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The variable correlation between genotypes and phenotypes in cardiomyopathies and arrhythmogenic syndromes

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Introduction: Cardiomyopathies and arrhythmogenic syndromes have a considerable variability in genotypes and phenotypes. Modifier genes, epigenetic and environmental factors have been suggested as main determinants for different phenotypes associated with the same genotype.
Methods: We carried out Next Generation Sequencing (NGS) analysis on PGM-Ion Torrent platform in 9 probands with cardiomyopathies or arrhythmic syndromes, using a panel targeted approach which included 21 disease-causing genes. A Sanger sequencing was taken to confirm the results and a co-segregation analysis was performed in family members.
Case series examples: Case 1. In a 9-years-old female with QT-long syndrome, molecular testing detected a de novo likely pathogenic variant in KCNH2 (c.205C>G;p.Leu69Val) and 3 variants of uncertain significance (VUS) in DSP (c.5056C>T;p.Gln1686Ter), MYH6 (c.5465G>A;p.Arg1822Gln) and CAV3 (c.387C>A;p.Cys129Ter), all found in her mother affected by Dilated Cardiomyopathy (DCM). Case 2. A 6-years-old male with hypertrophic obstructive cardiomyopathy (HOCM), presented a VUS in MYBPC3. This was also found in his mother, who did not suffer of any cardiac disorder. Case 3. In a 1-year-old male with diagnosis of DCM, a likely pathogenic variant of MYH7 and a VUS of RYR2 were detected. The first variant was found in his father and the second in his mother. Although carriers both parents were phenotypically healthy.
Discussion: Our case series confirm that: 1. A single gene mutation often is not sufficient to bring a cardiac disease. 2. The same gene mutation can produce different types of diseases. 3. Some genetic heart disorders come from the combination of multiple gene mutations. The relationship between genotype and phenotype is made even more complex by incomplete penetrance and variable expressivity of some genes.
Conclusion: NGS-based analysis has an high diagnostic potential, since it allows to identify gene mutations that are likely related to genetic heart disease. Pooled data from collaborative studies and larger case series are needed to define more accurately the complex relation between genotype and phenotype in cardiomyopathies or arrhythmogenic syndromes.