Analysis of mutations associated with idiopathic restrictive cardiomyopathy

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Idiopathic restrictive cardiomyopathy (RCM, MIM# 115210) is the least common type of cardiomyopathies, often of genetic origin, characterized by impaired ventricular filling and reduced end-diastolic volume in the presence of normal systolic function and normal or near normal myocardial thickness [1,2]. It is associated with high risk of pulmonary hypertension and supraventricular arrhythmias, often requiring heart transplantation. Due to the rareness of the disorder, the genetic spectrum of RCM has remained largely unknown, with only a handful of studies focused on the genetic etiology of RCM [3–6].

Recently we described a spectrum of variants – classified as pathogenic, likely pathogenic and variants of unknown significance - in 24 patients suffering from idiopathic RCM [7]. Pathogenic variants, detected in half of the RCM cases, were found in sarcomeric genes that have a predominant role in the development of RCM.

Here we carried out a detailed structure-based analysis of the impact of variants on protein structure, function and stability in an effort to elucidate their role in cardiomyocyte dysfunction.

We analyzed 66 missense variants in cardiomyopathy and arrhythmia-associated genes, identified in patients with RCM. Our data indicate that 35% of observed variants are found in intrinsically disordered regions which lack stable secondary and ordered tertiary structure. Moreover, half of pathogenic and likely-pathogenic variants fall in disordered regions; some of them lead to disorder-to-order transition and influence posttranslational modifications.

A number of mutations occurred in the structural domains of titin and myomesin proteins. These filaments are multi-domain structures, composed of repetitive immunoglobulin-like (Ig) and fibronectin-type III (FnIII) domains, that confer elastic properties to proteins. A number of destabilizing amino acids substitutions, found directly in the interface regions between Ig and FnIII domains, could disturb protein elasticity in sarcomeric filaments. In summary, the variants described here are predicted to disrupt interdomain interfaces, interfere with protein interactions, and affect protein stability, potentially destabilizing the multi-domain architecture of myofibrils and leading to myocardial stiffness in patients with idiopathic restrictive cardiomyopathy.

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