Narrative Review Article

Gene Therapy Targeting PKP2 in Arrhythmogenic Cardiomyopathy: Mechanisms, Challenges, and Future Directions

Ramkumar Babu

Langley High School, 6520 Georgetown Pike, McLean, VA 22101, United States

ABSTRACT

Arrhythmogenic cardiomyopathy (ACM) is a heritable cardiac disease characterized by progressive myocardial dysfunction, life-threatening arrhythmias, and an elevated risk of sudden cardiac death. Mutations in the *PKP2* gene, encoding the desmosomal protein plakophilin-2, represent the most common genetic cause of ACM, accounting for approximately 21–35% of diagnosed cases. Plakophilin-2 is an essential scaffold protein within cardiac desmosomes, maintaining the mechanical and electrical integrity of cardiomyocytes through interactions with desmoplakin, desmogleins, desmocollins, and intermediate filaments. Loss-of-function *PKP2* mutations disrupt desmosomal assembly, impair gap junction-mediated electrical conduction, and trigger downstream fibrofatty replacement of myocardium via the TGF-β1/p38 MAPK pathway. Current therapies, including implantable cardioverter defibrillators (ICDs) and antiarrhythmic drugs, manage symptoms but do not address the underlying molecular defect. Adeno associated virus (AAV)-based gene replacement therapy has emerged as a promising disease-modifying strategy, with several Phase 1/2 clinical trials now underway. However, significant obstacles remain, including off-target tissue tropism, immune-related adverse events, and the difficulty of translating preclinical findings from murine models to human patients. This review synthesizes current knowledge on *PKP2*'s role in cardiac biology, the molecular consequences of its mutation in ACM, the status of ongoing clinical trials, and the key challenges and future directions for gene therapy development.

Keywords: Arrhythmogenic cardiomyopathy (ACM); *PKP2* gene; PKP2 proteins; Adeno-associated virus (AAV); Gene replacement therapy

INTRODUCTION

Arrhythmogenic cardiomyopathy (ACM) is a heritable myocardial disease characterized by fibrofatty replacement of the myocardium, progressive ventricular dysfunction, cardiac arrhythmias, and an elevated risk of sudden cardiac death. While historically classified as Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) due to an exclusive focus on right ventricular involvement, ACM is now recognized as a broader clinical spectrum encompassing right-dominant, left-dominant, and biventricular phenotypes. At the cellular level, ACM is primarily driven by disruption of the cardiac desmosome; among the implicated variants, mutations in the plakophilin-2 (*PKP2)* gene are the most prevalent, found in approximately 21–35% of diagnosed patients (1). Plakophilins (PKPs) are members of a subfamily of armadillo proteins belonging to the p120-catenin (p120ctn) family. This family comprises

Corresponding author: Ramkumar Babu, E-mail: ram18babu@gmail.com.

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seven members, four of which are found primarily in adherens junctions (p120ctn, NPRAP/δ-catenin, ARVCF, and p0071/PKP4), whereas PKP1–3 localize primarily at desmosomes (2). *PKP2* encodes plakophilin-2, a critical structural protein in desmosomes—intercellular junctions that maintain the mechanical and electrical integrity of cardiomyocytes. Disruption of desmosomal function due to *PKP2* mutations compromises cell adhesion, impairs electrical signaling, and accelerates cardiomyocyte death (3).

While current interventions such as ICDs and antiarrhythmic drugs help reduce the risk of sudden cardiac events, they do not address the underlying molecular defects. As a result, gene therapy has emerged as a promising strategy to correct *PKP2*-related dysfunction at its source. Several Phase 1 and Phase 1/2 clinical trials are currently underway and published efficacy data remain unavailable, and major challenges must be addressed before gene therapy can be considered a reliable clinical intervention. These include the development and optimization of efficient gene delivery systems, sustained transgene expression in cardiomyocytes, immune-related adverse events, and prevention of off-target effects.

This review aims to synthesize current knowledge on the role of *PKP2* in cardiac structure and function, explore the molecular consequences of *PKP2* mutations in ACM, and evaluate the progress and limitations of emerging gene therapy strategies targeting this gene. It also reviews the current clinical trials utilizing *PKP2* gene replacement approaches.

