Current Knowledge on Exostoses Formation in Hereditary Multiple Exostoses: Where do Exostoses Originate and in What Way is their Growth Regulated?

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Abstract

Multiple hereditary exostoses is an autosomal dominant inherited disease causing exostoses: growth on the bones of children. The disease is mainly caused by mutated exostosin (EXT)-1 or EXT-2 genes. These mutations yield non-functional EXT-gene products. Lack of functional proteins cause a defect in heparan sulphate synthesis and therefore in proteoglycan modification and cell signalling. It is assumed that a subset of chondrocytes form an exostoses, through a growth and differentiation process which is only partially understood. The place of origin of these exostoses-forming chondrocytes is still unknown. We also do not know in detail which processes influence the exostoses growth, and what shelters the exostoses from being resorbed by osteoclast activity. In this paper we systematically review the major pathophysiological theories of exostoses, with a focus on the aforementioned knowledge gaps.

Keywords: Osteochondroma; Exostoses; Hereditary multiple osteochondroma (HMO); Hereditary multiple exostosis (HME)

Abbreviations:

BMP: Bone Morphogenic Protein; EXT: Exostosin; FGF: Fibroblast Growth Factor; HME: Hereditairy Multiple Exostosis; HMO: Hereditary Multiple Osteochondromas; HS: Heparan Sulphate; Ihh: Indian hedgehog; LOH: loss of heterozygosity

Introduction

The World Health Organisation (WHO) defines exostoses as a cartilage-capped bony outgrowth on the external surface of long bones. Per definition it contains a bone marrow cavity continuing in the normal cavity of the long bone [1,2]. With a proportion of 30-50% of all benign bone tumours, it is the most frequently occurring bone lesion. Hereditary multiple exostoses (HME) constitutes a separate, but clinically and radiographically indistinct disease entity that encompasses 10-15% of all exostoses patients. Approximately 1:50,000 people suffer from HME [3,4]. The disease is also termed hereditary multiple osteochondroma, diaphyseal aclasis, osteochondromatosis and multiple cartilaginous exostoses [5].

The diagnosis of HME is based on radiological and clinical presentation of multiple outgrowths (Figure 1), supplemented with, if available, histological evaluation. Approximately 65% of all patients have a positive family anamnesis [6]. HME is an autosomal dominant inherited disease mainly caused by mutated exostosin (EXT)-1 or EXT-2 genes. This causes a lack of functional proteins influencing heparan-sulphate synthesis, thus affecting the proteoglycan modification and cell signalling which play a role in exostoses growth [7].

Growth of the exostoses occurs as long as a child is growing, and new exostoses will form continually. After closure of the growth plates the exostoses stop growing and no new ones are formed [5]. Both sessile and pedunculated exostoses have been described. Through its shape, the pedunculated more than the sessile variant can compromise overlaying tissue and therefore has a greater risk of becoming symptomatic [8,9]. The exostoses can lead to compression of tendons, nerves, muscles, ligaments and of the spinal cord. Patients may experience pain or fatigue. The growing exostoses are known to cause a set of growth anomalies, including Madelung-like deformity (40-60%), unequal limb length (10-50%), joint deformity (2-55%) and a disproportionally short stature (37-45%) [3,6,10].

Further the exostoses can fracture (5%) and they can give vascular problems, abnormal scar formation, bursa formation, and joint impingement [10-13].

The direction of growth of the exostoses is pointed away from the adjacent growth plate and away from the adjacent joint [14]; they are not in line with the axis of the bone and are therefore not submitted to the axial load. We know from normal bone formation that non-loaded bone will remodel according to the laws of Wolff. This implicates that we expect the exostoses to be remodeled by creeping substitution and to eventually disappear as a result of osteoclast resorption [15,16]. Until now it is still unknown why exostoses after formation do not disappear.

Apart from the unknown mechanism of growth, the place of origin of the exostoses also remains unclear. Most exostoses are found in the metaphys under the peristeum, suggesting a metaphyseal origin. However, epiphyseal-like cartilage is found on top, suggesting an epiphysial origin [15]. There is no medication to cure exostoses or to slow its growth. Non-recurrence on site is only ensured after radical surgical removal of the exostoses. However, removal of exostoses in a skeletally immature patient may lead to epiphyseal damage and growth deformities [16,17].

