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Genetics in arrhythmogenic cardiomyopathies: where are we now and where are we heading to?

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Advances in understanding the genetic architecture and novel imaging techniques have profoundly impacted research on arrhythmogenic right ventricular cardiomyopathy (ARVC). As knowledge of ARVC has evolved, so has its classification: originally termed "arrhythmogenic right ventricular dysplasia", it was later broadened to "arrhythmogenic cardiomyopathy" (ACM) to include left ventricular forms. However, the 2023 European Society of Cardiology guidelines advocate reintroducing ARVC for fibro-fatty right ventricular disease and adopting "non-dilated left ventricular cardiomyopathy" for left-sided phenotypes previously labelled as ACM variants. Genetic testing has become critical in ARVC diagnosis, particularly for identifying mutations in desmosomal genes (e.g., *PKP2*, *PKP2*, *PKP2*, *PKP2*, *PKP2*), which are the primary genetic contributors to ARVC and inform family screening and diagnostic decisions. Recent expert consensus confirmed that only *PKP2*, *PKP2*, and *PKP2* gene mutations among non-desmosomal genes had sufficient evidence to suggest a causative relationship. While genotype-specific risk assessment models are being developed, at present, genetic background does not represent an independent risk factor for patients with ARVC. Novel gene therapies, particularly AAV-mediated *PKP2* gene replacement, have recently been demonstrated to be useful in reversing ARVC phenotypes in preclinical models. FDA-approved trials are currently evaluating *PKP2*-targeted therapies, and CRISPR/Cas9 methods are being explored for *PKP2*-R14del mutations. Overall, current evidence supports distinct gene-specific manifestations within ARVC, aligning clinical phenotypes with specific genetic variants. This progress points to a future in which risk stratification and management are personalized through gene- and mutation-specific approaches, advancing the potential for precision medicine in ARVC care.

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Introduction

The field of cardiomyopathies has undergone profound changes in the last decade, particularly due to advances in the understanding of genetic architecture and the application of new imaging techniques. The European Society of Cardiology has therefore recently published clinical guidelines for the treatment of cardiomyopathies. Particular attention has been paid to so-called arrhythmogenic cardiomyopathies, a generic term for a spectrum of cardiomyopathies characterized by the presence of ventricular arrhythmias.[1]

The term 'arrhythmogenic cardiomyopathy' represents the historical evolution of the disease initially described as 'arrhythmogenic right ventricular dysplasia' (ARVD)[2] and later renamed 'arrhythmogenic right ventricular cardiomyopathy' (ARVC).[3] In the earliest reports, ARVD was erroneously associated with Uhl's anomaly,[4] leading to the misnomer 'dysplasia', but the seminal work of Thiene *et al*.[5] demonstrated that it was not a dysontogenetic, but a degenerative condition, triggering its renaming. Identification of the mutations on genes encoding for desmosomal proteins as causes of ARVC led to the growing understanding that ARVC is not exclusively limited to the right ventricle and resulted in introducing the term 'arrhythmogenic cardiomyopathy'.[6] The introduction of this umbrella term, which encompasses diverse, sometimes divergent, clinical phenotypes, has generated much debate, such that the 2023 ESC Guidelines recommended against using the term arrhythmogenic cardiomyopathy (ACM) as a distinct cardiomyopathy.[1] This led to the re-introduction of the term ARVC, to be applied to the disease caused by fibrofatty infiltration of the right ventricle (RV), and the introduction of a novel term 'non-dilated left ventricular cardiomyopathy', encompassing disease forms previously referred to as 'arrhythmogenic left ventricular cardiomyopathy', 'arrhythmogenic dilated cardiomyopathy', and 'left-dominant ARVC'.[1]

The history of ARVC begets thus two fundamental questions: what is the role of genetics in the contemporary understanding of arrhythmogenic cardiomyopathy? and what does the future hold for genetics in arrhythmogenic cardiomyopathy?

Contemporary role of genetics

Overall, genetics plays an important role for the phenotyping and diagnosis of ARVC, while its role for risk stratification is more limited.

