One gene, two modes of inheritance, four diseases: A systematic review of the cardiac manifestation of pathogenic variants in *JPH2*-encoded junctophilin-2 ☆☆

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Abstract

Rare variants in *JPH2* have been associated with a range of cardiac disease, including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmias, and sudden cardiac death (SCD); how-ever, our understanding of how variants in *JPH2* correspond to specific modes of inheritance and correlate clinical phenotypes has not been comprehensively explored. In this systematic review, we assess current case reports and series that describe patients with *JPH2* variants and cardiac disease. We identified a total of 61 variant-positive individuals, approximately 80% of whom had some form of cardiac disease, including 47% HCM, 18% DCM, and 14% arrhythmia/SCD. In analyzing the 24 probands described in the studies, we found that autosomal recessive, loss-of-function variants are associated with severe, early onset DCM, while autosomal dominant missense variants are associated with a wider range of cardiac disease, including HCM, arrhythmia, SCD, and cardiac conduction disease.

Subject Terms

Arrhythmias; Cardiomyopathy; Genetics; Sudden Cardiac Death

Keywords

Arrhythmia; Conduction disease; JPH2; Junctophilin-2

Introduction

JPH2-encoded junctophilin type 2 (JPH2) is a member of the junctophilin family of proteins with an emerging role in genetically mediated cardiac disease. While *JPH1* is expressed in skeletal muscle cells and *JPH3* and *JPH4* are expressed in the brain, *JPH2* is major isoform of the heart.[1] Each junctophilin protein has eight highly conserved membrane occupation and recognition nexus (MORN) domains joined by linker regions and a C-terminal transmembrane domain.[1] JPH2 serves to bridge the plasma membrane and sarcolemma, and interacts with L-type Ca^{2+} channels (LTCC), caveolin-3, and RyR2 to regulate Ca^{2+} induced Ca^{2+} release (CICR).[1] In addition to the full-length *JPH2* transcript, the N-terminal portion of *JPH2* is cleaved by calpain to generate a 565 residue-long transcription factor that is involved in regulating the cardiac stress response.[2–4]

In the normal heart, CICR is responsible for governing excitation-contraction (E-C) coupling and coordinated cardiac contraction. In the action potential, depolarization of the cardiomyocyte via inward Na^+ current triggers opening of LTCC, which permit influx of Ca^{2+}. This influx triggers opening of RyR2 on the sarcolemma, induces further Ca^{2+} release from the sarcoplasmic reticulum (SR), and triggers myofilament contraction. CICR occurs at the cardiac dyad, where JPH2 links LTCC on t-tubules to RyR2 on the sarcolemma, ensuring efficient CICR and E-C coupling. Loss of coordinated Ca^{2+}-handling can lead to structural and electrical remodeling of the myocardium result in both cardiomyopathy and arrhythmia predisposition. For example, patients with high premature ventricular contraction (PVC) burden can develop PVC-induced cardiomyopathy, while patients with atrial fibrillation are predisposed to left atrial dilatation.[5, 6] Notably, JPH2 intersects these processes, making it a target for investigation and treatment.[7]

Pathologic variants in *JPH2* have been identified in patients with hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmias, and sudden cardiac death (SCD). Currently, ClinGen considers *JPH2* to have moderate evidence for association with HCM in an autosomal dominant inheritance pattern, and moderate evidence for association with DCM in a semidominant inheritance pattern.[8–10] HCM is characterized by ventricular hypertrophy, diastolic dysfunction, and in some cases, left ventricular outflow tract obstruction. The hypertrophy and increased myocardial fibrosis of HCM serves as an arrhythmic substrate and makes HCM the most common cause of sudden cardiac in young athletes in the United States.[11] Similarly, DCM is characterized by ventricular dilation, systolic dysfunction, and can present with high arrhythmia burden in some patients.[12–14] Though cardiomyopathies are caused by diverse etiologies, including neuromuscular disorders, inherited metabolic disorders, and infectious agents, most inherited cardiomyopathies are due to sarcomeric gene variants However, as our understanding of the genetic etiology of cardiomyopathy has evolved, non-sarcomeric causes of inherited cardiomyopathy have come to light. One important non-sarcomeric

etiology of cardiomyopathy are proteins involved in Ca^{2+}-handling, for example, in *JPH2*. [15, 16]

Despite several reports of *JPH2*-mediated cardiac disease, the pathophysiologic manifestations of *JPH2* variants have not been systematically described. Further, the interplay between heterogenous disease variants and the dual role of JPH2 in maintaining efficient CICR and orchestrating myocardial response to stress remains unclear. Thus, the goal of this systematic review is to assess the clinical characteristics of patients with *JPH2*-mediated cardiac disease described in the existing literature to narrow our gap in the understanding of genotype-phenotype correlations.

