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Editorial

The complex molecular genetics of arrhythmogenic cardiomyopathy

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Arrhythmogenic cardiomyopathy (AC) is a heart muscle disease clinically characterized by life-threatening ventricular arrhythmias and pathologically by an acquired and progressive dystrophy of the ventricular myocardium with fibro-fatty replacement [1,2]. Due to an estimated prevalence of 1:2000–1:5000, AC is listed among rare diseases [3]. Gross pathognomonic features of AC consist of right ventricle (RV) aneurysms, single or multiple, located in the so-called "triangle of dysplasia".

AC is currently considered a genetically determined, autosomal dominant disease with reduced penetrance and variable clinical expression. It is considered as a disease of the desmosomes since causative variants are found in about 50% of AC patients in genes coding for desmosomal components i.e. plakoglobin (*JUP*), desmoplakin (*DSP*), plakophilin-2 (*PKP2*), desmoglein-2 (*DSG2*), and democollin-2 (*DSC2*) [3]. Variants in non-desmosomal genes, such as transforming growth factor-β3 (*TGFβ3*), transmembrane protein 43 (*TMEM43*), lamin A/C (*LMNA*), desmin (*DES*), catenin alpha 3 (*CTNNA3*), titin (*TTN*), phospholamban (*PLN*), filamin C (*FLNC*) and N-cadherin (*CDH2*), have been reported in a minority of AC patients (1–3%). AC is characterized by presence of a large spectrum of "private" causative variants making challenging genetic testing and counseling. The presence of a pathogenic variant is considered diagnostic based on the current Task force Criteria [4], thus caution should be paid in the selection criteria by which mutations are considered causal. Missense mutations in *PKP2*, the most common causal gene for AC accounting for up to 45% of the cases, are frequently found also in the general population. Compound/digenic heterozygosity of desmosomal gene mutations is identified in about 10–25% of AC patients, predicting a more severe arrhythmic outcome [5]. Heterozygous Copy Number Variations (CNVs) have been recognized in about 2–3% of AC patients, characterized by low disease penetrance (~30%) in family carriers [6]. Finally, founder mutations have been also reported in both desmosomal and non-desmosomal encoding genes [3,7–9] mostly in western countries.

To address the frequency of *DSG2* variants in East Asia and the impact of homozygous *DSG2* variants, Chen and colleagues investigated 14 AC causal/putatively causal genes in the largest Chinese cohort (118 AC index patients), by massive parallel sequencing [10]. In this study, more than half of AC cases (56.8%) were mutation-positive, harbouring mostly desmosomal variants: 22 (18.6%) patients were mutation carriers in *PKP2*, 5 (4%) in *DSP* and 2 (2%) in *DSC2*. Focusing on *DSG2* variants, the Authors observed a higher prevalence of mutations in this gene in East Asia (15.3%) compared to most western AC populations. Specifically, 11 different *DSG2* rare variants were reported, of which a frameshift and 10 missense variants, in 18 AC probands. Of note, the majority of *DSG2* AC probands (83.3%, 15 out of 18) were compound heterozygotes (n = 6) or homozygotes (n = 9) carriers.

Eight of the 9 *DSG2* homozygotes AC probands shared the same variant c.1592 T>G (p.Phe531Cys). Although, all *DSG2* homozygotes exhibited full disease penetrance, clinical presentation varied from heart failure to late-onset (>50 yrs) symptoms, indicating that other factors/genes are necessary to modulate or exacerbate disease onset. Cascade genetic screening and parallel clinical evaluation was carried out in 31 relatives, recruited from 7 families with a homozygote *DSG2* proband. Twenty-three of 31 family members were mutation-positive, 22 heterozygotes and 1 homozygote for c.1592 T>G *DSG2* variant. This last exhibited fully penetrant AC phenotype and received ICD implantation. None of the 22 heterozygous family members fulfilled definite diagnostic criteria, supporting the evidence of a recessive inheritance trait.

This otherwise rare missense variant (minor allele frequency in the gnomAD database, 5.78e−5), was demonstrated by haplotype analysis to be a founder one, with 0.12% frequency in East Asia distributed in North China, South China Taiwan and Japan. The authors hypothesized that demic diffusions from north to south China during Western Jin Dynasty (265–316 CE) and Dan Dynasty (1127–1279 CE) might be responsible for the founder effect of the haplotype distribution. Previous studies described the effect of geographic limits or demic diffusion in haplotype distribution (founder effect) underlying the complex genetic architecture of the disease. Specifically, *DSC2* homozygous variants such as the truncated variant c.1660C>T (p.Gln554X) and the missense variant c.536A>G (p.Asp179Gly) were identified to be founder mutations in the Hutterite [3] and in Chioggia (Venice) populations [7], respectively. Moreover, in the Dutch population the *PLN* in-frame deletion,

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c.40_42delAGA (p.Arg14del) and the *PKP2* truncated variant c.235C>T (p.Arg79X) were identified as founder mutations due to their prevalence among AC cases [8]. Finally, the founder mutation of Newfoundland Canada, *TMEM43* missense variant c.1073C>T, (p.Ser358Leu), was probably caused by migration from continental Europe to Canada [9].

In summary, Chen and colleagues extended our knowledge regarding the genetic heterogeneity of AC in East Asia and highlighted the regional importance of certain gene mutations [10].

Defining selection criteria by which rare variants are considered causal is mandatory; indeed, this study demonstrated that stringent criteria should be established, taking into account cohort location and ethnicity in order to avoid misinterpretation of genetic variants. Systemic studies of disease prevalence and gene-variants frequency are required to determine population divergences underlying phenotypic variability.

Further, the Authors highlighted the need of cascade genetic screening to determine rare variants causality. Extensive phenotype-genotype correlation studies of large families are mandatory to establish the role of disease related variants in clinical expression and phenotypic variation.

Finally, the identification of this new founder mutation by Chen and colleagues [10] provided compelling evidence of an autosomal recessive inheritance pattern in AC given by *DSG2* rare variants, supporting the idea that the inheritance pattern of AC is more complex than previously appreciated, with frequent requirement for more than one 'hit' for fully penetrant disease (co-dominant or recessive trait). Genetic testing by massive parallel sequencing remains essential to identify other genetic factors involved in the disease pathogenesis.

It is clear that AC, previously regarded as a monogenic condition whose inheritance followed simple Mendelian principles, perhaps should be envisioned as a group of conditions with variable inheritance patterns, molecular aetiologies and clinical presentations. As such, AC phenotype characterization is the starting point to find disease modulator factors, either genetic or environmental, underlying phenotypic variability.

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