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Transcriptomic analysis of CRISPR-Cas9 knock-in mice with the patient-specific *FLNC* c.7416_7418delGAA mutation linked to restrictive cardiomyopathy

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Restrictive cardiomyopathy (RCM) is a severe rare myocardial disease with a poor clinical prognosis. A novel heterozygous in-frame deletion in *FLNC* (c.7416_7418delGAA) was recently identified in a pediatric patient diagnosed with RCM. This mutation is hypothesized to exert a dominant-negative effect, potentially impairing the normal function of the Filamin C protein. To study disease mechanisms and evaluate gene therapy approaches, we previously generated a knock-in mouse model carrying this *FLNC* mutation using CRISPR-Cas9 genome editing. In the present study, we performed RNAseq analysis of cardiac tissue from mutant and wild-type mice to investigate gene expression changes associated with the pathogenic *FLNC* variant. Differential gene expression analysis identified 178 genes, with KEGG enrichment analysis indicating transcriptional changes associated with ECM-receptor interaction (mmu04512), muscle cell cytoskeleton (mmu04820), focal adhesion (mmu04510), and ABC transporters (mmu02010). We then evaluated alternative splicing and detected a total of 63 differential splicing events, including 43 exon skipping (SE), 5 alternative 5′ splice site (A5SS), 9 alternative 3′ splice site (A3SS), 2 mutually exclusive exon (MXE), and 4 retained intron (RI) events. Notably, genes affected by alternative splicing, including *DEPDC5* (A3SS, SE), *Myh7* (A5SS), and *MYRF* (SE), were associated with biventricular hypertrophy (HP:0200128) according to the Human Phenotype Ontology database. Thus, RNA-seq analysis of cardiac tissue from *FLNC* c.7416_7418delGAA knock-in mice revealed significant alterations in gene expression and splicing patterns. Further studies are required to clarify their association with the cardiomyopathy phenotype and to determine the biological significance of these changes.