The aim of this review is to explore the literature in the light of the following clinically raised questions: What factors influence the
growth of exostoses? Do exostoses escape Wolff’s law and if so, in what way? What is the place of origin of exostoses? In order to answer these questions as much as possible, the epidemiology, pathophysiology, marker expression and growth regulation are discussed, and the major pathophysiological theories are reviewed and put into historical perspective.

**Epidemiology of Exostoses**

Exostoses are a common isolated bony outgrowth of the long bones. It affects 1-3% of the general population. About 10-15% of these exostoses are in the context of the genetic form, multiple hereditary exostoses (MHE). MHE has its onset from early infancy to puberty. The exostosis ceases to grow and calcifies when the patient reaches skeletal maturity. Thereafter, no new exostoses develop [4,5]. The patients in average suffers from 15-18 exostoses, but up to a number of 80 exostoses have been described. The metaphysis of the tibia, femur and humerus is the most common location [18-20].

Affliction is usually symmetrical. Caucasians are more often affected than other races, affecting 0.9 - 2 individuals per 100,000. Caucasian men in particular have a higher predilection to suffer from MHE [10,21]. Male predilection (1.5: 1) however, is possibly due to an easier overlooked milder female phenotype [21]. The exostoses have a cartilage cap, the thickness of the cap differs and ranges from 1-2 mm to several centimetres. Increasing thickness correlates with pain and increasing size, with chondrosarcomatous potential in adults. These exostoses often have a more proximal location and a larger size [1,2,18,22]. MHE patients have a 1-3% risk of malignancy and the progression to malignancy is quicker than in non-hereditary (solitary) counterparts [1-3,6,10,23,24].

**Pathophysiology of the Exostose**

**Histology**

Exostoses have a strikingly consistent morphology, typically forming a cylinder pointing at various angles away from the epiphyseal disc and the joint. An exostose of a skeletally immature patient consists of a bony stalk and a cartilage cap. The cap is lineated peripherally with the perichondrium, which is continuous with the periosteum of the underlying bone. The cortex of the stalk is in continuity with the cortex of the normal bone, thus creating a continuous medullary cavity. In the skeletally immature patient the medullary cavity is delineated with the cartilaginous cap. The cap has the histological appearance of an epiphyseal growth plate with chondrocytes lined up in columns (Figure 2) [18,24].

**Genetics**

MHE is an autosomal dominant inherited condition caused by mutations in the exostosin (EXT) -1 and EXT-2 genes. The EXT gene family comprises 6 members, all located on different chromosomes and chromosomal regions [25-27]. EXT-1 and EXT-2 mutations together explain over 90% of all cases of MHE [28,29]. Mutations in EXT-1 account for 44-70% of the MHE cases and in 27-40% mutations in EXT-2 are causative for MHE. In a subset of patients both genes are affected [21,30-32]. In males, mutations in EXT-1 lead to a more severe HME phenotype as compared to mutations in EXT-2. Typically male carriers of mutations in EXT-1 present themselves with more and bigger exostoses [33-39].

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**Figure 1:** X-ray AP views of the right knee of adolescent female patient with HME, the lines on the distal femur mark the bony outgrowth of the exostoses.

**Figure 2:** (A) affranine-O staining of the cartilaginous cap of an exostosis, showing the presence of similar zones as the mouse epiphysis but separated in clusters. (B) Haematoxiline staining of the epiphysis of a 6 week old mouse as a representative example of a general growth plate.
The risk of malignant transformation cannot be linked to the specific genetic mutation. Genetically mutated mice carrying Ext-1(+/−) as well as Ext-2(+/−) heterozygous mutations mimic the genetic status of human HME and have shown to be able to format exostoses. The formation of stereotypic exostoses seems to require a significant, but not complete, loss of Ext expression [40]. Despite the identification of causative genes, the pathogenesis of HME remains unclear.

**Cellular biology**

EXT-1 and EXT-2 gene products are type II transmembrane proteins. They contain a single 17 amino acid long transmembrane domain and a short amino-terminal cytoplasmatic tail. EXT-1 and EXT-2 form a complex (EXT-1/2) in the Golgi apparatus, acting as regulated. To answer this question we focus on the influence of genetic status of human HME and have shown to be able to format HS specific polymerisation of a N-acetylglucosamine (GlcNAc) residue to a HS-specific tetrasaccharide linker. This initial polymerisation of the GlcNAc residue is a prerequisite for further HS chain elongation carried out by EXT-1 and EXT-2 [40,43,46-54].

