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LETTER TO THE EDITOR

Identification by Next Generation Sequencing of a Novel PKP2 Mutation in Arrhythmogenic Right Ventricular Dysplasia

To the Editor,

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C, OMIM #107970) is a familial form of cardiomyopathy with frequent autosomal familial occurrence typically caused by mutations in genes that encode an element of the cardiac desmosome (1,2). There is a genetic heterogeneity of some mutations in several genes that cause this syndrome. All related genes (PKP2, DSG2, DSC2, DSP, JUP, TMEM43, TGFB3, TTN, and RYR2) are associated with cardiac desmosome and finally produce cardiomyopathy (2).

In association with Brugada Syndrome, ARVD is one of the main causes of sudden cardiac deaths. For this reason, early detection is very important especially among high-risk individuals such as families with this affection and athletes. There are clinical evidences for this syndrome (structural and functional alterations in right ventricle, arrhythmia, among others); however, there is a high relevance of genetic (autosomal dominant) inheritance, which makes genetic analysis as relevant biomarkers.

This study aimed to confirm the pathogenicity of c.2293 G>T, a previously undescribed variant detected in a 46-year-old man suspected to be affected by ARVD. Although not having previous familial antecedents, his clinical symptoms suggest ARVD but must be confirmed by genetic analysis. DNA from blood was extracted using an organic protocol (phenol:chloroform:isoamyl alcohol) after written informed consent. Next Generation Sequencing (NGS) was done using HaloPlex Target Enrichment System (Illumina) following the sequencing protocols provided. Ultra-sequencing was performed in MiSeq platform (Illumina) and analysis of the results by DNAnexus software. Reference sequences for the analysis were PKP2 (plakophilin-2, NM_004572.3), DSG2 (desmoglein-2, NM_001943.3), DSC2 (desmocollin-2, NM_024422.3), DSP (desmoplakin, NM_004415.2), TMEM43 (transmembrane protein 43, NM_024334.2), JUP (plakoglobin, NM_002230.2), TGFBR3 (nondesmosomal transforming growth factor receptor β3, NM_003243.4), DES (desmin, NM_001927.3), LMNA (lamin A/C, NM_005572.3) and PLN (phospholamban, NM_002667.3).

Although there were no reports in point mutations in exonic or intronic regions of TMEM43, DSP, DSG2, DSC2, JUP, TGFB3, DES, LMNA and PLN genes related to ARVD, a new point variant was discovered in PKP2 gene. This point mutation (c.2293 G>T) in heterozygosis is located in exon 11 producing an amino acid change p.Glu765Stop (p.E765X). It is a nonsense variant producing a stop codon and a reduction of 13.16% of original amino acidics, with a pathologic clinical effect. This variant has not been previously described in the main databases Genecards (http://www.genecards.org/), Uniprot (http://www.uniprot.org/), HGMD (http://www.hgmd.org/), LOVD (http://www.lovd.nl/3.0/home) and ARVCDATABASE (http://www.arvcdatabase.info/) or published journals. The variant was confirmed by Sager sequencing in an ABI 3130.sequencer (Figure 1).

Our findings and others (3) highlight the importance of having an updated mutation database. Moreover, in genes related to ARVD, this could help clinicians by offering a more accurate risk stratification of these patients. It has been proven that molecular genetic analysis has a high importance in risk stratification in ARVD because cascade screening allows early detection of presymptomatic

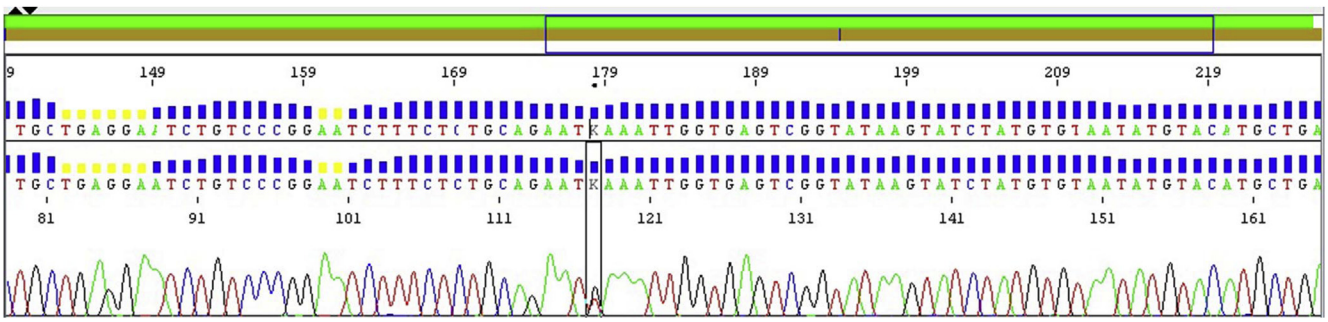

Figure 1. Sanger sequence of PKP2 gene. (A color figure can be found in the online version of this article.)

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disease, identification of individuals at risk, and genetic counseling for this sudden death predisposing disease (4).

Genetic diagnosis and genetic counseling are very important, even more so in diseases like ARVD for the inheritance patterns that imply a high risk in the remaining family members.

Conflict of Interest

The authors declare no competing of financial interests in relation to the work described.

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