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Greater awareness of genetic testing possibilities for impaired fetal movement can save babies' lives

Barcelona, Spain: New genetic mutations responsible for impaired fetal movement, which leads to a multitude or problems in later life as well as early spontaneous abortion, have been identified by a group of scientists, the annual conference of the European Society of Human Genetics will hear today (Saturday 31 May). Dr. Katrin Hoffmann, of the Charité University Hospital, Berlin, Germany, will say that her team's findings could lead to strategies to prevent multiple miscarriages, and for children born with fetal akinesia deformation sequence (FADS) due to impaired fetal movement in the womb.

FADS is a frequent genetic condition, affecting about 1 in 3000 pregnancies, and manifests itself in a number of ways – growth retardation, fetal hydrops (abnormal accumulation of fluid in the fetal organs), pulmonary hypoplasia (incomplete development of the lungs) and joint contractures. Studying a family in Oman with four affected children, and a history of multiple abortions, the scientists identified for the first time a genetic mutation on chromosome 2 which appeared to be implicated.

"The children in the family had contractures, a curved spine, and skin webbing" says Dr. Hoffmann. "When we carried out the genetic mapping we identified a mutation that encodes one of the sub-units of the acetylcholine receptor (AChR). Acetylcholine is a neurotransmitter; it transmits signals from nerve to muscle, enabling an individual to move. The genetic changes we found seriously disrupt the functioning of this receptor, meaning that the fetus cannot move properly in pregnancy." Such a defect has multiple effects, since normal fetal movement is essential for normal fetal development and growth.

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The scientists sequenced the DNA of 75 patients with severe FADS and found that not all of them had mutations in the gamma sub-unit of the AChR. Reasoning that other components of the AChR pathway might be affected, they tested additional genes and found disease-causing changes there. "It has previously been shown that milder mutations in the AChR pathway cause myasthenic syndrome, a form of muscle weakness that starts later in life", says Dr. Hoffmann. "But until now we did not know that the same genes could have such an impact on the prenatal development of a baby."

The scientists intend to continue testing for FADS diseases, and to look at other genes of the AChR pathway, which they believe may hold the clue to the disease in other families. "The AChR pathway is one of several possible causes of the disease group, and we want to distinguish the different causes and to study other pathways in collaboration with existing specialist teams", says Dr. Hoffmann.

Dr. Hoffmann and her team believe that their work will be important for genetic counselling of families with multiple spontaneous abortions or prenatal death of the baby. "In addition, some of the babies born with contractures and breathing problems could benefit from medication such acetylcholine esterase inhibitors, currently used for the treatment of myasthenia gravis and inherited myasthenic syndrome, she says.

Awareness of the condition could be life-saving. In one of the families studied, both affected children had contractures and breathing problems, but the reasons for this were unclear. The first child died. After identification of mutations in the AChR pathway, the second child was started on an acetylcholine esterase inhibitor. Her ability to move improved greatly, her muscle weakness also improved, and she later began to walk. "This underlines the obvious therapeutic relevance of early clinical and genetic consideration of AChR pathway mutations", says Dr. Hoffmann. "Doctors in pre and neonatal care should be aware of the importance of the AChR pathway in this group of diseases. Clinical examination and genetic testing can confirm the diagnosis and help to identify appropriate treatment."
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