Distal myopathy induced the onset of arrhythmogenic right ventricular cardiomyopathy in a pedigree carrying novel DSG2 null variant

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Background:
Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare cardiac disease predominantly caused by variants in desmosome genes. Variants in human Desmoglein-2 (DSG2) gene can cause ARVC with incomplete penetrance. However, it remains unknown whether ARVC would penetrate by distal myopathy.

Methods:
We performed targeted next-generation sequencing using a cardiomyopathy/ion channelopathy panel in a Chinese ARVC pedigree. Plasmids of DSG2 were constructed, and pathogenicity of the DSG2 variant was investigated by real-time PCR, western blots, Immunofluorescence, and electron microscope.

Results:
We identified a novel nonsense variant in DSG2 (c.710T>A, p.Leu237Ter) and a reported pathogenic missense variant of distal myopathy in MYH7 (c. 1322C>T, p.Thr441Met) in the proband of an ARVC pedigree. The functional analyses suggested that the nonsense variant could affect the expression and cell location of DSG2, and the number and shape of desmosomes were affected as well, indicating that the variant was implicated in the pathogenesis of ARVC. We found only patients carrying the distal myopathy pathogenic variant would manifested early-onset severe ARVC phenotype, which suggested that MYH7-p.Thr441Met variant could induced the onset of ARVC in the DSG2-p.Leu237Ter variant carriers.

Conclusions:
Our study identified a novel null variant in DSG2 gene (c.710T>A, p.Leu237Ter) in an ARVC pedigree with incomplete penetrance. Only patients who carried a distal myopathy associated variant in MYH7 (c. 1322C>T, p.Thr441Met) would induce the onset of ARVC with early-onset and severe symptoms.