What you give, might not always be received

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A fundamental process in the transmission of genes from mother to child has been identified by researchers at the Montreal Neurological Institute, McGill University. The new study published in the December issue of the journal *Nature Genetics* identifies a mechanism that plays a key role in how mutations are transmitted from one generation to the next, providing unprecedented insight into metabolic diseases.

DNA that is only passed on from mothers to their children is stored in mitochondria, a compartment of cells which functions to supply energy to the body. Mutations in mitochondrial DNA (mtDNA) are important causes of over 40 known types of diseases and disorders which primarily affect brain and muscle function, some of which are severely debilitating, with symptoms including stroke, epilepsy, deafness and blindness. One very common mutation in Quebec causes maternally inherited blindness which has now been traced back to a Fille du Roi sent by the king of France in the 1600s to rectify the imbalance of gender in the newly colonized country.

MNI researchers have located a genetic bottleneck that determines the proportion of mutated mtDNA that mothers transmit to their offspring. This is important because there are many copies of mitochondria in cells and their distribution in tissues has a role in the severity and symptoms of the disease. Therefore knowing how mtDNA is transmitted is essential for the understanding and treatment of a range of maternally inherited diseases, and provides an opportunity for genetic counselling and treatment.

"The proportion of mutated DNA copies shifts rapidly and unpredictably from mother to child making it very hard to predict what proportion of mutated DNA will be passed on." says Dr. Eric Shoubridge, neuroscientist at the MNI and lead investigator in the study. "We now understand that this is partly due to the genetic bottleneck, in which just a small number of the original mtDNA copies from the mother are actually transmitted to the child. This bottleneck occurs during the development of eggs in affected females.

Only a small set of the female's mtDNA is selected to replicate resulting in the individual producing eggs with a wide range of proportions of mutated mtDNA. These eggs give rise to offspring with proportions of mutated mtDNA that differ from each other and are different from the proportion of mutated mtDNA in the mother. This explains why the occurrence and severity of a disease from mutated mtDNA can vary in offspring of an affected mother. The identification and location of the genetic bottleneck in our study strengthens our knowledge of the rules and processes of transmission and improves our capacity for genetic counselling."

An important application of this study is in the prevention of the disease at the prenatal stage because therapies for sick patients are usually ineffective, and the diseases are often fatal. The study locates the bottleneck as occurring during the process of egg maturation in early postnatal life of a female, supporting the knowledge that mature oocytes or egg cells contain the full set of copies of mtDNA. This evidence makes possible pre-implantation genetic diagnosis, in which an oocyte is screened for harmful mutations prior to fertilization, for in-vitro fertilization for example. This prevents the transmission of harmful mutations and can avoid the termination of a pregnancy in cases where an embryo is carrying a fatal neurological disorder.

Source: Montreal Neurological Institute and Hospital