

# The Genetics of Multiple Hereditary Exostoses

## A Simplified Explanation

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### Multiple Hereditary Exostoses - General aspects

#### Introduction

Multiple Hereditary Exostoses (MHE), also often referred to as Hereditary Multiple Exostoses (HME), is a bone disorder that affects mainly the long bones. Recently the term Multiple Osteochondroma (MO) was suggested by the World Health Organization (WHO) as the preferred term to refer to this disorder and throughout this article both abbreviations MHE / MO / HME will be used. MHE / MO / is characterized by the presence of bony protuberances, which are described as osteochondromas or exostoses. They are located mainly near the joints and are often accompanied by skeletal deformities.

MHE / MO / HME was first described in the year 1786, while the name multiple exostoses was first proposed in 1876. In the literature one can find many other names describing this disorder; such as diaphyseal aclasis, chondral osteoma, osteochondromata, multiple cartilaginous exostoses, (multiple) exostosis, deforming chondrodysplasia, osteogenic disease, etc.

Single osteochondromas or exostoses are very common in the general human population (1 to 2%) but the incidence of multiple osteochondroma is estimated to be 1 in 50,000. However, isolated communities have been described where a much larger fraction of the population is affected. MHE / MO / HME is not a unique human disease, as osteochondromas have been found in many species including cats, dogs, sheep, horses, lizards, lions, etc. A large osteochondroma was even found on the bones of a dinosaur.

#### Clinical aspects

MHE / MO / HME is a condition a person is born with and osteochondromas can be present at birth but in most patients they are noticed within the first six years of life. By the age of 12, almost all patients have been diagnosed.

Most affected bones are the femur, tibia and fibula, but this is very variable from patient to patient. In theory every bone which is formed by endochondral bone formation (a process of bone formation in which cartilage is formed first, which then is replaced by bone) can be affected. Facial bones remain normally unaffected. MHE / MO / HME is characterized by great variation in number, size, location and shape of the osteochondromas, even within a family. The osteochondromas continue to grow until closure of the growth plates at the end of puberty. Development of new osteochondromas or further growth at later age is not common but has been described. In addition to the presence of the bony outgrowths, skeletal deformities such as bowing and shortening of the forearm, knee, hip and ankle deformities can be present. Mild short stature is also observed in many patients.

Many complications have been observed in MHE / MO / HME patients, including compression of tendons, nerves, muscles, ligaments and spinal cord. The pressure of the osteochondromas on neighboring tissues and organs causes often almost permanent pain. The most serious complication is the development of a malignant tumor (a [chondrosarcoma](#)) out of an osteochondroma, mostly occurring at adult age. This event is observed in 1 to 5% of the cases and is often preceded by abnormal growth of the osteochondroma or changes in the cartilage cap which covers the osteochondroma. The only known treatments for MHE / MO / HME are surgical removal of the osteochondromas, (which often grow back at the original site) and surgical procedures to correct bone deformities and [limb length discrepancies](#). Surgery, physical therapy and pain management are currently the only options available to MHE / MO / HME patients, and their success varies from patient to patient and many struggle with pain, fatigue and mobility problems throughout their lives. At present there is no definite cure for MHE / MO / HME.

In addition to MO/MHE, two syndromes have been described where multiple exostoses are one of the symptoms: the Langer-Giedion syndrome (LGS) and the Proximal 11p deletion syndrome (P11pDS). Patients suffering from LGS have multiple osteochondromas, but also show typical characteristic features such as a bulbous nose, protruding ears, sparse hair, cone-shaped epiphyses and often mental retardation. Patients with P11pDS syndrome (also called Potocki-Shaffer syndrome) have multiple osteochondromas, skull defects and often mental retardation.

## Genetic aspects

MHE / MO / HME is an autosomal dominant hereditary disorder. This means

that a patient with MHE / MO / HME has a 50% chance of transmitting the disorder to his/her children, so he/she has a 50% chance that his/her child will also have MHE / MO / HME and 50% that this is not the case. This is equal for both male and female patients. Normally the disorder does not skip a generation. So if one of the parents does have MHE / MO / HME and the child does not, this child will normally only have unaffected children. However, some patients have very mild symptoms so it may only look like they are unaffected. In this case, their children are still at 50% risk of developing MHE / MO / HME. This may create a situation where it seems that the disorder skips a generation. In such cases, genetic analysis may reveal the true status. In a large number of patients there is no previous family history of MHE / MO / HME and both parents are unaffected. In these patients a new mutation has occurred. These patients have then again a 50% risk of transmitting the disorder to their children.

