Genetic factors in arrhythmogenic right ventricular cardiomyopathy: need for a DNA bank!

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The prevalence of arrhythmogenic right ventricular cardiomyopathy (ARVC) in the general population varies from 1 in 2000 to 1 in 5000. The disease affects more men than women with an estimated ratio of 3:1. As early as in 1982, Marcus et al.[1] observed that ARVC occasionally occurred within families. The clinical findings related to ARVC suggested a familial occurrence of 30 to 50% with autosomal dominant inheritance, various degrees of penetrance, and polymorphic phenotypic expression. As a result, the diagnosis of ARVC may have important consequences for direct relatives as they have an increased chance of having the disease. Genetic screening for early detection of healthy carriers may play a fundamental role in primary prevention, considering sudden death often occurs as the first manifestation of the disease. The genes involved and the molecular defects are not fully known, although recently several ARVC loci have been identified. Genetic disorders have been identified on chromosomes 14q23-q24 (ARVD1), 1q42-q43 (ARVD2), 14q12-q22 (ARVD3), 2q32 (ARVD4), 3p23 (ARVD5), 10p12-p14 (ARVD6), 10q22 (ARVD7), 6p24 (ARVD8) and 12p11 (ARVD9).[2]

Desmoplakin was the first disease-causing gene identified in autosomal dominant ARVD; the affected family had a missense mutation linked to 6p24 (ARVD8).[3] The mutation affected the N-terminal of desmoplakin, in the region of the plakoglobin-binding domain. The phenotype of this and four additional families with ARVC caused by desmoplakin mutations was 'classic ARVC' with a clinical presentation of arrhythmias, sudden death, and left ventricular involvement as the disease progresses.[3,4] Desmoplakin is a key component of desmosomes and adherent junctions that is important for maintaining the tight adhesion of many cell types, including those in the heart and skin. When these junctions are disrupted, cell death and fibrofatty replacement occur.

An autosomal recessive variant of ARVC that is associated with palmoplantar keratosis and woolly hair ('Naxos disease') has been mapped on chromosome 17q21 whereby plakoglobin has been identified as the responsible gene.[5] Plakoglobin participates in cell-to-cell junctions and it has been postulated that inadequate cell adherence injures the cardiac cell membranes leading to cell death and fibrofatty replacement. Recently, it was reported that mutations in the desmosomal protein plakophilin-2 are common in ARVC patients.[6] The gene at locus 12p11 (ARVD9) encodes the desmosomal protein plakophilin-2. In a genetic analysis of 120 unrelated individuals with ARVC, 32 (27%) had 25 different mutations in the gene encoding plakophilin-2.[6] In recently published studies, the number of probands diagnosed for ARVC according to the criteria set by the Task Force[7] for having mutations in plakophilin-2 was 11%[8], 14%[9] and 43%.[10,11] The last two studies by Dalai et al.[10] and Van Tintelen et al.[11] failed to identity a PKP2-specific clinical phenotype. In a concomitant editorial to these two studies, Corrado and Thiene concluded that molecular genetic analysis has limited value for predicting clinical phenotype and risk of sudden death.[12]

Also the gene encoding the cardiac ryanodine receptor (RyR2) of the sarcoplasmic reticulum may be involved in the disease. RyR2 mediates the release of calcium from the sarcoplasmic reticulum that is required for myocardial contraction. The RyR2 gene is located at locus 1q42-q43 (ARVD2). If mutations of the RyR2 gene that are associated with stress-induced ventricular tachycardia were expressed in isolated cardiomyocytes, intracellular calcium homeostasis was impaired due to calcium leak from sarcoplasmic reticulum.[13] The FK506 binding protein (FKBP12.6) stabilises RyR2, preventing aberrant activation and calcium leakage. The mutations in RyR2 interfere with the interaction with FKBP12.6, increasing channel activity under conditions that simulate

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exercise.[14] In 2001 several missense mutations in the RyR2 gene were described in probands and family members suffering from ARVD2,[15] catecholaminergic polymorphic ventricular tachycardia[16] and familial polymorphic ventricular tachycardia.[17] The mutations found in patients with ARVC appear to act differently from those in familial polymorphic ventricular tachycardias without ARVC.

The gene-encoding transforming growth factor-β3 (TGF-β3) has been mapped to the ARVD1 locus on chromosome 14. Sequencing studies failed to identify any disease-causing mutations in the exonic regions of TGF-β3.[18] This led to screening of the promoter and untranslated regions, where a mutation of the TGF-β3 gene was found in all clinically affected members of a large family with ARVD1.[19] According to Beffagna et al.[19] regulatory mutations outside the TGF-β3 locus result in overexpression of TGF-β3, which contributes to the development of ARVC in these families. TGF-β3 induces a fibrotic response by promoting expression of extracellular matrix proteins and by suppression of the activity of matrix metalloproteinases. TGF-β3 may increase expression of desmosomal proteins which could be involved in the pathogenic mechanism leading to ARVC.[19]

Future directions

It has been suggested that the advent of genetic testing will provide the gold standard for diagnosis.[20] However, the findings of polymorphisms in ARVC and the fact that 50% of ARVC families do not show any linkage with the identified chromosomal loci stress the need to set up an ARVC registry and install tissue DNA banks. In this regard, it is worth mentioning that the Dutch study[11] is the result of a multicentre study undertaken as an ICIN project. In addition, analysis of functional consequences of gene mutations associated with ARVC will provide information about the (patho)physiological mechanisms underlying the disease. Expression studies in model cells, in combination with stimuli mimicking for example an activated sympathetic drive, may also identify targets to be treated with drug therapy. Although implantation of a defibrillator device prevents death from ventricular fibrillation, effective pharmacotherapy will ultimately improve the quality of life of affected individuals. ■

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