O12-6

A novel compound heterozygous loss-of-function mutation in KIF20A is associated with a rare, lethal cardiomyopathy in two siblings.

Louw J.J.(1,2), Verdood C. (2), Nunes Bastos R. (3), Chen X. (4), Corveleyn A. (2), Jia Y.(2), Breckpot J.(2), Gewillig M.(1), Peeters H.(2), Santoro M.(4), Barr F.(3), Devriendt K.(2)
Department of Congenital and Pediatric Cardiology, University Hospitals Leuven, Belgium(1);Centre of Human Genetics, University Hospitals Leuven, Katholieke Universiteit Leuven, Belgium (2);Department of Biochemistry, University of Oxford, Oxford, England, United Kingdom (3); Laboratory of Endothelial Molecular Biology, Department of Oncology, Vesalius Research Center, VIB, Katholieke Universiteit Leuven, Leuven, Belgium(4)

Introduction
We present a small family with three siblings of which two are affected by an undescribed and lethal cardiomyopathy, i.e. restrictive cardiomyopathy of the right ventricle. The parents are non-consanguineous of Caucasian descent. An autosomal recessive hypothesis is most likely, as this is a very rare and unique phenotype, occurring in a male and female sibling.
Methods
Exome sequencing analysis was done in unaffected and affected siblings. Genomewide SNP typing and parametric linkage analysis was done in a recessive model. Genes were identified in the linkage regions with variants in the patients, inherited from both parents, and for which the unaffected sibling is heterozygous or reference. One candidate gene was identified using functional data and genotype phenotype correlations. Results were confirmed by Sanger sequencing.
Results
We identified two compound heterozygous variants in the KIF20A as the most likely cause. Further functional studies were performed showing increased multiploidy segregation patterns and demonstrating delayed cell growth with lowered transcription and protein steady-state levels. Translational blocking of KIF20A in a zebrafish model resulted in a cardiomyopathy phenotype.
Conclusions
Reaching a genetic diagnosis in rare disorders remains a challenge. We illustrate that even in a small family with only two affected individuals, the identification of the underlying mutation is feasible, using a combination of the sophisticated genetic tools, functional studies and a zebrafish model.