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Novel disease genes for childhood-onset cardiomyopathy: TMOD1 and NRAP

Vasilescu C. (1), Ojala T.H. (2), Hinterding H. (1), Brilhante V. (1), Ojanen S. (1), Lohi J. (3), Carroll C.J. (1), Suomalainen A. (1,4,5)
Research Programs Unit, Molecular Neurology, Biomedicum-Helsinki, University of Helsinki, Helsinki, Finland (1)
Department of Paediatric Cardiology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland (2)
Department of Pathology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland (3)
Department of Neurology, Helsinki University Hospital and Clinical Neurosciences, University of Helsinki, Helsinki, Finland (4)
Neuroscience Center, University of Helsinki, Helsinki, Finland (5)

Introduction
The discovery of molecular underpinnings of childhood cardiomyopathies raises expectations for new, more tailored forms of treatment. Only 35% of the children suspected of genetic cardiomyopathy receive a molecular diagnosis with current genetic approaches, suggesting that many new disease genes are yet to be discovered. From the single center in Finland performing cardiac transplants, we have collected the KidCMP cohort of 74 paediatric patients, cohort that offers unique opportunities to discover novel disease genes for severe childhood cardiomyopathies.
Methods
The patients' DNA underwent whole-exome sequencing. The subsequent screening of family members involved Sanger sequencing. The patient's heart and/or skeletal muscle biopsies enabled the evaluation of functional consequences of mutations at mRNA and/or protein level. Similar experiments were performed in myotubes differentiated from patient myoblasts, supporting the findings from tissue samples. Moreover, we used molecular modeling with Discovery Studio 4.5 to assess the possible functional implications of the TMOD1 variant.
Results
We uncovered the homozygous missense variant p.R189W in TMOD1 (Tropomodulin-1) as the genetic cause of a teenage-onset dilated cardiomyopathy with short episodes of ventricular tachycardia. Ventricular tachycardia responded to beta-blocker treatment, and cardiac function stabilized to the level of mild dysfunction. TMOD1 localizes to the pointed end of actin filaments, regulating their dynamics and stability. In the three dimensional structure of TMOD1, the patient's variant determines the exposure of a hydrophobic amino acid at the protein surface. This is the first report of TMOD1 dysfunction causing human disease.
Exome analysis of a second patient, presenting with dilated cardiomyopathy at 3.5 years of age, led to the identification of the homozygous nonsense variant p.Y448* in NRAP (Nebulin-related-anchoring protein). NRAP anchors the terminal actin filaments to the membrane. Our results showed that the patient's NRAP mRNA is present in cells, escaping at least partially the nonsense-mediated decay. Recently, another homozygous nonsense variant in NRAP has been described in adult-onset dilated cardiomyopathy with incomplete penetrance.
Conclusions
Whole-exome sequencing enabled the identification of two novel disease genes in childhood dilated cardiomyopathy: TMOD1 and NRAP. The molecular diagnoses facilitate the causative understanding of the diseases, crucial for future development of individualized treatment choices.