Pathogenic mechanism of DSG2-F531C mutation caused arrhythmogenic right ventricular cardiomyopathy

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Objective

Mutations in the Desmoglein-2 (DSG2) are associated with arrhythmogenic right ventricular cardiomyopathy (ARVC). We previously identified a highly conserved F531C (c.1592T>G) variant of the cardiac desmosome gene DSG2 in the proband with a positive family history. The aim of this study is to investigate the mechanism(s) of DSG2-F531C variant in the pathogenesis of ARVC.

Methods

A large Han Chinese family with five generations was enrolled in this study, physical and clinical examinations were performed. Seven members were diagnosed with ARVC. Subsequently five desmosomal genes (PKP2, DSG2, DSP, DSC2 and JUP), TMEM43 and PLN were sequenced directly from genomic DNA. Seven patients diagnosed with ARVC were homozygous for DSG2-F531C, while five members of the family with normal phenotype were heterozygous for DSG2-F531C. To further explore the role of DSG2-F531C in ARVC pathogenesis, we generated a knock-in (KI) mouse model, which was carrying the mouse equivalent form (DSG2-F536C) of this variant.

Results

The homozygous KI mice (DSG2-F536C+/+) revealed a robust cardiomyopathy phenotype with left ventricular systolic dysfunction, histopathology showed accumulation of collagen, spotty calcification and fat droplets with extensive fibrosis in ventricular tissue in all DSG2-F536C+/+ mice. Further detections showed widening of the intercalated disc and regional loss of DSG2 in the hearts of these mice. The marked reduction in immunoreactive signal for sodium voltage-gated channel alpha subunit 5 (NaV1.5) was observed with no apparent changes in plakoglobin and connexin-43. In addition, dramatically elevated expression of transforming growth factor β1 (TGF-β1) was also found in the DSG2 mutant mice. Intriguingly, the heterozygous KI mice (DSG2-F536C+/−) expressed a similar level of TGF-β1 versus homozygous ones (DSG2-F536C+/+), but exhibited slight changes in morphology.

Conclusions

The DSG2-F536C KI mice produce a similar pathological phenotype of human ARVC, which supports DSG2-F531C as a causative mutation for ARVC. Additionally, the DSG2-F536C+/+ mutation induced
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Conclusions

The DSG2-F536C KI mice produce a similar pathological phenotype of human ARVC, which supports DSG2-F531C as a causative mutation for ARVC. Additionally, the DSG2-F536C+/+ mutation induced cardiac fibrosis through the activation of TGF-ß1 signaling will open new opportunities for further mechanistic and therapeutic studies in DSG2-related ARVC.