Desmosomal gene mutations have been definitively linked to ARVC and represent the most common cause of the disease, with approximately half of probands testing positive for a desmosomal gene mutation.[7] Specifically, mutations on genes encoding for plakophilin-2 (*PKP2*), desmoplakin (*DSP*), desmocollin-2 (*DSC2*), desmoglein-2 (*DSG2*), and plakoglobin (*JUP*) are considered causative.[7]

Over the years, following the progressive inclusion of LV-prevalent forms, the relative contribution of *PKP2* gene mutations has progressively reduced,[8] but these, usually truncating mutations, remain the most commonly reported gene mutations in patients with ARVC. In contemporary cohorts, *DSP* gene mutations represent the second most common cause, followed by mutations in *DSC2* and *DSG2* genes. Lastly, plakoglobin mutations, typically inherited in an autosomal recessive manner, represent a rare cause of ARVC.

An identification of a pathogenic or likely pathogenic mutation associated with ARVC represents a major diagnostic criterion according to the 2010 revised Task Force Criteria[3] and can trigger cascade family screening, which in turn may identify asymptomatic family members. In this context, it is clear how the variant evaluation of the genetic variant identified assumes particular relevance and should be performed by a multidisciplinary team led by an experienced geneticist.[1] These aspects have been recognized by both the 2022 and the 2023 ESC Guidelines, which suggest that genetic testing is indicated in all index patients with ARVC and that genetic counselling, preferably in specialized centres, should be part of common clinical practice.[1,9]

Over the years, numerous other genes, in addition to the aforementioned desmosomal genes, have been associated with ARVC, but a recent expert-led reappraisal concluded that only *TMEM43*, *PLN*, and *DES* gene mutations had sufficient evidence to suggest a causative relationship.[10] Curiously, both *TMEM43* and *PLN* were initially associated with ARVC due to a segregating founder variant (p.S358L on *TMEM43* in Newfoundland, Canada, and p.R14del on *PLN* in the Netherlands).[11,12] *In vitro* data suggest that these non-desmosomal gene mutations lead to reduction and/or dysfunction of desmosomal proteins, as shown by reduced staining of desmosomal proteins, positing in principle a shared common pathway converging on the desmosomal proteins.[13–15]

Although ARVC exhibits markedly incomplete, age-dependent, and sex-dependent penetrance, current data suggest that genotypes may explain at least a proportion of phenotypic variability observed. The growing body of evidence suggests that truncating *PKP2* gene mutations are typically associated with prototypical ARVC[8]: T-wave inversion in right precordial leads, found in three-quarters of patients; left bundle branch block morphology of ventricular arrhythmias; and RV dilatation in two-thirds of the cases, frequently accompanied by characteristic RV wall motion abnormalities. In terms of outcomes, the available evidence suggested that up to a third of *PKP2* mutation carriers experienced severe arrhythmic events, while only a small minority of patients (1–2.5%) progressed to terminal heart failure and heart transplant.[16] On the other hand, truncating *DSP* gene mutations have been associated with a distinct form of LV-prevalent cardiomyopathy that frequently presents a distinct, ring-like pattern of late gadolinium enhancement at cardiac magnetic resonance imaging.[17] Relevantly, up to 15% of patients affected by *DSP* cardiomyopathy experienced episodes of acute myocardial injury[17] and may be misdiagnosed more often as acute myocarditis, which may contribute to the diagnostic delay. Initial evidence suggests that heart failure events may be more frequent in carriers of *DSP* gene mutations, when compared with carriers of *PKP2* gene mutations.[16]

Beyond the desmosomal mutations, low voltages of the QRS complexes represent a well-described electrocardiographic feature of the Dutch founder mutation (p.R14del) on the *PLN* gene, which may present with ARVC or with dilated cardiomyopathy (DCM). Interestingly, immunohistochemistry studies on myocardial samples revealed absent or depressed plakoglobin levels at

intercalated disks in the majority of samples from patients with the diagnosis of ARVC, while these were normal in most samples from patients with the diagnosis of DCM.[14]

