

Unexpected results of panel targeted next generation sequencing (NGS) in patients with cardiomyopathies

Meliota G. (1), Lombardi M. (1), Varvara D. (2), Resta N. (2), Tagliente M.R. (1), and Vairo U. (1)
Cardiologia Pediatrica, Ospedale Pediatrico Giovanni XXIII, Bari, Italy (1); Medical Genetics,
Department of Biomedical Sciences and Human Oncology, University of Bari "A. Moro", Bari, Italy (2)

Introduction: Next Generation Sequencing (NGS) panel targeted strategy is increasingly being used to identify mutations associated with cardiomyopathies.

Methods: We carried out NGS-analysis on PGM-Ion Torrent platform in 24 probands with cardiomyopathies, using a panel targeted approach which included 21 disease-causing genes.

Results: We identified at least one pathogenic/likely pathogenic variant in 6 cases, at least one variant of uncertain significance (VUS) in 8 cases, and a co-detection of pathogenic/likely pathogenic variants/VUS in 5 cases. To get insight into the clinical role of the genetic variants detected in the probands, co-segregation analysis was performed in family members.

Case series

Case 1. A 9-year-old boy was diagnosed with Hypertrophic Cardiomyopathy (HCM) when he was 2 year-old. His father was diagnosed with HCM at the age of 20 and suddenly died at the age of 32 years. Molecular testing of the child detected a likely pathogenic variant in TRPM4 (c.1744G>A; p.Gly582Ser) and a VUS in PDLIM3 (c.937C>T; p.Arg313Trp). Despite a negative familiar history and an unremarkable cardiac work-up, the genetic analysis of the mother's proband showed that she carried the variant in TRPM4.

Case 2. A 9-year-old girl was referred to us for acute myocarditis, which later evolved in dilative cardiomyopathy. A previous echocardiogram work-up performed because of a familial history of HCM had turned out unremarkably. Genetic analysis revealed a pathogenetic variant, VCL C.829 C>A; P. Leu277Met. Although her father carried the same genetic variant at genetic screening, he did not suffer of any cardiac disorder. Conversely, her mother was affected by hypertrophic cardiomyopathy, but did not carry her daughter's genetic variant. It has been reported that genetic defects in structural proteins may predispose the myocardium to the induction of inflammation by a pathogenic agent, i.e. the common viral infections of children.

Conclusion: Despite its high diagnostic value, interpretation of NGS-based analysis in patients with cardiomyopathy is often challenging because of unexpected results, such as multiple variants in the same individual or VUS. For a better evaluation of the clinical significance of genetic variants obtained by NGS-based strategy in the clinical practice, pooled data from collaborative studies are required.