To understand why MHE / MO / HME is an autosomal dominant disorder one has to understand the basic principles of heredity. All our genetic information, which determines a great deal of the development of our body, lies within our DNA. This DNA is organized in [chromosomes](#), which are numbered from 1 to 22 while the sex determining chromosomes are named X and Y. At the moment of conception, the egg cell which comes from the mother fuses with the sperm cell, which is provided by the father. The egg cell contains 23 chromosomes (chromosome 1 to 22 and an X chromosome) and the sperm cell contains 23 chromosomes (1 to 22 and an X or Y chromosome). After fertilization, a fertilized egg with 46 chromosomes is formed from which an embryo and eventually a human being will develop.

During this process the cells will divide with duplication of the DNA. Therefore, in the human body (almost) every cell (with the exception of the egg and sperm cells) contains the 46 chromosomes containing the entire DNA content. Males have one X and one Y chromosome, females have two X chromosomes. Certain parts of our DNA, the so-called genes, contain all the information necessary to make proteins. Every gene is located on a certain chromosome. If such gene contains an error, which is called a mutation, this can affect the formation and/ or function of this gene and thus the function of the corresponding protein. Loss of altered function of this protein can then result in a visible defect or disorder.

At present we know that there are two such genes, the EXT1 gene on [chromosome 8](#) and the EXT2 gene located on [chromosome 11](#), which are important with respect to MHE / MO / HME. If a [mutation](#) in one of these two genes occurs, this inactivates this gene and/or the corresponding

EXT1 or EXT2 protein. Therefore, MHE / MO / HME patients have only one functional EXT1 or EXT2 gene, so have only half of the functional EXT1 or EXT2 proteins compared to people without a mutation in EXT1 or EXT2.

Both EXT1 and EXT2 have a function in cartilage and bone development and it appears that the remaining EXT proteins are not enough for normal bone development. The fact that MHE / MO / HME patients still have one functional EXT gene (and EXT protein) is not enough and therefore the effect of the mutation is dominant. This is in contrast with the so-called recessive diseases, such as, for example, cystic fibrosis (CF) where you only develop the disease if you have a mutation in both genes. People with a mutation in only one of their CF genes do not get CF but are only carriers of the disease. The chance for two parents who are both carriers of having an affected child is in this case 25%.

Approximately 60 to 70 % of MHE / MO / HME patients have a mutation in the EXT1 gene and 20 to 30% have an EXT2 mutation. In 10 to 20% of the patients, no mutation is found. This can be explained by the presence of a yet unknown, additional EXT-causing gene or by the fact that not all mutations can be detected by the techniques commonly used in DNA diagnostics for MHE / MO / HME. The fact that most of the families have a different mutation makes genetic analysis for MHE / MO / HME very laborious and expensive, and it is therefore only performed in a few laboratories worldwide. At present, the outcome of genetic testing has no effect on determining orthopedic care but genetic testing may give more options in making choices in reproduction. Once the mutation is identified in one patient, testing of family members is relatively easy and it can confirm their affected/non-affected status. Moreover, presymptomatic and prenatal diagnostics through [chorionic villus sampling](#) (CVS) at 10-12 weeks gestation or [amniocentesis](#) at 16-18 weeks gestation is available and also [preimplantation diagnostics](#) (PGD) can be offered to those families for whom the disease-causing mutation has been identified.

At present, it is still not very clear whether the differences in severity of the disease are related to whether the patient has an EXT1 or EXT2 mutation. There seems to be a tendency that EXT1 mutations cause a more severe type of MHE / MO / HME, but this needs to be confirmed in larger studies. In addition, there is no explanation for the variation in severity that is observed between patients within one family, thus with the same mutation. It is therefore at present impossible to make predictions with regard to severity of the condition based upon mutation type.

## Concluding remarks

Although still many questions remain unanswered, many aspects of MHE / MO / HME have been elucidated in the past years. The increasing understanding of the genetic and biological aspects of this disorder will increase the quality of the (genetic) counseling of MHE / MO / HME patients, which should always be offered when a diagnosis of MHE / MO / HME is made.

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