffusion of Ihh and thereby stimulating the differentiation of chondrocytes. Hedgehog blocking agents can be used in a neo-adjuvant fashion, to reduce tumour load before surgery and are currently used in several studies on brain and skin cancer.

Surgical treatment

Indications for surgery are pain, cosmetic complaints, vascular and neurologic complications, clinically important malalignment and of course malignancy.

The causative factor for many complaints is extrinsic compression by the exostosis of the soft tissue envelope, affecting tendons, vessels or nerves. Hence treatment is relatively easy and consists of removal of the exostosis. The exostosis should be sent for pathology examination. The osteotomy is performed at the base of the lesion; sometimes an osteoplasty is performed to contour the bone. Care is taken to leave a smooth bony surface. A compression bandage is used postoperatively whenever feasible to diminish postoperative haematoma. The use of drains is debatable and in our personal opinion to be avoided if a compression bandage can be applied. Treatment for instability secondary to deformations of joints is however difficult and usually not indicated. Axis corrections are sometimes necessary, especially in the lower limb.

Knee

The knee joint is often a site where excision is performed for cosmetic or clinical reasons, especially in skinnier patients. Symptomatic lesions of the distal femur or proximal tibia are treated by simple open resection, preserving the soft tissue envelope. An endoscopic technique has also been described. The fibular head is often a site of symptoms due to
Ankle

Distal lesions in the lower limb involve the tibia and fibula and often result in axial deformity. Resection of symptomatic exostoses in HME at the ankle level is delayed until skeletal maturity in most cases due to the high recurrence rate in children. Symptoms usually occur in the second decade of life with ankle restriction, a palpable mass and a painful ankle joint (3). Sometimes the progressive axial deformity necessitates an intervention at younger age. Various techniques have been described; the Ilizarov technique with external frame is particularly useful in this setting.

Elbow and forearm

Since ulnar shortening and radial head instability at the elbow is the main complaint in HME of the distal upper limb, resection of a symptomatic exostosis of the forearm is sometimes not sufficient to relieve symptoms. Ulnar lengthening with external fixation has been described, providing improvement in instability symptoms (4). However a recent review of 31 forearm corrections in 23 patients for HME evaluating various corrective procedures (resection of exostoses, ulnar and/or radial lengthening, corrective osteotomy of radius/ulna, radial head resection or open reduction) showed no benefit of these corrective procedures. Ulnar lengthening was particularly prone to complications. Therefore it was suggested by the authors that one should only resect the exostoses. It was shown that forearm rotation and cosmesis were improved by resection of forearm exostoses in HME (14).

Resection of exostoses at other sites is extremely rare; usually they are performed for neurological deficit.

At a later age, degenerative hip and knee disease can sometimes warrant joint replacement surgery. In the case of HME with malformations, this may lead to a challenge from a technical point of view, and sometimes custom implants and/or concurrent osteotomies need to be performed.

An interesting finding is that HME patients have higher scar tissue production after surgery. It is speculated that this is related to EXT mutations having an effect on wound healing. This scar tissue is a major determinant of patient satisfaction after surgery (20). Most patients are satisfied after surgery and 66% would take the decision sooner. Most symptoms are relieved by surgery, although pain can persist in up to 16% of all patients. Therefore it is recommended to adopt a conservative approach if pain is the main complaint. It is strongly advised not to remove exostoses on a prophylactic basis (8).

In chondrosarcoma, a wide oncologic excision is advised. Extensive reconstructions and difficult dissections frequently present an important surgical challenge, so this surgery should only be performed by experienced surgeons in centers of excellence.

CONCLUSION

HME is a complex disease which still holds many secrets for paediatricians, orthopaedic surgeons and researchers. In the past 20 years the genetic and cellular mechanisms of HME were unraveled. However the complex and fascinating interactions of cells and molecules at the growth plate still remain under investigation. Research and findings on HME may offer interesting views on other diseases. They give us a better understanding of the role of heparansulfate in signal transduction, and of the physiopathology of other bone and cartilage diseases and an insight in skeletal embryology.

