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Cytopathology-2015: Genetic confirmation of germline mosaicism in a Duchenne muscular dystrophy Tunisian family - Manoubi Wiem - Farhat Hached University Hospital, Tunisia

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Introduction:

Duchenne muscular dystrophy (DMD) is a deadly neuromuscular disease. It is a dystrophinopathy with an X-linked recessive genetic disorder linked to the absence of a cytoskeletal protein: Dystrophin. In general, this disease mainly affects only boys and women are vectors. In some cases, these women may not have the genetic defect responsible for the condition of germinal mosaicism. This situation was often suspected but rarely confirmed by genetic studies.

Objective: In this context, we report a Tunisian family; their children have DMD. Genetic analysis has exposed a particular transmission profile indicating maternal germinal mosaicism.

Methods: It is a Tunisian family made up of two parents, four boys and two girls. Two of the four boys had physical, enzymatic and electrophysiological signs very favorable to DMD. The genetic study allowed an analysis of the deletions and duplications of different exons of the dystrophin gene by MLPA (Multiplex Ligation-dependent Probe Amplification). Genotyping by analysis of six microsatellite markers surrounding or inside the dystrophin gene made it possible to establish the haplotype of each individual and to follow the transmission of the haplotype associated with the disease.

Result: The MLPA exhibited in equally affected boys, a deletion of the exons 61 and 62 of the Dystrophin gene. However, the indirect study by genotyping revealed the presence of the haplotype stage associated with the disease in three boys with one of which is phenotypically healthy and does not have the deletion responsible for the disease in his two brothers.

Discussion and conclusion: We have a case of germinal mosaic. In fact, the mother transmitted the same haplotype of the X chromosome to three of her sons, only 2 of whom are sick and carry the deletion of exons 61 and 62 of the Dystrophin gene. This is explained by the presence in their germ cells (oocytes), of 2 cell populations; one carries the suppression and the other does not, allowing a random transmission of the disease to his sons. This represents a rare case of genetically confirmed germinal mosaicism.

What does it mean to have a germinal mosaicism?

In Duchenne, there are two types of carriers:

Somatic carriers: females who have the genetic mutation throughout their body

Germline carriers: females who only have the genetic mutation in their ovaries / ova

If a woman has a child with Duchenne and she has had a carrier genetic test and it is negative, you might think that she is not at risk of having another child affected since her carrier was negative. But several studies have reported that women have a second affected child even after a negative carrier test. This is due to "germline mosaicism", which means that some of his eggs (his "germline") carry the Duchenne gene mutation while other eggs do not. However, she does not carry the Duchenne gene mutation in her blood cells, which is why her genetic test was negative.

Germinal mosaicism is not considered to be very common, although it is almost impossible to determine how many women are germinal mosaics. The majority of Duchenne carriers are somatic carriers, which means that they carry the Duchenne gene mutation in every cell in their body.

There are probably no health problems for carriers of germinal mosaics. The cells in the rest of their bodies have two working copies of the gene, so women with

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germline mosaicism may not have an increased risk of skeletal muscle symptoms or heart changes, although no studies have was carried out to confirm it with certainty.

How do you find germinal mosaicism?

Women with germline mosaicism will not be judged to be carriers via the genetic carrier test, as the carrier test is performed on blood or saliva cells. Women with germline mosaicism have mutations in their eggs, which will not appear during the blood or saliva test.

Since laboratory tests do not identify carriers of germline mosaics, health care providers are responsible for assuming that germline mosaicism accounts for most cases where women have not found any mutations in carrier test but have more than one affected child.

All women who have an affected child and no mutation found during the carrier test have a small chance of having germinal mosaicism. It is not known exactly how often this occurs, although some studies have suggested up to 15%.

How is Duchenne passed through germline mosaic carriers?

Women with germline mosaic are more likely to have children born with Duchenne, but the exact chance is impossible to know. Women with germinal mosaicism can transmit to their children

• An egg with a working copy of the dystrophin gene, causing no increased risk of Duchenne, or

• An egg with the copy of the dystrophin gene with a mutation, resulting in an affected son or carrier daughter (who may not have any symptoms or may be a manifesting carrier).

The overall chance of having an affected son or daughter depends on the amount of eggs with the working copy of the dystrophin gene versus the amount of eggs with a mutation in the dystrophin gene. Unfortunately, it is not possible to say how many egg cells have the dystrophin gene mutation.

For this reason, all women who have an affected child should be offered a prenatal test in future pregnancies, whether their screening test is positive or negative. Learn more about the prenatal test.

A mutation of an allele acquired by a somatic cell at the beginning of its development can be transmitted to its daughter cells, including those which will later specialize in gametes. With such a mutation in gamete cells, a pair of medically typical individuals may have a repeated succession of children who suffer from certain genetic disorders such as Duchenne muscular dystrophy and osteogenesis imperfecta due to germinal mosaicism. It is possible for parents not affected by germline mutations to produce offspring with autosomal dominant disorder (AD) due to a new random mutation within their gamete cells known as the sporadic mutation; however, if these parents produce more than one child with AD disorder, germline mosaicism is likely to be the cause rather than a sporadic mutation. In the first documented case of this type, two descendants of a French woman who had no phenotypic expression of AD disorder, hypertrophic cardiomyopathy, inherited the disease.

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