Spina bifida can be caused by uninherited genetic mutations

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Genetic mutations which occur naturally during the earliest stages of an embryo's development can cause the severe birth defect spina bifida, finds a new experimental study in mice led by UCL scientists.

The research, published in *Nature Communications,* explains for the first time how a 'mosaic mutation' - a mutation which is not inherited from either parent (either via sperm or egg cell) but occurs randomly during cell divisions in the developing embryo—causes spina bifida.

Specifically the scientists, based at UCL Great Ormond Street Institute of Child Health, found that when a mutation in the gene Vangl2 (which contains information needed to create spinal cord tissue) was present in 16% of developing spinal cord cells of mouse embryos, this was sufficient to produce spina bifida.

Researchers say the findings add to scientists' understanding of how and why mosaic mutations can affect and disrupt cell function, including those of neighbouring cells, helping cause birth defects.

For parents, the findings may help reduce the burden felt by those who believe their child inherited spina bifida from them via genes, and believe future children could also inherit the condition. This is often discussed during genetic counselling.

Spina bifida and current knowledge

Spina bifida is one of a group of birth defects called neural tube defects, affecting the brain or spinal cord. They happen in the first month of pregnancy, often before a woman even knows that she is pregnant. People born with this condition suffer nerve damage because part of their spinal cord remains exposed while in the womb. Advances in recent years now allow surgeons in a few centres around the world, including at Great Ormond Street Hospital and University College London Hospital, to perform surgery on foetuses in the womb to reduce the neurological consequences of their condition*.

Some neural tube defects can be prevented by taking folic acid supplements before and during early pregnancy, yet these conditions continue to affect around one in every thousand pregnancies globally. Researchers say they do not fully understand why mosaic mutations occur—though environmental factors may be involved—and cannot yet draw a link with taking (or not) folic acid during pregnancy. Notwithstanding this they say folic acid is known to help embryonic cells make DNA and encourage all expectant mothers to add folic acid to their diets from before conception.

Commenting on the potential causes, Principle Investigator, Dr. Gabriel Galea (UCL Great Ormond Street Institute of Child Health), said: "Some environmental factors are known to increase the risk of these conditions occurring and very few affected individuals or their parents receive a meaningful genetic diagnosis. The discovery that mosaic mutations, which cause spina bifida, may not be inherited from either parent, and are not necessarily present in blood or saliva commonly used for genetic testing, may explain why."

Genetic mutations

Genetic mutations happen in every cell throughout development. In order to grow from a fertilised egg cell into a foetus, each of our cells must replicate and divide in order to increase in number and grow. Cells must copy their DNA every time they divide, but mistakes can happen which change the DNA sequence in the daughter cells. These DNA code mistakes, called mutations, are then inherited by all cells derived from that cell. If these mutations happen in germ cells—the egg and sperm cells—they are inherited from parent to offspring. Many mutations do not happen in germ cells, but rather in cells which give rise to specific tissue types. These are known as mosaic mutations.

Experimental study approach

In humans with spina bifida a number of gene mutations have been identified, but in many cases it had not been known whether they could cause spina bifida.

In this experimental study, researchers caused a specific mutation, which inactivates a single gene called Vangl2 in mouse embryos. This gene is part of a cellular signalling pathway which tells cells which way they are facing within a tissue. Mutations in this pathway had been identified in people who have neural tube defects, and recent reports from the U.S. and China previously found mosaic Vangl2¬-pathway mutations in 15% of human foetuses with spina bifida. For the cellular signalling pathway to function normally, cells must interact with their neighbours in order to communicate directional information.

For the study, researchers induced this mutation of Vangl2 in a small proportion of cells which form the developing spinal cord of mice. This was done in a number of mouse embryos. Researchers then counted the proportion of spinal cells which harboured this mutation in those which had successfully covered their spinal cord with skin (ie had developed normally), versus those which had an exposed spinal cord (had spina bifida).

Researchers found that when the mutated Vangl2 gene was present in just 16% of developing spinal cord cells, spina bifida occurred.

They say, these results show that the cellular signalling process is surprisingly vulnerable to the uninheritable mosaic mutations. Each mutant cell stops each of its neighbouring cells from functioning to promote spinal cord development. And each cell has six neighbouring cells on average, massively amplifying the effects of each mutant cell.

Explaining the findings, Dr. Gabriel Galea said: "We found that the requirement for cells to talk to each other makes them exquisitely vulnerable to mutations in the signalling pathway that Vangl2 acts in. We now need to understand whether this vulnerability extends to other genes which could cause spina bifida. Detecting these mosaic mutations in living people will require technological advances and careful analysis of tissues resected during surgery."

More information: Cell non-autonomy amplifies disruption of neurulation by mosaic Vangl2 deletion in mice, *Nature Communications* (2021). DOI: 10.1038/s41467-021-21372-4

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