Homozygous or compound heterozygous variants in DSG2 are mainly causative of Japanese arrhythmogenic right ventricular cardiomyopathy

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Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy mainly caused by desmosomal gene variants. Previously, we showed that the genetic backgrounds of ARVC in Japanese was different from those in Caucasian and that DSG2 was the most common causative gene.

Purpose: We aimed to confirm the inheritance mode of Japanese ARVC caused by pathogenic variants in DSG2. Furthermore, we reassessed the difference of phenotypes depending on the genotype.

Methods and results: Among 153 ARVC probands diagnosed with definite, borderline or possible by TFC2010 excluding the criteria of family history, 66 had one or more DSG2 variants (25 homozygous, 26 compound heterozygous, 11 multiple variants with unknown allele origin and 4 heterozygous). In the family screening, 62 relatives carried DSG2 variants (2 homozygous, 6 compound heterozygous, 54 heterozygous). All family members with a heterozygous DSG2 variant were not fulfilled ARVC diagnostic criteria. These results indicate that most of ARVC caused by DSG2 variants is an autosomal recessive disease. Therefore, 62 probands who have multiple DSG2 variants were included as pathogenic DSG2 variants carriers in following analysis. Figure A shows the genotypes in Japanese ARVC probands. We compared the clinical characteristics of the probands with DSG2 variants to those with PKP2 ones (N = 28). DSG2 variant carriers hospitalized for heart failure at younger age (42 ± 17 vs. 64 ± 13 years, P = 0.003) and had lower LVEF at diagnosis (51 [39 - 60] vs. 60 [55 - 65] %, P = 0.004). On the other hand, PKP2 variant carriers suffered atrial fibrillation more frequently (N = 7 (25%) vs. N = 5(8%), P = 0.04) and sustained VT at younger age though it was not statistically significant (38 ± 18 vs. 47 ± 15 years, P = 0.055). Finally, we analyzed the genotype effect on the incidence of lethal ventricular arrhythmia (LVA). The cumulative incidence in probands with each causative gene is shown in Figure B. Using multivariable analysis, we confirmed that PKP2 variant carriers had higher risk for LVA after adjusted by sex, medication, catheter ablation and device implantation (HR 2.904; 95% CI 1.530 – 5.513, P = 0.001).

Conclusion: DSG2 was the most common causative gene for ARVC in Japanese, and their mode of inheritance was mainly autosomal recessive. While DSG2 variants were associated with LV involvement and heart failure, PKP2 variants were risk for ventricular arrhythmia. Our findings would be helpful for diagnosis and prognosis for the ARVC patients.

Genotype of Japanese ARVC probands
Cumulative incidence of LVA

Causative gene
- DSG2
- Other
- PKP2
- Unknown

Gray's test: p-value = 0.173

Cumulative incidence

Age (years)
- DSG2: 62 61 55 48 40 28 17 9 7 2 0
- Other: 7 7 7 7 6 5 3 0 0 0 0
- PKP2: 28 28 24 19 17 11 7 5 3 3 1
- Unknown: 56 56 54 48 44 37 25 17 8 3 0