PKP2 ROLE IN CARDIAC STRUCTURE AND FUNCTION

Desmosomes are large, symmetrical protein complexes that span the cytoplasm to the intercellular space and serve as the primary mechanical junctions linking adjacent cardiomyocytes. As illustrated in Figure 1, plakophilin-2 occupies a central position on the cytoplasmic face of the desmosomal plaque, where it acts as a scaffold to recruit and stabilize multiple components of the complex (1, 2). Specifically, PKP2 organizes transmembrane cadherins (desmogleins and desmocollins), plakoglobin (JUP), desmoplakin (DSP), and intermediate filaments such as keratin to form a cohesive, mechanically resilient junction. Desmoplakin directly binds keratin, and PKP2 associates with desmoplakin, thereby linking the cytoskeletal network indirectly to the desmosomal plaque. This linkage ensures mechanical continuity across the myocardium and allows heart tissue to withstand the repeated stress of contraction. In the heart, PKP2 is the predominant plakophilin isoform; unlike other tissues where partial redundancy exists among desmosomal proteins, neither PKP1 nor PKP3 can compensate for PKP2 loss due to

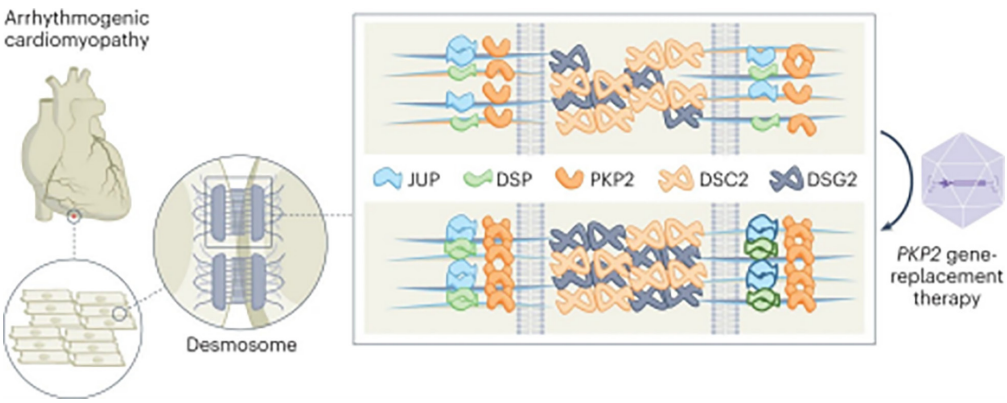

Figure 1. *Schematic of the cardiac desmosome and the rationale for PKP2 gene-replacement therapy in arrhythmogenic cardiomyopathy. The left panel illustrates the molecular architecture of the cardiac desmosome, showing key structural proteins at the intercalated disc: plakophilin-2 (PKP2), plakoglobin (JUP), desmoplakin (DSP), desmocollin-2 (DSC2), and desmoglein-2 (DSG2). PKP2 occupies a central scaffolding role on the cytoplasmic plaque, linking transmembrane cadherins (DSC2, DSG2) to desmoplakin and intermediate filaments. The right panel depicts the gene therapy rationale: AAV-mediated delivery of a functional PKP2 transgene into cardiomyocytes to restore desmosomal integrity, gap junction organization, and electrical conduction in the setting of PKP2 loss-of-function (7).*

differences in tissue distribution, binding partners, and functional context (3, 4).

Beyond its structural role, PKP2 is also essential for organizing the intercalated disc, the specialized region of cardiomyocyte contact where desmosomes, gap junctions (composed primarily of connexin-43), and voltage-gated sodium channels are co-localized to facilitate synchronized contraction (5, 6). This architectural organization is critical: gap junctions propagate electrical impulses between cardiomyocytes, and sodium channels initiate the action potential. When PKP2 is mutated or absent, structural disorganization of the desmosome leads to downregulation and mislocalization of connexin-43, impairing gap junction-mediated electrical conduction and slowing action potential propagation (4).

PKP2 MUTATIONS

The majority of *PKP2* mutations are truncating variants that result in translational frameshifts and loss of functional protein. Among pathogenic and likely pathogenic (P/LP) variants, approximately 46% are frameshift mutations, 25% are nonsense mutations, 17% are splice-site alterations (±1 or ±2 intronic positions from the exon boundary), 6% are large deletions, and only 5 variants (6%) are missense substitutions. This distribution contrasts sharply with variants of uncertain significance (VUS), among which approximately 59% are missense variants—a finding that reflects the difficulty of predicting pathogenicity for amino acid substitutions in the absence of functional data (6).

At the protein level, both missense and frameshift mutations lead to protein instability and degradation, supporting haploinsufficiency as the primary pathogenetic mechanism (5). Complete loss of PKP2 expression typically produces earlier onset and more severe phenotypes, while partially functional missense variants may delay or attenuate disease progression (8,9). Among the most recurrent truncating mutations in ACM are frameshift variants such as c.2013delC (p.Ser672Valfs*7) and nonsense variants such as c.2386C>T (p.Arg796*), which have been identified across multiple unrelated families.