Notwithstanding the important phenotypic differences across genotypes, the contemporary role of genetic background in risk stratification in patients with ARVC remains limited. Within the realm of desmosomal mutations, the Padua group demonstrated[18] and a recent meta-analysis confirmed[19] that carriers of more than one desmosomal gene mutation were at a significantly increased arrhythmic risk. These data are in line with what has been reported for other inherited arrhythmia syndromes where homozygous or compound heterozygous forms have more severe outcomes; for example, in the field of the long QT syndrome, patients with Jervell and Lange Nielsen syndrome have been recognized as very high-risk patients.[20]

Registry-based data have reported unusually high rates of sudden cardiac death at presentation in patients carriers of *DSP* gene mutations, and this has been further corroborated by the identification of *DSP* gene mutations in survivors of 'idiopathic ventricular fibrillation'.[21] However, two of the largest studies with genotype-specific follow-up data failed to identify increased arrhythmic risk in carriers of *DSP* gene mutations when compared with patients with *PKP2* gene mutations.[16,17] Additionally, data from a multicentre cohort showed that while there were no significant differences among genotypes, gene-elusive patients had a lower rate of ventricular arrhythmia at follow-up.[22] This evidence should be interpreted cautiously, keeping in mind that the heterogeneity of the study endpoints used, ranging from sudden cardiac death and its surrogates such as life-threatening arrhythmic events to composite outcomes including sustained monomorphic ventricular tachycardia and appropriate implantable cardioverter defibrillator interventions, may have contributed to the differences in outcomes reported.[23] At present, it is fair to say that in patients carriers of a single desmosomal gene mutation the genetic background is not an independent risk factor for arrhythmic outcomes.

This is not to say that the genetic background is clinically irrelevant and can be ignored when approaching risk stratification. Recently, Protonotarios *et al.*[22] assessed the performance of the 2019 ARVC risk model. Their data demonstrated that the performance of the risk calculator was best in carriers of *PKP2* gene mutations (Uno's concordance index 0.83, 95% CI 0.75–0.91) but that it performed less well in patients with different genetic backgrounds.[22] The analysis of the individual predictors revealed that the *PKP2* group had the most significant predictors and the *DSP* group the least among the clinical variables that were studied.[22] Considering the aforementioned, larger studies are needed to ascertain the relationship between genotype and outcomes and that different forms of ARVC may need tailored approaches to risk stratification.

In terms of a personalized approach to risk stratification, the greatest progress has been made in carriers of the Dutch founder mutation (p.R14del) on the *PLN* gene. Leveraging on the availability of a large cohort, in 2021 Verstraelen *et al.*[24] developed a mutation-specific prediction model and showed that the use of mutation-specific phenotypic features can improve accuracy compared with a more generic approach.

In summary, currently, the available evidence supports the concept of gene-specific diseases within the umbrella term of 'arrhythmogenic cardiomyopathy', in terms of both clinical manifestations and phenotype, and it is possible to envision a future of truly personalized medicine with gene- and even mutation-specific approaches for risk stratification.

Gene therapy: no longer a distant dream

Gene therapy represents the holy grail for the affected patients, treating physicians, and basic scientists studying the disease, as no therapeutic intervention has been shown to avert the often severe clinical course of ARVC. Since the milestone approval of Alipogene tiparvovec back in 2012, as the first european medicines agency-approved gene therapy, there has been a growing scientific and commercial interest in the development of gene therapies in almost every field of medicine.

