A CRELD1 GENE VARIANT LEADS TO ATRIOVENTRICAL SEPTAL DEFECTS IN DOWN SYNDROME

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Congenital heart defects (CHD) are seen in around 40% of the Down syndrome (DS) patients. Atrioventricular Septal Defect (AVSD) or endocardial cushion defect is commonest form of CHD in these children. CRELD1 gene is implicated in causation of sporadic AVSD. In the present study, we evaluated the association and significance of CRELD1 variants with AVSD in Down syndrome (DS) patients. Sequencing was done in blood samples from 3 groups: group I (DS with AVSD), group II (DS without AVSD) and group III (non-syndromic AVSD cases). Twenty two variants in CRELD1 gene were identified, comprising of sixteen novel and six previously reported variants. However, on the basis of sequence, as well as structure analysis, the variant c.973G > A(p.Glu325Lys) variant was identified only in DS having AVSD group which was predicted to have significant effects on calcium binding of putative CRELD1 protein. Since CRELD1 gene acts as a regulator of calcineurin/NFATc1 signaling which is crucial for the regulation of cardiac development by dephosphorylation of the transcription factor, NFAT (nuclear factor of activated T cells), in cytoplasm, the variation in cb-EGF-like calcium binding domain in CRELD1 protein is likely to have pathogenic consequences. Thus, we conclude that the CRELD1 gene is likely to have a major role in causation of AVSD phenotype in selected DS patients.

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