Severe forms of congenital heart disease caused by variants of the NR2F2 gene

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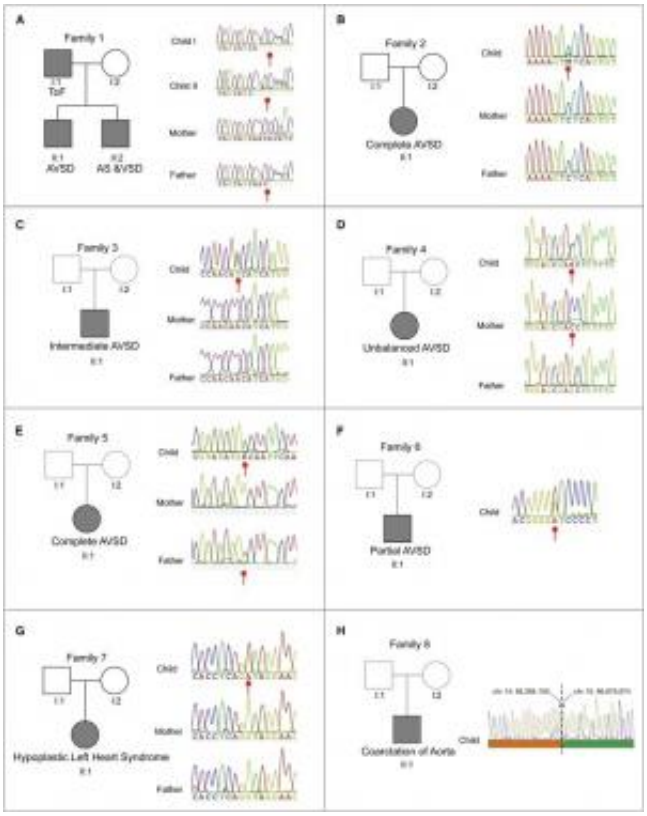

Family charts and sequencing results of NR2F2 variants in eight families affected by congenital heart disease. Solid lines in pedigree charts indicate both whole-exome sequencing data and capillary sequencing are available; dashed lines indicate samples with NR2F2 capillary sequencing data only.

(Medical Xpress)—Researchers have explored the role of a master gene that controls the functioning of other genes involved in heart development. Variations in this gene - NR2F2 - are responsible for the development of severe forms of congenital heart disease.

Approximately one per cent of all babies are born with congenital heart disease, where the normal workings of the heart are affected. Because the damage to the heart is structural, most babies will need surgery to correct the problem. Although genetic causes are known to underlie the disease, these causes are not very well understood.

Scientists have previously shown that mice with a less active NR2F2 gene had abnormal heart development. To see if the gene was involved in severe forms of human congenital heart disease, the team looked at DNA sequences of parents and affected children and found that variation on the NR2F2 caused the structural damage that underlies these conditions.

The team found that these genetic variants were typically only present in the child and not the parents, revealing that congenital heart disease producing variants occur in the womb.

"What we see is that these rare variants in the NR2F2 gene interfere with the normal heart development and cause severe forms of congenital heart disease during human development," says Saeed Al Turki, first author from the Wellcome Trust Sanger Institute.

NR2F2 is a master regulator for other genes involved in the development of a healthy functioning heart - once the activity of NR2F2 is affected it has a knock-on effect on these other genes affecting the healthy development of the heart.

The team found that different types of damage in the NR2F2 gene cause different types of heart defects. Genetic variants that completely deactivate the NR2F2 gene tended to cause damage to the left side of the heart. In contrast, genetic variants that alter activity of the gene but do not deactivate it more commonly caused a specific sub-type of holes in the hearts of patients.

"With this knowledge, we are getting closer to understanding the full genetic causes behind congenital heart disease, which will provide better

diagnoses and in turn provide better patient management," says Dr Matthew Hurles, senior author from the Wellcome Trust Sanger Institute.

More information: "Rare Variants in NR2F2 Cause Congenital Heart Defects in Humans." Al Turki, Saeed et al. *American Journal of Human Genetics* , Volume 94 , Issue 4 , 574 - 585. DOI: dx.doi.org/10.1016/j.ajhg.2014.03.007

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