Chain elongation by EXT-1/2 involves the alternating polymerisation of GlcA (glucoronic acid) and GlcNAc disaccharide units, maturation of the HS polymerisation process is completed, the proteoglycans are transported to the cell surface and located in the extracellular matrix or at the cell surface, where they function in high affinity binding of growth factors, cytokines, extra cellular enzymes and even viral enzymes [43,49,55-57].

As only EXT-1 and EXT-2 are specifically associated with HME, the major mechanism that is thought to underlie the HME pathogenesis involves impaired HS-polymerase activity by dysfunctional EXT-1/2 activity, leading to improper HS synthesis and aberrant cell signalling due to improper binding of essential signalling molecules.

**What influences the growth of the exostose?**

From clinical follow up it is known that exostoses sprout and grow while the patient is actively growing. After closure of the growth plates the exostoses stop growing and no new exostoses are being formed [5,18]. This raises the question how the growth of the exostoses is regulated. To answer this question we focus on the influence of mutated EXT genes on the signalling pathways and the major regulatory systems of normal growth regulation.

In patients with HME we know that the mutations in either EXT-1 or EXT-2 result in reduction or absence of HS in the exostoses cartilage compartment. This impaired HS synthesis has been linked to disturbed cellular signalling responses leading to growth disturbance of chondrocytes and maybe to the formation of exostoses [15,40,58,59].

There are two major classes of heparan sulphate proteoglycans (HSPGs). Glypicans are located at the cell surface and are glycosphosphatidylinositol (GPI)-linked molecules, solely bearing heparan sulphate. The other main class of signalling HSPGs are syndecans, which are transmembrane proteins decorated with both chondroitin sulphate and heparan sulphate [60]. HS and HSPG act as co-receptors for several growth factors, including bone morphogenic proteins (BMPs), fibroblast growth factors (FGFs), Wingless-members (Wnt), transforming growth factor β (TGF-β) and Indian hedgehog (Ihh) [61-69].

Normal endochondral ossification of long bones is a highly regulated process characterized by proliferation of chondrocytes, differentiation, calcification, and programmed cell death. The epiphysis of a long bone is divided into three well defined zones in which these cellular processes take place: the resting zone with the immature cells (also known as the germinal zone), the proliferating zone with more mature chondrocytes, and the hypertrophic zone with large calcifying and apoptotic chondrocytes. In the growing child the growth plate matures. During this process the hypertrophic cells synthesize collagen type X and then undergo calcification and cell death. After degradation of calcified cartilage by chondroclasts, the resulting cavities are invaded gradually by osteoblasts secreting bone matrix. At the end of puberty, the width of the epiphysis decreases and eventually the epiphysis is completely closed and replaced by bone. This process is controlled by various endocrine, autocrine, and paracrine factors [70].

The exact mechanism of epiphyseal fusion is still not completely understood. Paracrine regulators like parathyroid hormone-related protein (PTHrP) and Indian hedgehog (Ihh) are considered key factors in the regulation of the growth plate [71].

These growth factors coordinate endochondral ossification by regulating chondrocyte proliferation. Looking at one of the major regulatory systems we zoom in on the possible effects of the HME-associated EXT-1 and EXT-2 gene mutations on the Indian hedgehog – parathyroid hormone related protein feedback loop.

HME related to the Indian hedgehog/parathyroid hormone-related protein signalling

Indian hedgehog (Ihh) seems to orchestrate the chondrocyte proliferation and differentiation and the osteoblast differentiation [72]. Ihh is expressed and secreted by post-mitotic hypertrophic chondrocytes simultaneously with expression of the parathyroid hormone-related protein receptor (PPR) during the bone formation. Ihh diffuses throughout the growth plate and binds to its receptor, Patched-1 (Ptc-1) expressed by chondrocytes in the resting zone. This, in turn, activates downstream signalling that in turn leads to elevation of PThrP expression [73]. Since inactivation of either Ihh or PPR in chondrocytes leads to abrupt fusion of the epiphyseal growth plate in mice [74,75], it is suggested that the loop is crucial for maintaining the growth plate in the open phase. In humans inactivating mutation in Ihh results in acrocapitofemoral dysplasia, which is associated with premature closure of the growth plates [76].

