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New disease gene will lead to better screening for pediatric heart disease

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Cardiomyopathy, or a deterioration of the ability of the heart muscle to contract, generally leads to progressive heart failure. It is frequently inherited, and, because approximately 40% of children born with it are likely to die within five years of diagnosis, being able to identify its genetic basis is particularly important. Now, an international team of researchers has identified a new disease gene which is implicated in the development of severe paediatric cardiomyopathies. The gene is probably also involved in a milder, adult-onset form of the condition.

Presenting the results of the study to the annual conference of the European Society of Human Genetics today (Tuesday) Johanna Herkert, MD, a clinical geneticist at the University Medical Centre of Groningen, The Netherlands, will describe how analysis of the exomes (the parts of the genome that produce proteins) of children who were seriously ill with early-onset cardiomyopathies led to the finding that a mutation in the gene alpha-kinase 3 (ALPK3) had been inherited from both their fathers and mothers. In cases where both parents carry the mutation, the risk of having a child with a severe cardiomyopathy is 25%. Since the child does not carry a normal copy of gene the condition will develop at an early age.

"However, several family members who carried only one mutated gene copy also developed cardiac disease, albeit at a later stage in life," says Dr Herkert. "The identification of these mutations enables us to provide genetic counselling, predictive testing of family members, and prenatal testing in future pregnancies. It also allows us to provide early treatment,

and a potential target for drug development in the future."

The researchers studied five children with cardiomyopathy from three unrelated families of different ethnic backgrounds. The families had previously been screened for mutations in other cardiomyopathy-related genes. Four patients were diagnosed during foetal life, or within hours of birth, and the fifth only developed symptoms at four years old. Three of the children died between 35 weeks of gestation and five days of birth; the other two were still alive at 11 years old, but showed signs of severe cardiomyopathy.

"We knew that mice without a functional ALPK3 gene displayed very similar cardiomyopathy related features to those observed in our paediatric patients," says Dr Herkert, "but we did not quite know how dramatic its effect would be in humans. Our findings show that we now should include this gene in routine diagnostic screening in order to be able to identify affected children and their family members at risk. This will also give us an insight into the prevalence of ALPK3-related cardiomyopathy in the general population."

Although the possibility of treating an affected foetus in the womb is still a long way off, the gene could provide a drug development target for a medicine to be administered immediately after birth before the disease has a chance to develop further. Affected family members with only one ALPK3 mutation could also be treated later in life.

"We are currently studying the effect of the ALPK3 mutations on the production of the protein in heart muscle, but also in skeletal muscle, as ALPK3 gene mutations may result in skeletal muscle problems too. Moreover, a large genome study has shown a possible link between ALPK3 and cardiac hypertrophy, or thickening of the heart muscle. We would like to explore this finding further as it may well mean that ALPK3 is implicated in other heart diseases in the general population,

and once again this could suggest new treatment possibilities.

"Better knowledge of the precise role of the gene in disease development, as well as the elucidation of the molecular pathways involved, should lead us towards improved clinical care from the point of view of screening and surveillance, and to targeted drug development ," Dr Herkert will conclude.

Provided by European Society of Human Genetics

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