

## [The Genetics of Hereditary Multiple Exostosis \(HME\)](#) [Sandra A. Darilek, MS and Jacqueline T. Hecht, PhD](#)

### **Introduction**

Hereditary multiple exostosis (HME) is a skeletal disorder characterized by the presence of numerous bony outgrowths (osteochondromas or exostoses) that develop next to the growth plates of all the long bones (Solomon 1963). The most striking clinical feature of HME is the numerous cartilage-capped exostoses, which are associated with the entire skeleton. Skeletal surveys suggest that a solitary exostosis can be found in 1-2% of the general population (Mirra 1989). A diagnosis of HME is made in individuals where the presence of multiple exostoses has been noted on clinical and/or radiologic examination. The average age at identification of a first exostosis is three to four years with 96% of individuals with HME developing exostoses by the age of 12 (Schmale et al. 1994; Wicklund et al. 1995).

In addition to having exostoses, individuals with HME can have other skeletal and non-skeletal complications. Skeletal complications include limb discrepancy and bony deformities such as bowed radius, conical ulna, and valgus deformity of the hip and ankle (Solomon 1963; Karasick et al. 1997; Vanhoenacker et al. 2001). Mild short stature is also a characteristic feature of the condition with the mean height being  $170 \pm 7.9$  cm for males and  $155 \pm 6.9$  cm for females (Wicklund et al. 1995). The presence of exostoses can lead to a number of non-skeletal complications such as compression of tendons, muscles, ligaments, blood vessels, and nerves, all of which can cause pain. Blood vessel involvement has been found in 11.3% of individuals with HME, while peripheral nerve compression and spinal cord compression have been found in 22.6% and 0.6% of individuals with HME, respectively (Wicklund et al. 1995). A recent study focusing on pain in HME found that 84% of individuals report having pain as a result of having HME (Darilek et al. 2004). By far the most severe complication of HME is the malignant transformation of an exostosis into a chondrosarcoma. Recent studies estimate the lifetime risk of malignant degeneration to be about 2-4% for individuals with HME (Schmale et al. 1994; Wicklund et al. 1995; Darilek et al. 2004). Many individuals with HME undergo surgery as a result of having HME-related complications. Studies have shown the 66-74% of individuals with HME undergo at least one operation for their exostoses, with the average number of surgeries being two to three (Schmale et al. 1994; Wicklund et al. 1995).

### **Inheritance**

HME is an autosomal dominant condition with a penetrance ranging from 96 to 100% (Schmale et al. 1994; Wicklund et al. 1995). Estimates of the prevalence of HME have ranged from 0.9 in 100,000 in a European population to 100 in 100,000 in a small, closed population of the Chamorros of Guam (Voutsinas and Wynne-Davies 1983; Krooth and Cunningham 1986; Hennekam 1991). A more recent study in the state of Washington found the prevalence to be at least one in 50,000, however, this is thought to be an underestimate as more mildly affected individuals do not come to medical attention (Schmale et al. 1994). Most people with HME have a family history of the condition. Solomon (1963) reported that 66% of individuals with HME have a family history while more recent studies have increased this estimate to 70-90% (Schmale et al. 1994; Wicklund et al. 1995)

## Gene Linkage

Linkage studies were conducted to locate the gene or genes leading to HME. It was long suspected that a gene for HME would map to the Langer-Giedion region on chromosome 8. Langer-Giedion syndrome is a rare, autosomal dominant disorder in which individuals have multiple exostoses, characteristic facial features, and cone-shaped epiphyses and are frequently mentally retarded (OMIM #150230). The exostoses found in HME and Langer-Giedion syndrome are indistinguishable. In addition, a patient with HME and a balanced chromosomal translocation involving chromosomes 8 and 11 had been described, adding to the evidence for the presence of an HME gene on chromosome 8 (Ogle et al. 1991). In order to determine if a gene for HME was indeed located on chromosome 8, Cook et al. in 1993 conducted linkage analysis on eleven multigenerational families with HME. They found significant evidence for linkage of a disease locus to the Langer-Giedion region on chromosome 8 for 70% of the families studied. This finding also indicated that HME is a genetically heterogeneous disorder, having at least one other locus somewhere else in the genome. In 1994, Wu et al. studied two large, multigenerational families with HME, for which linkage to chromosome 8 was excluded, in order to try to localize other genetic loci for HME. They performed a genome-wide search and found evidence for a second locus for HME on chromosome 11. Linkage to a third locus on chromosome 19 was also reported by Le Merrer et al. in 1994. In 1996, the linkage to chromosomes 8 and 11 was confirmed by Blanton et al. and in 2001 linkage analysis conducted by Francannet et al. confirmed that there are at least three *EXT* loci, with 69% of their families showing linkage to *EXT1* on chromosome 8, 21% to *EXT2* on chromosome 11, and 3% to *EXT3* on chromosome 19 (Blanton et al. 1996; Francannet et al. 2001). These findings suggested that these three loci account for over 90% of cases of HME, but that at least one additional HME locus might exist. However, neither the *EXT3* gene nor any additional *EXT* genes have been cloned and these findings have not been confirmed in other studies.

