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Review

The genetic background of arrhythmogenic right ventricular cardiomyopathy

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ABSTRACT

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by degeneration of the right ventricle and ventricular tachycardia originating from the right ventricle. Additionally, the disease is an inherited cardiomyopathy that mainly follows the autosomal dominant pattern. More than 10 genes have been reported as causative genes for ARVC, and more than half of ARVC patients carry mutations in desmosome related genes. The desmosome is one of the structures involved in cell adhesion and its disruption leads to various diseases, including a skin disease called pemphigus. Among desmosome genes, mutations in PKP2 are most frequently identified in ARVC patients. Although the genotype–phenotype correlations remain to be fully studied, many studies have reported clinical manifestations of, prognosis for, and appropriate therapies for ARVC from the perspective of gene mutations. A collective review of these reports would enhance the understanding of ARVC pathogenesis and clinical manifestation. This review discusses the clinical issues of ARVC from the genetic background.

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1. Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC), previously called arrhythmogenic right ventricular dysplasia (ARVD), is an inherited disease characterized by right ventricular degeneration and ventricular arrhythmias. ARVC is one of the important causes of sudden cardiac deaths in young people, and especially in young athletes [1]. The disease seems to be reported at the end of the 19th century as “cor adipose” [2]. In 1982, Marcus et al. first summarized 22 cases of adult ARVC patients, including their clinical characteristics such as male predominance, onset at around 40 years of age, T wave inversion in precordial leads, and fibro-fatty replacement of the myocardium [3]. These clinical characteristics are still applied in the latest diagnostic task force criteria [4].

Familial cases of ARVC have been reported since the early 1980s. In 1985, 3 out of 5 siblings from a family were diagnosed with ARVC, and the authors hypothesized incomplete autosomal dominant inheritance mode with low penetrance [5]. Thus, ARVC was suspected to be an inherited disease from the beginning, and many physicians and researchers started to explore the genes responsible for ARVC. Studies related to the identification of causative genes are summarized in the next section.

The first diagnostic criteria for ARVC published in 1994 included family history as one of the criteria [6]. Familial disease confirmed at necropsy or surgery was classified as a major criterion. A familial history of premature sudden death (<35 years of age) due to suspected right ventricular dysplasia or a familial history based on clinically diagnosed disease as per the criteria were classified as minor criteria.

To understand the pathogenesis of ARVC, many researchers have studied the genetic background of the disease, and many causative genes have been identified in the last decade. Among these, the identification of involvement of desmosomal genes in ARVC patients was a significant discovery [7].

Presently, genetic mutations are identified in more than 60% of ARVC patients, and familial cascade screening is useful to diagnose the disease before its onset in young family members.

In this review, I have described the causative genes, the characteristics of the genotype, and the future perspectives for ARVC from the viewpoint of genetics.

2. History of desmosome genes as the cause of ARVC

Desmosomes are a complex formed by proteins and function to bind the myocardial cells to each other. In the heart, desmosomes are composed of five proteins that is, junctional plakoglobin encoded by JUP, plakophilin-2 by PKP2, desmoplakin by DSP, desmoglein-2 by DSG2, and desmocollin-2 by DSC2 (Fig. 1). Desmosomes are indispensable for electrical conduction and mechanical contraction in myocardial cells.

In 1986, the Greek cardiologist Protonotarios and his colleagues reported cardiac abnormalities in 9 patients with familial palmoplantar keratosis and wooly hair [8]. All patients originated from families on the Greek island of Naxos, and therefore the disease was named as Naxos disease. The island of Naxos has nearly 200 unrelated families. Medical doctors and scientists in Naxos and London collaborated and recruited all families living on the island of Naxos for the study. They identified 9 affected families and performed linkage analysis for 38 members, including the 14 affected members. Using this analysis, they reported a homozygous genotype on 17q21 in 1998 [9].

In 2000, a homozygous deletion mutation in JUP was finally identified in 19 patients with Naxos disease [7].

After the discovery of JUP as a causative gene for ARVC in the recessive form, many researchers started genetic analysis for other desmosome genes in ARVC patients. DSP was confirmed as a causative gene in 2002 [10]. PKP2 mutations in ARVC patients were reported in 2004 [11], while DSG2 and DSC2 mutations were reported in 2006 [12,13].

Although most ARVC patients show the autosomal dominant inheritance, two recessive inheritance modes have been reported in syndromic ARVC. One of these is the Naxos disease caused by homozygous mutations in JUP [7], and another is the Carvajal syndrome caused by homozygous DSP mutations [14]. At first, Carvajal syndrome was reported as a syndromic dilated

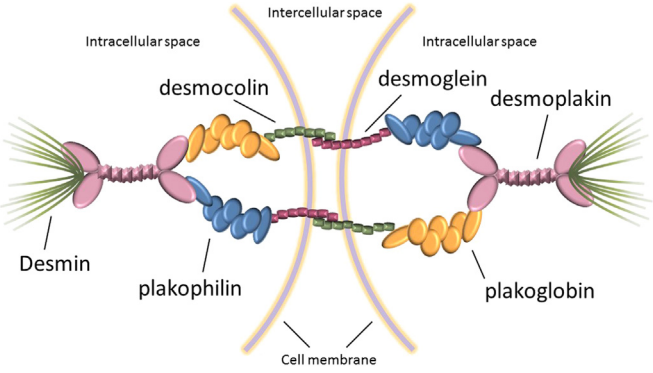

Fig. 1. A schematic diagram of the desmosome. Desmoglein and desmocolin located in the transmembrane region connect with the corresponding molecules on the neighboring cell and are linked to desmoplakin by plakophilin and plakoglobin.

Table 1
Genotypes, gene names, and locations related to ARVC.

Genotype	Gene	Location	Recessive form	Reference
ARVC1	*TGFB3*	14q24.3		[24]
ARVC2	*RYR2*	1q43		[27]
ARVC3	Unknown	14q12-q22		[54]
ARVC4	*TTN*	2q32.1-q32.3		[29]
ARVC5	*TMEM43*	3p25.1		[33]
ARVC6	Unknown	10p14-p12		[55]
ARVC7	*DES*	2q35		[37]
ARVC8	*DSP*	6p24.3	Carvajal syndrome	[10]
ARVC9	*PKP2*	12p11		[11]
ARVC10	*DSG2*	18q12.1		[12]
ARVC11	*DSC2*	18q12.1		[13]
ARVC12	*JUP*	17q21.2	Naxos disease	[7]
Others	*PLN*	6q22.1		[40]
	LMNA	1q22		[41]
	SCN5A	3p21		[44]
	CTNNA3	10q 22.2		[45]

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