Faulty gene stops cell 'antennae' from transmitting

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An international group of researchers has identified the genetic cause of an inherited condition that causes severe fetal abnormalities.

The work, co-led by geneticists at the UCSD Institute for Genomic Medicine, together with colleagues from institutes and universities in Paris, Rome and England, should allow couples at risk of conceiving babies with the profoundly disabling Meckel-Gruber and Joubert syndromes to be identified beforehand through genetic screening.

The researchers' findings - which show how the disease gene stops cells' finger-like antennae or 'cilia' from detecting and relaying information - may ultimately lead to treatments for more common related disorders, such as spina bifida, retinal blindness and polycystic kidney disease. The paper will be published May 30 issue in Nature Genetics.

"By understanding the science behind this relatively rare condition, we can gain insight into other pediatric diseases that are far more frequent," said UCSD researcher Joseph Gleeson, MD, professor of neurosciences and pediatrics at UC San Diego School of Medicine and Howard Hughes Medical Institute Investigator, who directed the research. "Spina bifida, for example, is one of the most common birth defects, affecting one in every 1000 newborns."

Meckel-Gruber syndrome and Joubert syndrome are part of a wider family of disorders known as 'ciliopathies' - so-called because the cilia are not working as they should and do not respond properly to signals.

This lack of communication can prevent growing embryos from developing a correct neural tube, which leads to abnormalities of the brain. Affected embryos can also develop abnormalities in the eyes, extra fingers or toes, and multiple cysts in their kidneys.

"These abnormalities are often observed in prenatal ultrasounds, but expectant parents want to have a sense of what their child will be like, will he or she learn to walk, talk, and see," said lead author Professor Enza Maria Valente from the Mendel Institute in Rome. "This type of research can give us answers to these important questions."

To find the gene responsible for Meckel-Gruber and Joubert syndromes, the researchers examined DNA from families with a history of the disorder, from skin cells donated by patients, and from cells grown in the laboratory. They also studied zebrafish, which were used because the embryos are transparent during development.

The work identified a previously unknown gene - TMEM216 - as a cause of Meckel-Gruber and Joubert syndromes. They also showed that the faulty TMEM216 gene stopped cells from making a protein that is needed for cilia signalling.

Because Meckel-Gruber and Joubert syndromes are recessive genetic disorders, only couples who both have a copy of the disease gene are at risk of conceiving babies with these birth defects. The condition is more common in certain close-knit populations where the gene has been passed down from generation to generation. These include families of Ashkenazi Jewish origin.

"Accurate genetic testing for TMEM216 will be particularly important for families throughout the world that have a history of ciliopathies caused by mutations to this gene," said Professor Attie-Bittach from the University of Paris.

"Now that we have identified a gene that causes Meckel-Gruber syndrome and Joubert syndrome, the role of particular signalling pathways as the embryo is developing can also be more clearly understood," added Professor Colin Johnson from the University of Leeds in the UK.

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