## Genes

Of the three genes linked to HME, two have been cloned: *EXT1* on chromosome 8q23-q24 and *EXT2* on chromosome 11p11-p12. Homologous genes have been found in mice, *Caenorhabditis elegans*, *Drosophila*, and *Xenopus* (Lin and Wells 1997), Stickens et al. 1997, (Bellaiche et al. 1998; Katada et al. 2002)]. *EXT1* and *EXT2* are large genes. *EXT1* is made up of eleven exons spanning over 250 kilobases while *EXT2* contains fourteen exons and is spread over a region of more than 100 kilobases (Ludecke et al. 1997). The genes code for ubiquitously expressed proteins of 746 (*EXT1*) and 718 (*EXT2*) amino acids and share approximately 70% similarity at the amino acid level (Ahn et al. 1995; Wuyts et al. 1996). Both the *EXT1* and *EXT2* proteins have been found to localize predominately to the endoplasmic reticulum but function in the Golgi apparatus as hetero-oligomers to synthesize heparan sulfate chains (Lin and Wells 1997; McCormick et al. 1998; McCormick et al. 2000). Normally functioning *EXT1* and *EXT2* proteins are required for proper bone growth. Since both proteins play a role in the development of benign bone tumors and there is an increased risk for individuals with HME to develop chondrosarcoma, it is thought that the *EXT* genes function as tumor suppressors. This role has been supported by loss of heterozygosity (LOH) studies that have revealed that both the *EXT1* region on chromosome 8 and the *EXT2* region on chromosome 11 show LOH in HME-related and isolated chondrosarcomas (Hecht et al. 1995; Raskind et al. 1995; Hecht et al. 1997).

Mutations Research has shown that approximately 64-76% of families with HME have a mutation in the *EXT1* gene and approximately 21-30% have a mutation in the *EXT2* gene (Dobson-Stone et al. 2000; Wuyts and Van Hul 2000; Francannet et al. 2001). Currently, 66 different mutations have been found in the *EXT1* gene and 31 different mutations have been found in the *EXT2* gene. The *EXT1* mutations include thirteen nonsense mutations, twelve missense mutations, and four splice sites mutations as well as 37 mutations that consist of small insertions or deletions. The majority of the *EXT1* mutations have been found to cause premature termination of the EXT1 protein. While most of the mutations reported are private mutations, two mutations, 1469delT and C1018T, have been reported in nine and ten unrelated patients, respectively (Wuyts and Van Hul 2000; Francannet et al. 2001). The distribution of the mutations over the *EXT1* gene has been analyzed and reveals that while mutations occur throughout the entire length of the gene, most of the mutations are distributed over the first six exons of the gene with the last five exons, which contain a conserved carboxyterminal region, having significantly fewer mutations (Wuyts and Van Hul 2000). The *EXT2* gene has been shown to have a comparable spectrum of mutations. Eleven of the 31 reported mutations are nonsense mutations while four are missense mutations, three are splice site mutations, and thirteen are frameshift mutations (Wuyts and Van Hul 2000; Francannet et al. 2001). As in *EXT1*, most of the mutations are private mutations that are distributed over the first eight exons of the gene, again leaving the carboxyterminal region with fewer mutations than one would expect with a random distribution (Wuyts and Van Hul 2000). The majority of the *EXT* mutations are expected to cause premature termination of the EXT proteins leading to loss of function of the proteins (Francannet et al. 2001). A multi-step model was proposed to describe the development of an exostosis but there is little experimental data to support this model. Only heterozygous mutations have been identified in the vast majority of exostosis samples with only a few exostosis samples demonstrating multiple mutations or LOH (Hall et al. 2002).