Methods

Eligibility criteria

In this systematic review, we included case reports and case series describing the clinical characteristics of patients with *JPH2* variants and cardiac disease. Studies not published in English, abstracts without full text studies, editorials, letters, commentaries, and reviews were excluded. Further, studies that performed mechanistic studies of variants without detailing clinical characteristics of a patient with that variant were excluded. If two studies reported clinical characteristics of the same patient, the article with more clinical detail and/or earliest publication date was selected for inclusion.

Search strategy

A medical librarian composed a search mixing subject headings and keywords to represent the concept of Junctophilin-2. The databases MEDLINE via PubMed, Embase via Elsevier, and Scopus via Elsevier were searched from inception to February 25, 2021. All search results were compiled in EndNote and imported into Covidence for removal of duplicates and screening. All search strategies are available in Appendix 1.

Study selection

Two independent reviewers (LP and AL) evaluated the selected studies titles and abstracts, followed by retrieval and evaluation of full-text papers. Conflicts were resolved through discussion with a third moderator (RK).

Variant adjudication

All variants were independently adjudicated by ACMG criteria, and all variants considered benign or likely benign by these standards were excluded from final analysis. Subjects reported to host a concomitant variant(s) in other cardiomyopathy-associated genes identified as pathogenic or likely pathogenic variant by ClinVar or ACMG criteria were also excluded.

Synthesis methods

Summary statistics of the patient population, including diagnosis, sex, variant zygosity, mode of inheritance, and presence of concomitant arrhythmia or cardiomyopathy were included. Given that testing and reporting of relatives varied between studies and could

overrepresent certain variants, only probands were included in the final description and analysis unless otherwise noted. Age at diagnosis and age at death are reported as mean +/− standard deviation. In patients with complex phenotypes, such as a cardiomyopathy and a concomitant arrhythmia, the cardiomyopathy was considered the dominant phenotype, while patients with arrhythmia or conduction disease alone were considered separately.

Statistical analysis

To evaluate relationships between phenotype and disease severity, we used Student's t-test, Fisher Exact test, and Chi Square Calculator for Goodness of Fit. Subgroup analysis was performed based on type of cardiomyopathy or arrhythmia and survival status.

Assessment of bias

The Joanna Briggs Institute (JBI) Critical Appraisal tools for case reports and case series were used to evaluate the quality of published studies during study extraction and identify areas of potential bias.

Results

Overall cohort

Fourteen studies met inclusion criteria for this systematic review which described 61 patients from 30 unrelated families with *JPH2* variants associated with cardiac disease (Figure 1, Table 1). Upon variant adjudication, the G505S variant is considered benign in ClinVar, and the six HCM patients described with the G505S variant were excluded from final analysis. The T286A variant was considered benign and one patient with arrhythmia was excluded. Further, 3 HCM patients with T161K variants also hosted the pathogenic MYBPC3-G1061* variant and were excluded from final analysis. The subsequent final phenotype positive cohort had a male predominance with 30 male patients and 12 female patients, while the sex of 3 patients was unknown ($X^2 = 7.7$, p = 0.005, n = 42. The clinical phenotype of the overall cohort was 47% HCM, 18% DCM, 14% arrhythmia/other, and 21% had no cardiac phenotype. There were 18 *JPH2* variants described, inherited in an AD fashion in 23 patients, AR in 8, and unknown in 27. Variants were heterozygous in 58 patients, homozygous in 2, and compound heterozygous in 1 (Figure 2).

Autosomal recessive/biallelic loss-of-function variants in JPH2 are associated with DCM through a likely genetic knockout mechanism

There are four probands with *JPH2* variants and DCM described in 4 studies. These include 2 male and 2 female patients. The average age at diagnosis was 14 +/− 25 years (n = 4, range = 0.6 – 51 years). Two of the probands were alive at time of reporting, one of whom received heart transplant at age 4, while two died as children due to complications of non-ischemic DCM. Two patients hosted concomitant conduction defects, including PR prolongation (1 patient) and 3rd degree AVB (1 patient). The average age at death or transplant of DCM probands was 3.2 +/− 2.3 years (n = 3, range = 0.7 – 5 years). Notably, all heterozygous biological parents of children with homozygous or compound heterozygous variants did not have a cardiac phenotype at a mean age of 25.3 +/− 15.3 years (n = 5, range = 0.25 – 38 years). Taken together, these results suggest that AR inherited *JPH2* variants are

associated with typically early onset, severe DCM, and carry a high risk of conduction disease. Moreover, absence of a cardiovascular phenotype in biological parents suggests that heterozygous loss-of-function variants maybe tolerated physiologically, while two loss-of-function alleles, akin to a genetic "knockout", leads to severe disease. In the case of one family with heterozygous G85K variants and highly penetrant DCM, haploinsufficiency may drive comparatively milder disease.