Now we look at the EXT-genes as tumour-suppressor genes with a major role in angiogenesis and malignant degeneration. Our hope is that HME and the findings on EXT genes and heparansulfate pathways may one day lead to the development of an effective cancer therapy.

The orthopaedic surgeon is often the first to diagnose the disease and should be aware of the clinical presentations of HME in all its forms. Surgical treatment usually involves removal of clinically important exostoses. Sometimes re-alignment of axial bones is required. Surgical treatment of
chondrosarcoma is reserved for the oncologic orthopaedic surgeon.

GLOSSARY

**EXT1 gene**: exostosin glycosyltransferase 1. This gene encodes an endoplasmic reticulum-resident type II transmembrane glycosyltransferase involved in the chain elongation step of heparan sulfate biosynthesis. Mutations in this gene cause the type I form of multiple exostoses [provided by RefSeq, Jul 2008]

**EXT2 gene**: exostosin glycosyltransferase 2. This gene encodes one of two glycosyltransferases involved in the chain elongation step of heparan sulfate biosynthesis. Mutations in this gene cause the type II form of multiple exostoses. Alternatively spliced transcript variants encoding different isoforms have been noted for this gene. ([provided by RefSeq, Jul 2008])

**EXTL-1 gene**: exostosin-like glycosyltransferase 1. This gene is a member of the multiple exostoses (EXT) family of glycosyltransferases, which function in the chain polymerization of heparan sulfate and heparin. The encoded protein harbors alpha 1,4- N-acetylglucosaminyltransferase activity, and is involved in chain elongation of heparan sulfate and possibly heparin. [provided by RefSeq, Jul 2008]

**EXTL-2 gene**: exostosin-like glycosyltransferase 2

**HSPG's**: Heparansulphate proteoglycans. Ubiquitous macromolecules associated with the cell surface and extracellular matrix of a wide range of cells of vertebrate and invertebrate tissues. They are essential cofactors in cell-matrix adhesion processes, in cell-cell recognition systems, and in receptor-growth factor interactions. (From Cancer Metastasis Rev 1996; 15(2): 177-86; Heparology 1996; 24(3): 524-32)

**Hedgehog proteins**: A family of intercellular signaling proteins that play and important role in regulating the development of many TISSUES and organs. Their name derives from the observation of a hedgehog-like appearance in DROSOPHILA embryos with genetic mutations that block their action.

Mesh database

**Bone morphogenic protein (BMP)**: The protein encoded by this gene is a member of the bone morphogenetic protein family which is part of the transforming growth factor-beta superfamily. The superfamily includes large families of growth and differentiation factors. Bone morphogenetic proteins were originally identified by an ability of demineralized bone extract to induce endochondral osteogenesis in vivo in an extraskeletal site. This particular gene plays an important role in the onset of endochondral bone formation in humans, and a reduction in expression has been associated with a variety of bone diseases, including the heritable disorder Fibrodysplasia Ossificans Progressiva. [provided by RefSeq, Jul 2008]

**Indian hedgehog (Ihh)**: This gene encodes a member of the hedgehog family of secreted signaling molecules. Hedgehog proteins are essential regulators of a variety of developmental processes including growth, patterning and morphogenesis. The encoded protein specifically plays a role in bone growth and differentiation. Mutations in this gene are the cause of brachydactyly type A1 which is characterized by shortening or malformation of the phalanges. Mutations in this gene are also the cause of acrocapitofemoral dysplasia. [provided by RefSeq, Feb 2010]

**Parathyroid Hormone Related Protein (PTHrP)**: An ubiquitously expressed, secreted protein with bone resorption and renal calcium reabsorption activities that are similar to parathyroid hormone. It does not circulate in appreciable amounts in normal subjects, but rather exerts its biological actions locally. Overexpression of parathyroid hormone-related protein by tumor cells results in humoral calcemia of malignancy. (Mesh database).

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