In the context of ARVC, evidence regarding the potential efficacy of gene therapy has been provided recently. Of note, four studies, all published in late 2023–24,[25–28] reported the efficacy of a gene replacement strategy based on overexpression of *PKP2* in mouse disease models. Bradford *et al.*[27] designed a *PKP2* gene replacement strategy employing an adeno-associated viral vector serotype 9 (AAV9) coupled with the cardiac troponin T (cTnT) promoter, demonstrating that gene therapy not only prevented the development of the phenotype when administered in the early post-natal period (2 days after birth) but could also induce phenotype regression when administered later in life (4th post-natal week).[27] The benefits of *PKP2* replacement gene therapy strategies have been further investigated by the group of Kyriakopoulou *et al.*[26] They tested adeno-associated virus (AAV)-mediated gene therapy on both human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) and a mouse model carrying an equivalent of human mutation *PKP2* c.755delA. Via the infusion of high doses of AAV9 vector (2×10^{14} viral genomes/kg) delivering *PKP2* fused to a MYC epitope, a high percentage (76%) of cardiac myocytes were transduced, leading to recovery of *PKP2* and partial recovery of the levels of other desmosomal proteins, therefore resulting in improved electromechanical coupling.[26] Confirming these data, Wu *et al.*[25] demonstrated that gene therapy can restore physiological desmosomal protein structure and amend additional transcriptional defects, unrelated to the desmosome, that are present in *PKP2*-knockout mice. More in detail, they have engineered two distinct AAV9 vectors expressing either human PKP2 (TN-401) or its mouse orthologue (AAV9:mPkp2), obtaining food and drug administration (FDA) approval for the first vector.[25]

Despite differences in vector designs and disease models, these studies collectively highlight the potential of AAV-mediated gene therapy to treat *PKP2*-associated ARVC. Among the above-mentioned vectors, three AAV-based gene therapies for *PKP2*-associated ARVC received US FDA approval for phase 1 clinical trials: (i) TN-401, the rAAV9-hPKP2 vector variant studied by Wu *et al.*[25]; (ii) LX2020, the rAAVrh.10-hPKP2 vector developed by Lexeo Therapeutics Inc.; and (iii) RP-A601, the rAAVrh.74-hPKP2a vector tested by van Opbergen *et al.*[28]

In addition to studies on *PKP2*-mediated ARVC, gene therapy research also focused on the *PLN*-R14del mutation, a widespread variant associated with cardiomyopathies, particularly prevalent in the Netherlands. Initial studies by Karakikes *et al.*[29] investigated gene therapy for *PLN*-R14del using patient-derived iPSC-CMs. They developed an AAV6 vector able to down-regulate endogenous *PLN* through an intronic artificial miRNA (miR-PLN) while simultaneously overexpressing a miRNA-resistant PLN, achieving increased wild-type PLN expression and ~50% reduction in mutant *PLN* transcripts. After 7 days, treated cells exhibited fewer arrhythmic episodes compared with untreated cells. Subsequently, Dave *et al.*[30] designed an AAV9-CRISPR/Cas9 approach targeting the *PLN*-R14del allele in a heterozygous mouse model expressing *hPLN*-R14del. Eight weeks post-treatment, treated mice showed reduced right and left end-diastolic and stroke volumes, along with decreased susceptibility to ventricular arrhythmias.

Future directions and conclusions

Deciphering the genetic basis of ACM will continue to have significant implications for diagnosis, management, and treatment. Comprehensive genetic screening that includes both desmosomal and non-desmosomal genes is essential to fully understand the genetic architecture of ACM. Expanding these screening protocols will improve diagnostic accuracy, enhance risk stratification, and refine our understanding of disease mechanisms at the molecular level.

Risk stratification in ACM remains an effective but underutilized tool. Emerging evidence underscores the need for a tailored approach that combines genotype-specific data with advanced imaging and electrophysiological measurements to develop accurate predictors of the arrhythmic risk or progression to heart failure. Such integration could lead to sophisticated stratification models that account for the genetic and clinical heterogeneity of ACM.

With advances in gene therapy research, ACM represents a promising target for AAV-based therapeutic strategies, particularly for mutations associated with severe phenotypes. Standardizing vector design, ensuring robust patient safety, and validating therapeutic efficacy in diverse patient populations will be critical steps towards clinical translation. Ultimately, integrating genetic counselling as a fundamental element of ACM management will help both patients and physicians manage this complex, variable disease.

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Data availability

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