

Testicular tumors may explain why some diseases are more common in children of older fathers

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A rare form of testicular tumour has provided scientists with new insights into how genetic changes (mutations) arise in our children. The research, funded by the Wellcome Trust and the Danish Cancer Society, could explain why certain diseases are more common in the children of older fathers.

Mutations can occur in different cells of the body and at different times during life. Some, such as those which occur in 'germ cells' (those which create sperm or eggs), cause changes which affect the offspring; those which occur in other cells can lead to tumours, but are not inherited.

In work published today in [Nature Genetics](#), researchers at the University of Oxford and Copenhagen University Hospital describe a surprising link between certain severe childhood genetic disorders and rare testicular tumours occurring in older men: the [germ cells](#) that make the mutant gene-carrying sperm seem to be the same cells that produce the tumour.

Although the original mutations occur only rarely in the sperm-producing cells, they encourage the mutant cells to divide and multiply. When the cell divides, it copies the mutation to each daughter cell, and the clump of mutant sperm-producing cells expands over time. Hence, the number of sperm carrying this mutation also increases as men get older, raising the risk to older fathers of having affected children.

Professor Andrew Wilkie from the University of Oxford, who led the study, explains: "We think most men develop these tiny clumps of mutant cells in their testicles as they age. They are rather like moles in the skin, usually harmless in themselves. But by being located in the testicle, they also make sperm - causing children to be born with a variety of serious conditions. We call them 'selfish' because the mutations benefit the germ cell but are harmful to offspring."

The work helps to explain the origins of several serious conditions that affect childhood growth and development. These include achondroplasia and Apert, Noonan and Costello syndromes, as well as some conditions causing stillbirth. The research links these conditions to a single pathway controlling cell multiplication, and will be valuable to doctors explaining to parents why the disorder has arisen, and informing them about the risks of it occurring again: in most cases, future children are unlikely to be affected.

The findings may also help explain one of the mysteries of genetics: why scientists have yet to account for much of the genetic component of common diseases. Common diseases tend to be caused by the interaction of many genes, but despite powerful genome-wide association scans to search for these genes, relatively few have been uncovered. Several of these diseases, including breast cancer, autism and schizophrenia, seem to be more frequent in the offspring of [older fathers](#), but the reasons are unknown. Professor Wilkie suggests that similar - but milder - mutations might contribute to these diseases.

"What we have seen so far may just be the tip of a large iceberg of mildly harmful mutations being introduced into our genome," he explains. "These mutations would be too weak and too rare to be picked up by our current technology, but their sheer number would have a cumulative effect, leading to disease."

Further research is needed to find other genes that are affected by this process. However, DNA sequencing technology has recently undergone a step change in capacity, enabling more sequence to be obtained in one day than was possible in a whole year just a decade ago. As the sequencing data emerge over the next decade, we should discover just how vulnerable we are to men's selfish mutation factories.

Source: Wellcome Trust ([news](#) : [web](#))

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