EXT-1 and EXT-2 are expressed in the proliferating and the hypertrophic zones of the growth plate, and are responsible for an extracellular heparan sulphate proteoglycan (HSPG) gradient. Their expression coincides with the onset of Indian hedgehog signalling.
HME associated mutations in EXT-1 and EXT-2 may lead abnormal HS gradient formation in the growth plate [66,71]. De Andrea et al. showed in different studies of human growth plates and of different proteoglycan-deficient zebra fish mutants the disrupted diffusion gradients of morphogens and signal transduction in the epiphyseal growth plate [77]. As diffusion of Ihh is HSPG-dependent, proliferation zone EXT-/- chondrocytes could “encounter” an abnormal Ihh signal, leading to abnormal proliferation [78,79]. Evidence put forth independently by Hameetman and Benoist-Lasselins, shows the presence of Ihh in the cartilage cap of exostosis and proves Ihh signalling despite the lack of EXT proteins [80-82].

The above suggests an influence of HS and Ext in HME on the Indian hedgehog/parathyroid hormone-related protein signalling, possibly leading to premature closing of the epiphysis and thereby declaring the short stature in HME patients.

In addition to the hedgehog proteins and parathyroid hormone-related peptide, other important local regulators of the epiphyseal are the bone morphogenic proteins (BMPs) and the fibroblast growth factors (FGFs). Further local factors such as vascularisation, vitamin D and transforming growth factor beta (TGF-β) are not discussed in this context because they have no known relation with the EXT genes or HS. Also the systemic factors such as the GH/IGF-I system, glucocorticoids and oestrogens are not discussed.

HME related to para/autocrine regulators; the bone morphogenic proteins (BMPs), and the fibroblast growth factors (FGFs).

BMP’s have a role in every stage of endochondral bone formation and angiogenesis [83,84]. Lack of BMPs and/or their receptors in early stages have been shown to result in failure in mesenchymal condensation or digit formation in mice [85-87]. In a later stage the BMP proteins are expressed in the perichondrium as well as hypertrophic and proliferative chondrocytes. Indian hedgehog expression in prehypertrophic chondrocytes increases through BMP signaling thereby increasing both the rate of chondrocyte proliferation and the length of proliferative columns [70,88]. Since HS and HSPG act as co-receptors for BMP’s in HME patient we expect therefore a decrease in the rate of chondrocyte proliferation and a shortening of the proliferative columns, which may lead to shortage or axial deviation (in case of partial decreased growth rate) of the long bones.

Other local growth factors depending on the HSPG’s for cell-signalling activity are the fibroblast growth factors (FGFs). FGFs are essential for normal embryonic development.

FGF receptor 3 (FGFR3) is expressed in the resting zone of the epiphyseal disc, where it promotes hypertrophic differentiation and decreases proliferation. In mice it has been shown that FGFs can act as antagonists of BMP signalling and negatively regulate Ihh expression. FGFs acting via FGF receptor-3 (FGFR3) are the key negative regulators in chondrocyte proliferation. Mutations in FGFR3 lead to achondroplasia or hypochondroplasia [71].

The expression of FGFs and their receptors in postnatal growth plate cartilage suggests that these proteins contribute to growth plate senescence and thus help to determine the size of the adult skeleton [70,89].

In relation to HME, EXT mutation and thus HSPG deficiency would lead to a functional FGFR3 null state. Bovée et al showed defective (mostly absent) expression of FGF-2, FGFR1, FGFR3 in exostoses, presumably allowing skeletal overgrowth at the site of the exostoses [90].

In conclusion, in HME with mutations in either EXT-1 or EXT-2 it is likely that the absence or reduction of HS disturbs the three major regulatory systems of epiphyseal growth, being the Indian hedgehog – parathyroid hormone related protein feedback loop, the BMPs and the fibroblast growth factors. One of the striking observations is that the general genetic defect in all cells does not induce exostoses in or near all growth plates. This raises the question if there might be a secondary, unknown influence or factor. This suggestion is supported by multiple studies describing mixed cell populations with both mutant and wild cells in the cartilage of the exostoses [59,91,92].

Do exostoses escape Wolff’s law and if so, how?