Mutations or haploinsufficiency of *PKP2* disrupt protein-protein interactions within the desmosome, destabilizing its overall architecture and weakening cell-cell adhesion (10). This destabilization reduces the incorporation of other key desmosomal proteins, including DSP and desmoglein-2 (DSG2), and decreases the overall functional junctional area. Defective plakophilin-2 proteins may further exert a dominant-negative effect by competing with wild-type protein for binding sites within the desmosomal plaque. The resulting collapse of desmosomal integrity leads to cardiomyocyte detachment, death, and fibrofatty replacement of the myocardium—establishing the structural and electrical substrate characteristic of ACM (11).

MOLECULAR CONSEQUENCES OF PKP2 MUTATIONS IN ACM

The molecular consequences of *PKP2* loss extend well beyond the structural disruption of the desmosome. When desmosomal integrity is compromised, cell-cell adhesion is diminished, which in turn impairs the efficiency of gap junction-mediated electrical signal transduction between cardiomyocytes (5). Gap junctions, primarily composed of connexin-43, are responsible for the rapid and coordinated propagation of electrical impulses through the myocardium. Disruption of PKP2–connexin-43 interactions lead to gap junction remodeling and reduced connexin-43 expression, resulting in slowed and desynchronized conduction (4, 12). This electrophysiological dysfunction is an early manifestation of the disease—often preceding visible structural abnormalities—and can present clinically as premature ventricular contractions, conduction delays, or reentrant arrhythmias (12).

As conduction abnormalities persist, they trigger cardiomyocyte death and activate pro-fibrotic signaling cascades, most notably the TGF-β1/p38 MAPK pathway (13). Loss of PKP2 has been shown to directly promote transcription of TGF-β1 target genes in cardiomyocytes, driving the progressive replacement of healthy myocardium with fibrofatty tissue. This fibrofatty infiltration impairs the structural integrity of the ventricular wall, promotes local inflammation, and further exacerbates conduction defects by creating regions of heterogeneous electrical propagation that serve as substrates for reentrant arrhythmias (13, 14).

CURRENT CLINICAL TRIALS ADDRESSING PKP2

Several Phase 1 and Phase 1/2 clinical trials for AAV-based gene replacement therapy targeting *PKP2* are currently underway (Table 1). These trials represent the first-in-human evaluations of this therapeutic approach and are primarily focused on establishing safety and preliminary efficacy.

Table 1. *Ongoing clinical trials for PKP2 gene replacement therapy.*

Therapy Name	Vector	Current Phase	Number of Subjects	Study End Date	Clinical Trial Identifier
RP-A601	AAVrh.74	1	9	2026-09	NCT05885412
LX2020	AAVrh10	1/2	10	2027-02	NCT06109181
TN-401	rAAV9	1/1a	15	2029-10-01	NCT06228924
IC14	Antibody	1/2	5	2025-12-01	NCT06275893

CHALLENGES

Delivery challenges

Cardiac gene delivery presents unique challenges because the heart is a large, dynamic organ with limited regenerative capacity and strong barriers to gene uptake. Adeno-associated virus (AAV) vectors— particularly AAV9 and AAVrh74—are currently the gold standard for in vivo cardiac gene delivery, owing to their non-pathogenic nature, relatively low immunogenicity, and capacity for long-lasting transgene expression (15).

However, naturally occurring AAV serotypes with strong cardiac tropism, such as AAV8 and AAV9, also demonstrate high hepatic tropism. This creates several clinical problems: off-target transduction of liver tissue can cause hepatotoxicity, and vector sequestration in the liver reduces the effective dose reaching the heart. While increasing the administered dose could theoretically compensate, doing so is constrained by AAV immunogenicity and cost, as immune-related adverse events become more probable at higher titers (16).

To address off-target tropism, research is ongoing into engineering AAV capsids with improved cardiotropism through directed evolution and rational design. Parallel efforts focus on alternative delivery routes, including direct myocardial injection and intracoronary infusion, which may improve local vector concentrations and reduce systemic exposure (16, 17). Direct myocardial injections are not yet part of standard practice but may become more accessible as interventional cardiology techniques continue to advance.

In addition to naturally derived AAVs, adenoviral vectors were used in early gene therapy trials but have been largely supplanted due to significant immune-related adverse events. Lentiviral vectors occupy a niche role, primarily in ex vivo applications and iPSC-based research (18, 19). Non-viral delivery systems, particularly mRNA encapsulated in lipid nanoparticles, are gaining increasing attention for regenerative cardiac applications, though their use in the context of *PKP2* replacement remains investigational (18, 20, 21).

