PROBING THE STRUCTURAL IMPACTS OF ARG388 REPLACEMENTS IN PKP2 PROTEIN COMPLEX: SPESIFIC CASE IN ARVC

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ABSTRACT

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is form of heart disease associated with removal of right ventricle by scar tissue that results in heart rhythm problems [1]. It is caused by a set of mutations existing in desmosomal proteins that are listed as desmoplakin (DP), plakophilin-2 (PKP2), desmoglein-2 (DSDG2), and desmocollin-2 (DSC2), and they are all involved in cell-to-cell adhesion [2]. Within the scope of this project, we focus on the 388th position of PKP2 protein since there exist 4 missense mutations, e.g., Arg388Trp, Arg388Pro, Arg388Gln and Arg388 Gly. Among these four variants, only Arg388Trp and Arg388Pro are reported as pathogenic to ARVC, and others remain as 'VUS'. To understand more about disease mechanism caused by missense variants at 388th position of PKP2 protein as being either VUS or pathogenic, we performed 100 ns classical all-atom molecular dynamics (MD) simulations. Based on the results of MD simulations, we aimed to obtain more detailed information about Arg388Gln/Gly variants in terms of being pathogenic or not by comparing the structural features of native and mutant PKP2 proteins. The differences in intramolecular interactions with RMSD and Rg patterns of native and mutant protein structures demonstrated that the structural features of Arg388Trp and Arg388Pro were like those of Arg388Gly and Arg388Gln. The correlation coefficient analyses based on RMSD patterns of native and mutant protein structures validated the presence of structural alterations between Arg388Trp/Pro/Gly/Gln. By relying on the comparison of structural features of protein molecules, we concluded that Arg388Gly and Arg388Gln seem to be 'pathogenic' due to structural similarities with Arg388Trp and Arg388Pro.

References

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