

Novel LVNC genetic aetiology discovered by an original whole-exome sequencing data combinatory filtering method

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Background: Left ventricular non-compaction (LVNC) is a cardiomyopathy characterized by deep intra-trabecular recesses and prominent left ventricular trabeculae. This cardiomyopathy has remarkable phenotypic and genetic heterogeneity. Its molecular diagnosis via next generation sequencing is challenging due to the large amount of potential aetiological variants, especially in complex cases originating from mutations in various genes.

Objectives: This study sought to determine a novel diagnostic approach for identifying the molecular cause of LVNC in patients showing intra-familial phenotype variability and evoking a digenic aetiology.

Methods: We performed whole-exome sequencing (WES) in a three-generation family of patients affected by different degrees of LVNC. An enriched subset of 94 LVNC candidate genes was analysed in silico using an original WES data combinatory filtering method.

Results: We identified two novel heterozygous mutations, one in ACTC1 (c.740G>A; p.Gly247Asp) and another in ITGA7 (c.3280C>T; p.Gln1094Ter) which perfectly segregated with the phenotype. These variants underlined the disease's digenic origin, explaining intra-familial phenotype variability. We unambiguously determined that ITGA7 mutations lead to LVNC.

Conclusions: The results argues in favour of the final common hypothesis proposed as being involved in complex heterogeneous cardiovascular diseases. The genomic/computational approach presented here is an advantageous and efficient method for dissecting the molecular basis of LVNC's origin and we strongly recommend it for diagnostic/prognostic purposes. We have described the direct association of an ITGA7 mutation and LVNC pathophysiology for the first time, thereby enriching the repertoire of genes to be systematically analysed in LVNC patients.