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Structural consequences of FLNC mutations, associated with cardiomyopathies

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Introduction: FLNC gene (MIM #102565) encodes an actin-cross-linking protein filamin C which is mainly expressed in heart and skeletal muscle. Mutations in FLNC give rise to skeletal muscle diseases and all types of cardiomyopathies. In our study we aimed to analyze the published disease-associated variants in FLNC and performed structural analysis depending on the phenotype of cardiomyopathy and mechanism of the mutation.

Methods: We created dataset with disease-related mutations in FLNC using data from the literature and publicly available databases Clinvar and SwissVar. Domain organization of a filamin-C protein sequence was performed using Pfam database. The atomic structure of the Ig-like domain of human filamin C (PDB ID: 2D7M) was used as a template to introduce the mutations. In silico visualization were conducted using the PyMol software.

Results: We found 44 variants in human FLNC gene associated with restrictive cardiomyopathy, myofibrillar myopathy, left-dominant arrhythmogenic cardiomyopathy, hypertrophic cardiomyopathy, distal myopathy and dilated cardiomyopathy according to ClinVar database and published manuscripts. Structural analysis revealed that mutations leading to restrictive (RCM) and hypertrophic (HCM) cardiomyopathy are predominantly localized within immunoglobulin-like domains of filamin C in loops near the protein surface. These loops may participate in formation of interdomain interactions with neighbour Ig-like domains in the super-repeat segment of filamin C and with ligands. Most of HCM and RCM-associated mutations are point mutations while most of mutations leading to dilated or arrhythmogenic cardiomyopathy are "lost of function" truncation or splicing mutations.

Conclusion: Mutations within loops in Ig-like domains of filamin C protein may disturb mechanical strength and flexibility leading to increased cellular stiffness and influencing the mechanical properties of cells. The structural consequences of the mutation are linked to the type of myocardial remodeling, thus, explaining the broad phenotype variability of filaminopathies.