### ***Genotype-Phenotype Correlations***

In 2001, Francannet et al. conducted a clinical survey and mutation analysis for 42 families with HME, consisting of 217 affected individuals, in order to determine whether there is any correlation between HME phenotype and genotype. They divided the families into two groups based on the phenotypic expression of the disease. The first group, referred to as group S, included families with severely affected members while the second group (group M) included families whose members had a moderate HME phenotype. They also further divided group S into four subgroups labeling them as type IS to IVS, with IVS being the most severely affected group overall. Of the 42 families studied, seven belonged to group M and 35 to group S. Of the group S families, 10 were labeled type IS, five type IIS, eight type IIIS, and two type IVS. Most of the families with a moderate phenotype (group M) were found to have *EXT2* mutations, while all of the type IIS, IIIS, and IVS families except one were found to have *EXT1* mutations. The more severe HME phenotype (type S) was significantly associated with *EXT1* mutations while a more moderate phenotype was associated with *EXT2* mutations. Of note, chondrosarcomas were only found in patients with *EXT1* mutations. The only correlation found between phenotype and location of mutation in the *EXT* genes was found in the IVS group (most severe phenotype). Mutations associated with this group of patients were consistently located in the first exon of *EXT1*. Phenotypic variability has also been noted in HME. In this study, 2/3 of families with an *EXT1* mutation were noted to exhibit phenotypic variability, while in all but two families with *EXT2* mutations members showed a homogeneous phenotype (Francannet et al. 2001).

This genotype-phenotype analysis suggests that more severe HME phenotypes presenting with large number of exostoses, short stature, and/or vertebral exostoses are more commonly found in individuals with an *EXT1* mutation. One concern about the study is the criteria used for categorizing phenotype severity. The researchers used five factors to judge severity: age at onset (severe if less than or equal to 3 years), number of exostoses at time of evaluation (severe if greater than or equal to 10), location of exostoses (severe if vertebral exostoses noted), stature (severe if less than or equal to the tenth percentile), and functional rating (severe if the rating was “fair”). For an individual’s phenotype to be labeled severe, three or more of these factors had to be rated severe. The authors do not explain why these specific cutoffs are determined. There currently is no consensus as to what constitutes a severe versus a moderate HME phenotype and thus severity ratings can be extremely subjective. Of note, the genotype-phenotype correlations were based on family phenotype, not on individual phenotype, and a family’s phenotype was based solely on the degree of severity of the most affected members. As a result, a family with a number of mildly or moderately affected members could have been labeled as severe if a few of the members are found to have severe phenotypes. This can lead to a bias, as only those most severely affected family members are considered when making genotype-phenotype correlations. In addition, it is not clear whether the study population is made up of individuals ascertained from a clinic population or from the general population of individuals with HME. If the study population is a clinic population, it is possible that only more severely affected individuals and families were studied, again biasing the study toward a more severe phenotype by not including those individuals and families who never come to medical attention due to being mildly affected by HME. In order to determine whether genotype-phenotype correlations can be made in HME, additional studies should be carefully undertaken and consider disease severity by individual.

### ***Genetic Counseling and Genetic Testing***

Most individuals with HME have a parent who also has the condition, however, approximately 10% of individuals with HME have the condition as a result of a *de novo* mutation and are thus the first person in their family to be affected (Schmale et al. 1994). Individuals with HME have a 50% chance of having an affected child. Genetic testing for HME is available on a clinical basis. Testing consists of sequence analysis of the entire coding regions of both the *EXT1* and *EXT2* genes. The mutation detection rate has been found to be approximately 70%, as sequencing of the coding regions of the genes may not identify all mutations (Philippe et al. 1997; Raskind et al. 1998). If a mutation is not detected by sequence analysis, fluorescent *in situ* hybridization (FISH) analysis can be used to detect deletions in the *EXT1* and *EXT2* genes. Prenatal diagnosis through chorionic villus sampling (CVS) at 10-12 weeks gestation or amniocentesis at 16-18 weeks gestation as well as preimplantation genetic diagnosis (PGD) is available for individuals for whom genetic testing has identified a disease-causing mutation. Though genetic testing is available for HME, the severity of the condition cannot be predicted based on mutation type. In fact, the severity of the condition varies even within members of the same family. Genetic counseling is indicated for individuals and families with HME to aid them in understanding information about HME and making decisions based on this information.

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