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Genetic testing in arrhythmogenic cardiomyopathy: growing complexity embedded in doubts

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Introduction. Arrhythmogenic cardiomyopathy (AC) is a heart muscle disease characterized by life-threatening ventricular arrhythmias and progressive dystrophy of the ventricular myocardium with fibro-fatty replacement. AC is defined as a rare disease due to an estimated prevalence of 1:5000. AC displays mostly an autosomal-dominant transmission and incomplete penetrance. It is considered a disease of desmosomes, however about 1% of AC patients harbor a mutation in non-desmosomal proteins such as CTNNA3, TMEM43, RYR2, TTN, LMNA, DES, PLN, SCN5A. Non-desmomal proteins mutation frequency in AC patients might be underestimated due to gene size-related sequencing and interpretation difficulties.

The aim of this study was to assess the frequency of non desmomal rare variants in AC patients.

Methods. 189 consecutive AC index cases, fulfilling revised 2010 Task Force Criteria, underwent DNA sequencing on the MiSeq platform (Illumina) using the Trusight Cardio panel (174genes). Variant selection was based on current ACMG guidelines: a minor allele frequency (MAF) <0.0001 threshold in the general population, amino acid conservation across species and pathogenicity based on at least two in silico prediction algorithms. Cascade genetic screening in probands’ families was performed to study the segregation of rare variants and their impact on the clinical phenotype.

Results. Almost 45% (85/189) of AC index cases carried a rare nucleotide variant in AC-related genes: 40% (76/189) were desmosomal variant carriers and 5% (9/189) displayed rare variants in non-desmosomal AC-related genes (CTNNA3, DES, LMNA, SCN5A, TMEM43). Specifically, 18 were single-variant DSP carriers, 9 DSG2, 23 PKP2, 7 DSC2, 3 JUP, and 16 patients were compound or digenic heterozygous carriers in desmosomal genes.

All 85 genotype positive but also 104 genotype negative AC cases carried rare variants in AC-unrelated genes, mostly encoding sarcomeric proteins (OBSCN, MYH7, MYBPC3) or ion channels subunits (CACNA1B, CACNA1C, SCN10A, KCNQ1, KCND3). Interestingly 26% (51/189) of patients carried at least a rare variant in the TNN; its significance was assessed by cascade genetic screening.

Conclusions. Analysis of a large AC cohort reveals a combination of multiple rare variants in AC related and unrelated genes. Preliminary data demonstrate a high frequency of rare TTN variants in AC patients, which role in the etiopathogenesis of AC as modulatory factor will be clarified by genotype-phenotype correlation in large families. Our data highlights the importance of AC cascade genetic screening to determine the clinical significance of rare genetic variants.