Exostoses contain a bone marrow cavity continuing in the normal cavity of the long bone. The cap of the exostosis has the histological appearance of an epiphyseal growth plate with chondrocytes lined up in columns. The growth plate-like lesion grows at an approximately 60 degree angle relative to the normal growth direction of the bone [13]. When exostoses arise there can be spontaneous regression [93]. This applies not only to natural occurring exostoses but also for surgically created ones. Exostoses can be created by inverting a 60 degree span of the ring of LaCroix [94]. These surgically created exostoses disappear eventually due to spontaneous regression. One could expect all exostoses to disappear eventually, raising the question why the exostoses in HME do not resorb or regress. Possibly, the answer lies not only in the exostoses itself, but as well in the in the surrounding of the exostoses. The exostosis is covered with periosteum. This periosteal layer also covers the cartilaginous top. This layer consists of undifferentiated cells overlying the top of the exostoses. In culture they yield a rapidly proliferating homogenous population of fibroblast-like cells. These cells express FGFR9, FGFR3, and collagen type Ia [95]. Possibly influencing the cartilage cell in the top that resemble epiphyseal cells and may also have a similar function. The top of the exostoses than behaves like regular endochondral bone with active remodelling. Trebicz-Geffen assessed surgically created exostoses and found a lack of FGF receptor 3 (FGFR3), and down-regulated Indian hedgehog [96]. Perhaps the presence of the epiphyseal-like chondrocyt carrying cap and the presence of growth regulatory factors such as FGF and Ihh coming from the covering layer gives active regeneration of the exostoses which shields them from resorption due to remodelling. Explaining how the exostoses is constructed by the cartilaginous cells in the top and simultaneously broken down by the remodelling.

What is the place of origin of the exostose?

Although we know that most exostoses are found in the metaphysis under the periosteum we still don’t know where they originate. To find the place of origin, we first zoom in to the cellular marker expression. As mentioned, associations have been found between the epiphysis and exostoses. For example the proliferative zone resembling chondrocytes in the exostoses stain positive for PCNA [80]. PCNA is a specific marker for S-phase cells, showing that these proliferative zone resembling cells indeed preserve their proliferative character. The cartilage cap of the exostoses does not significantly thicken, which indicates that the proliferative cells undergo hypertrophy and the exostoses does retain a rudimentary epiphyseal function. Other similarities are found when using the proliferative marker Ki-67. Both the exostoses and the normal growth plate stained positive in equal measures, showing according to Huch that the exostoses and the normal growth plate share similar proliferation capacity [97].
Benouist-Lasselin proved growth plate phenotype by staining the exostoses positive for cartilage specific collagen type II, and hypertrophic zone specific marker collagen type X [80]. The above makes the epiphyseal disc as a place of origin likely.

Looking at the histopathologic studies of very young patients the earliest lesions are shown as a micro exostoses within the periosteum adjacent to the normal phyysis. This suggests the ‘groove of Ranvier’ as a possible place of origin. This idea that the origin of the exostoses is the groove of Ranvier is supported by the fact that the exostoses always grows close to the epiphysis but never in it [98-100].

Other histopathologic studies as the study by Milgram in 1983 showed that the exostoses are derived from aberrant cartilaginous epiphyseal growth plate tissue, which proliferates autonomously and separates from the normal growth plate near its edge. The aberrant tissue remains in a subperiosteal location, where it either disappears or proliferates [15]. This is bolstered by the finding that redistribution of Ihh from growth plate to perichondrium leads to ectopic cartilage formation [101]. Further supported by studies conducted in mouse models of HME that indicated ablation of Ext1 in growth plate chondrocytes leads to formation of ectopic cartilage around the epiphyses, not in it [91,92,102].

Looking at the above presented research the growth plate seems to be best possible place of origin of the exostoses both in cellular type as in cellular function of the chondrocytes found in the exostoses.