Translational challenges

Murine models are the predominant preclinical platform for ACM research, yet they imperfectly recapitulate human cardiac physiology. Mouse hearts beat at 400–600 beats per minute, compared to 60–80 in humans, and rely on fundamentally different ion channel compositions that shape action potential morphology and duration (22). ACM does not occur naturally in mice, meaning that disease models rely on genetic manipulation whose pathophysiology may not faithfully reflect the full spectrum of human disease, particularly in cases where a truncated but partially expressed *PKP2* protein may exert a dominant negative effect that knockout models cannot replicate.

To bridge this translational gap, researchers have increasingly turned to large animal models, including genetically modified pigs and companion animals with naturally occurring cardiomyopathies, which more closely approximate human cardiac anatomy and electrophysiology (17, 23). Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) and engineered heart tissues (EHTs) provide complementary tools for evaluating therapy efficacy in a human genetic background, particularly when maturation is enhanced through metabolic, mechanical, or biochemical conditioning (24, 25). While many cardiac gene therapy strategies have shown promise in animal models, only a few have progressed to and yielded meaningful results in human clinical trials (15, 23, 26).

FUTURE DIRECTIONS

The field of cardiac gene therapy continues to evolve rapidly, and several emerging approaches are likely to shape the next generation of *PKP2*-targeted therapies. On the vector development front, engineered AAV capsids generated through directed evolution—such as MyC-AAV and AAVMYO—have demonstrated substantially improved cardiac tropism in non-human primate models while reducing off-target hepatic transduction. These engineered serotypes could enable lower effective doses,

reduce the risk of immune-related adverse events and improve the therapeutic index for cardiac gene delivery.

Advances in hiPSC-CM maturation are also expanding the translational utility of in vitro models. Metabolic conditioning (e.g., fatty acid supplementation), mechanical stretch bioreactors, and co-culture systems have improved the functional maturity of hiPSC-CMs, enabling more physiologically relevant preclinical assessments of vector performance and PKP2 restoration (26). Complementary three-dimensional EHTs can now recapitulate aspects of the structural and electrophysiological remodeling seen in ACM, providing a platform for testing therapeutic interventions prior to animal studies (25).

Given the complexity of ACM pathophysiology—which involves fibrosis, inflammation, and ion channel remodeling in addition to desmosomal dysfunction—combination therapeutic strategies merit investigation. Pairing *PKP2* gene replacement with anti-fibrotic agents targeting the TGF-β1/p38 MAPK pathway, or with immunomodulatory approaches to reduce vector-related inflammatory responses, may produce more durable and comprehensive disease modification than gene therapy alone.

Finally, the field will benefit from more systematic natural history data in *PKP2* mutation carriers, which will inform the optimal timing and patient selection criteria for intervention, as well as the endpoints most likely to demonstrate clinical benefit in future pivotal trials.

CONCLUSION

The development of *PKP2*-targeted gene therapy represents a crucial step forward in addressing ACM at its genetic root rather than merely managing its symptoms. Current research has demonstrated that AAV mediated delivery of functional *PKP2* can restore plakophilin-2 expression, strengthen desmosomal connections, and improve overall cardiac conduction in animal and cell models (27). Early studies have shown that this approach can slow or reverse disease progression by enhancing the structural integrity of cardiomyocytes and reducing arrhythmogenic potential. The ongoing Phase 1 and Phase 1/2 human trials (Table 1) represent first-in-human evaluations of this approach; however, peer-reviewed efficacy data from these studies remain unavailable, and conclusions regarding improved ventricular function or reduced arrhythmia frequency in patients cannot yet be drawn from the published literature.

While murine models remain foundational for preclinical ACM research, their inherent physiological differences highlight the need for careful translation into human studies. PKP2-targeted gene therapy represents a promising disease-modifying strategy for arrhythmogenic cardiomyopathy by addressing the underlying genetic defect rather than only managing downstream symptoms. Future progress will depend on improving cardiac-specific delivery, strengthening translational models, evaluating combination approaches that address the broader disease pathway, and defining patient selection criteria through systematic natural history studies. Although this therapeutic approach remains investigational, continued research will be essential to determine whether PKP2 gene replacement can achieve durable safety, efficacy, and clinical benefit. Nevertheless, it offers a compelling and rapidly advancing therapeutic direction with the potential to reshape care for patients with PKP2-associated ACM.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this work.

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