Inheritance of mitochondrial disease determined when mother is still an embryo

October 8 2012

(Medical Xpress)—The risk of a child to inherit mitochondrial diseases - i. e. malfunction in what is usually referred to as the power plants of the cell - is largely decided when the future mother herself is still an embryo. This according to a novel study by scientists at Karolinska Institutet and the Max Planck Institute in Germany, which is published in the journal *Nature Genetics*.

Mitochondria are small structures within almost every cell in the body, responsible mainly for energy production and fat metabolism. Their function is very important, and they contain their own genome, called mitochondrial DNA (mtDNA). The mitochondrial genome is inherited via the mother, where hundreds of thousands of mtDNA copies are packed in the female germ cell.

"Mutations in the mitochondrial genome can cause a variety of severe diseases, such as muscle weakness, neurodegenerative diseases, heart disease and diabetes", says Christoph Freyer, one of the study authors. "Many of these diseases only develop once a certain ratio of mutant and normal mtDNA molecules is reached within the cell. It is therefore important that we learn more about how mtDNA is inherited from mother to child."

A mother carrying a mutation in her mitochondrial genome can pass on a mixture of normal and mutated mtDNA to her children, but what determines the levels inherited and the driving force behind this mechanism is poorly understood. In the current study in Nature

Genetics, scientists generated a novel mouse model, carrying a pathogenic mutation in the mitochondrial tRNA methionine gene. This allowed the group to look at the ratio of mutated to non-mutated genes, or mutation level, in three different phases of the hereditary process. First they analysed germ cells from mouse embryos and established how the degree of mutation varies from germ cell to germ cell. After birth they looked at that degree in the immature egg cells of the mouse. And later they examined the degree of mutation in the mtDNA of the offspring.

The analysis shows, that in contrast to the protein-coding genes, shown by recent research to be subject to prenatal selection, tRNA genes are not selected out by the female germline. So whether and to what extent mutant genes can be transmitted to the next generation is decided when the future mother is still herself an embryo, during the development of her germ cells. Mutant genes often coexist with normal genes, a condition called heteroplasmy, in the affected egg cells. In other words, mutated and non-mutated genes occur in each egg cell in a particular ratio and thus the mutation may or may not be transmitted to the next generation. This also explains the differences arising within a family.

At the same time, the scientists note that the mitochondria in these mice try to compensate for the defect, giving further insight into the hereditary mechanisms underlying mitochondrial disease.

"Understanding the signals required for this compensation will potentially help in treating mitochondrial disease, which is very exciting", says Christoph Freyer.

More information: Freyer, C., et al. Variation in germline mtDNA heteroplasmy is determined prenatally but modified during subsequent transmission. *Nature Genetics* AOP 7 October 2012, doi: 10.1038/ng.2427

Provided by Karolinska Institutet