Novel missense variant in TTN cosegregating with familial atrioventricular block.


Abstract

BACKGROUND: Cardiovascular diseases are the most common cause of death globally. In which atrioventricular block (AVB) is a common disorder with genetic causes, but the responsible genes have not been fully identified yet. To determine the underlying causative genes involved in cardiac AVB, here we report a three-generation Chinese family with severe autosomal dominant cardiac AVB that has been ruled out as being caused by known genes mutations.

METHODS: Whole-exome sequencing was performed in five affected family members across three generations, and co-segregation analysis was validated on other members of this family.

RESULTS: Whole-exome sequencing and subsequent co-segregation validation identified a novel germline heterozygous point missense mutation, c.49287C>A (p.N16429K), in the titin (TTN, NM_001267550.2) gene in all 5 affected family members but not in the unaffected family members, neither in the large population according to the Genome Aggregation Database (https://gnomad.broadinstitute.org/). The point mutation is predicted to be functionally deleterious by in-silico software tools. Our finding was further supported by the conservative analysis across species.

CONCLUSION: Based on this study, TTN was identified as a potential novel candidate gene for autosomal dominant AVB; this study expands the mutational spectrum of TTN gene and is the first to implicate TTN mutations as AVB disease causing in a Chinese pedigree.

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KEYWORDS: Atrioventricular block; Autosomal dominant inheritance; TTN; Whole-exome sequencing

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