Mitochondrial 'bottleneck' cracked

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Scientists have shown for the first time how a particular family of diseases are passed down from mother to child and how this can lead to the severity of the disease differing widely. The research, funded by the Wellcome Trust, offers hope of being able to predict a child's risk of developing a mitochondrial disease which can cause muscle weakness, diabetes, strokes, heart failure and epilepsy.

All human and animal cells contain many mitochondria, which are involved in energy production within the body. Mitochondria have their own genetic information, known as mitochondrial DNA, or mtDNA, which is inherited. However, whereas a child inherits one copy of DNA from each parent, a child may inherit many copies of mtDNA, which are only passed down from the mother.

Mutations in mtDNA can affect energy production within cells and therefore lead to disease. However, mitochondrial diseases differ both in location and severity depending on where and at what levels the mutations are distributed. Defective mitochondria cause most damage in muscles, nerves and the brain, the parts of the body which consume the most energy.

"Inheritance of mitochondrial diseases within families has proved incredibly difficult to predict," says Professor Patrick Chinnery, a Wellcome Trust Senior Clinical Research Fellow at Newcastle University. "A mother can pass on a small proportion of mutant mtDNA, or a very high proportion, and this can make the difference between a child being born without disease and another having a very severe form

of the disease."

A woman's eggs are formed at a very early stage in her development. As a precursor cell divides into a number of eggs, so the mitochondria from that cell are distributed randomly throughout these eggs. Hence different eggs can contain very different amounts of mutant mtDNA, which determine the amount of mutant genetic material that is passed on to the next generation. This difference is thought to explain the variation in the severity of the disease between siblings however the mechanism responsible for this variation was not understood for many years.

Now this research has proven that there is a "mitochondrial genetic bottleneck", where only a small number of mtDNA molecules in the mother are passed on to the next generation.

"In essence, it's a game of chance," explains Professor Chinnery. "If you have a mixture of red and white balls and pick handfuls at random, then some of those handfuls will contain very few red balls and other very few white ones. We have shown this is the reason for the different amounts of mutant mtDNA in different eggs."

Now, in research published online today in the journal *Nature Genetics*, Professor Chinnery and an international team of collaborators have shown in mice that this bottleneck does in fact exist and causes the dramatic reduction in the number of mtDNA molecules in the cells that eventually form the eggs. This leads to the wide variation in the severity of disease. Depending on which egg is fertilised, a high proportion of abnormal mitochondria may be passed on to the child. In this case, the child will be more severely affected than the mother.

Whilst once considered rare, mitochondrial diseases are now thought to affect as many as one person in 5,000. However, even when the precise proportion of abnormal mtDNA carried by the mother is known,

scientists have been unable to predict whether and how a child will be affected. Professor Chinnery hopes that this new research will open up opportunities for predicting disease risk.

"With conventional genetics, we're able to say, for example, that if you carry a certain gene, your child has a one in ten chance of developing a particular disease," he says. "Now that we understand how different levels of abnormal mtDNA are inherited, we may soon be able to predict a child's risk of disease and the level of severity."

Source: Wellcome Trust