Historical perspective on the theories about the formation of exostoses in HME

In the earliest publications at the beginning of the 20st century the exostoses was believed to arise from an erroneous differentiation of cells in the periosteum [103]. However many years later evidence showed that the perichondrium and the bony stalk were not of clonal origin, making it an unlikely pathophysiological source [82]. At the end of the 20st century, based on the observation that exposure to radiation could induce solitary exostoses formation the link with DNA damage was made. The “loss to follow-up” was then postulated as a mechanism to explain the formation. Researchers thought DNA damage to be a likely cause of diminished gene expression. Both in solitary and multiple, or familial, exostoses loss of heterozygosity (LOH) of the EXT1 gene has been shown [56,104,105]. This suggests a common pathophysiological mechanism, which seems plausible based on the extensive similarities in morphology. But laboratory results showed that while LOH can occur in exostoses, and can induce their formation, it is not a consistent and thus necessary step in their development. This led to search for a different explanation as to how gene expression can be down regulated. It seems obvious that since the EXT genes function in unison, their expression would also be regulated in a synchronized fashion. As the EXT genes are only expressed in specific zones of the normal epiphyseal disc, they might be that their expression is induced by differentiation. This defective differentiation is shown by the partial or absent signalling pathways in the exostoses [13]. With the knowledge of the DNA blueprint in the 21st century mouse, rat and zebra fish models were introduced. Many different authors than described the different pathways such as the defective Ihh signal and the Ihh-PTHrP feedback malfunctioning. Jones et al. in 2003 postulated a theory that an islet of EXT-/ chondrocytes would produce a defective Ihh signal, refraining the perichondrium from osteoblastic differentiation. Islet of chondrocytes differentiate, and form an internal growth plate forming an exostoses [79]. This theory emphasises the importance of the perichondrium but does not offer an explanation on how the chondrocytes gain their proliferative capacity nor does it incorporate the evidence of abnormal osteoblastic and hypertrophic marker expression in exostoses chondrocytes.

Other evidence showed that the cartilage cap of an immature exostoses is of clonal origin and therefore of neoplastic nature [56,104-106]. This makes the cartilage cap the likelier intermediate for exostoses development and the growth plate the most likely source of pathological chondrocytes [81]. Currently different authors believe the exostoses should be approached more like a derailed growth plate [4,59,80,97]. The growth plate like structure of the exostoses seems to be fed by a reservoir of proliferative zone resembling chondrocytes which are accompanied by hypertrophic zone resembling chondrocytes, which quite possibly are the differentiation products of the proliferative resembling cells [107].

Now that the causative gene mutations have been clarified and the site of origin might be found, it is a matter of finding the pathophysiological “missing” link that brings us from gene mutation to exostoses formation. Knowing that the general genetic defect does not induce exostoses near all growth plates, search for other explanations began. Different models were therefore introduced such as Knudson’s two hit model: the neoplastic theory [82,108]. It postulates that EXT null chondrocytes might lose their tumour suppressor function through loss of heterozygosity thereby causing the exostoses [58,99,109-112].

In summary, the well-preserved morphology of exostoses seems to entail a highly regulated process, deregulated in a highly consistent manner. The differentiation process is not of pathological nature in itself but steered in the wrong direction. It can therefore count on a highly constant and regulated physiological responds, also explaining the constant morphology. The EXT genes are only expressed throughout the proliferating and hypertrophic zone of the epiphyseal disc. Pathological derailment is likely to start as EXT heterozygous chondrocytes express less heparan sulphate. As heparan sulphate is essential to membrane bound and extracellular proteoglycans optimizing signalling transduction and gradient formation of several premier epiphyseal-signalling pathways, it seems apparent that part of the solution ought to be found in this aspect.

Possibly a malformation in gradient formation and signalling exposes chondrocytes to a unique dysphysiological morphogenic “cocktail”. To understand the exact cocktail these chondrocytes are subjected, more work is needed.

Conclusion

This review summarizes current knowledge about HME. The pathophysiology and genetics of the EXT genes and their possible role in heparan sulphate biosynthesis are described. The theories about the growth of the exostoses are analysed, finding clues in the mutations in either EXT-1 or EXT-2 that lead to the absence or reduction of HS. This seems to disturb the major regulatory systems of epiphyseal growth and of the exostoses. The question on how the exostoses escape Wolff’s law is highlighted referring to the peristial layer and the exostoses proper growth plate. The presence of this epiphyseal like chondrocyt caring cap might give the exostoses the possibility to regenerate and that might shield it from being resorpted due to remodelling. This active chondrocytic cap on the exostoses might be due to the place of origin of the cells that could very well be the growth plate. Thus also explaining their growth capacity in harmony with the
growth of the patient. Because the general gene defect doesn’t account for difference in penetration of the disease in patients, further studies might be focussed on the search for multiple causes or defects.

Statement of author contributions:

The review was designed by HS, AW, LvR and TW. The literature search was conducted by HS, AW and TdM. All authors contributed in writing and revising this manuscript and approved the final version.

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