Autosomal dominant variants in JPH2 are associated with HCM through a likely dominant-negative mechanism

We identified 16 probands from 16 unrelated families with *JPH2* variants associated with HCM published in 6 studies. These include 11 male patients, 3 female patients, and 2 patients whose sex is unknown ($X^2 = 4.6$, p = 0.03, n = 14). The average age at diagnosis of HCM probands was 29.9 +/− 23.6 years (n = 14, range = 0.41 – 86 years). All probands were alive at the time of study. In contrast to most of the DCM patients, where homozygous variants caused severe disease while heterozygous variants elicited mild to no cardiac phenotype, all probands with HCM hosted heterozygous variants. Family history was either autosomal dominant or presumed *de novo* if disease segregated in a family without genetic testing of both parents. This points towards a dominant negative mechanism of disease where expression of the mutant allele impacts the expression and/or function of the wildtype allele.

Autosomal dominant variants in JPH2 are associated with arrhythmia and sudden death

Four probands from 4 families in 4 independent studies hosting *JPH2* variants demonstrated an exclusively arrhythmic phenotype in the absence of cardiomyopathic disease. Two patients died of sudden cardiac arrest, one patient had atrial fibrillation, while one patient presented with drug-induced QT prolongation and *torsade de pointes* precipitated by quinidine with normal baseline QT interval. The average of diagnosis of probands was 39.7 +/− 24.0 years (n = 3, range = 22 – 67 years). Two probands were deceased, including a 22-year-old male with heterozygous A189T who died of sudden cardiac arrest without a previous diagnosis of cardiac disease; however, bilateral atrial dilation was found on autopsy suggesting a cardiomyopathic process with poor diastolic function such as HCM or restrictive cardiomyopathy. In addition, a 30-year-old female with a heterozygous E338G variant also died of sudden cardiac arrest without prior diagnosis of cardiac disease. This patient was found to have adipose deposition in the right ventricle on autopsy; however, no overt diagnosis of arrhythmogenic right ventricular cardiomyopathy was mentioned. Aside from these exceptions, all other probands had no overt evidence of cardiomyopathy, and all had heterozygous variants. Similar to HCM cases, this suggests that autosomal dominant heterozygous *JPH2* variants can cause both cardiomyopathy and isolated arrhythmia. Beyond the arrhythmia/SCD probands, four patients with HCM-associated T161K variants that had arrhythmia but no HCM were relatively young at diagnosis (16 and 19-years-old). This suggests that in some patients, the development of arrhythmia predisposition may precede cardiomyopathy development; however, additional patients are required to further evaluate the natural history of *JPH2*-associated arrhythmia and cardiomyopathy.

JPH2 variants are associated with nodal and conduction dysfunction in addition to cardiomyopathy

There was a high burden of AV nodal and conduction disease among *JPH2* variant-positive probands. We identified 9 probands from 9 families with *JPH2* variants published in 6 studies with evidence of concomitant nodal or conduction dysfunction. This was in the context of comorbid HCM or DCM. These included 7/16 (43.8%) of probands diagnosed with HCM and 2/4 (50%) of probands diagnosed with DCM. Eight of these patients hosted heterozygous *JPH2* variants, while the remaining patient was homozygous. Nodal and conduction defects represented included RBBB, (1 patient), LAFB (2 patients), LBBB (1 patient), 1st degree AVB/PR prolongation (3 patients), 3rd degree AVB (1 patient), SA nodal disease (1 patient), and unspecified conduction defect (2 patients). One patient received a pacemaker, two received ICD, and one received combination pacemaker/ICD. None were diagnosed with isolated conduction defects, and all were in the context of co-morbid cardiomyopathy.

Divergent modes of inheritance are associated with divergent clinical phenotypes

Although our statistical analysis is limited by low power due to the small case numbers reported in the literature, initial statistical analysis suggest association between the mode of inheritance and clinical manifestations of disease. First, autosomal recessive *JPH2*-mediated DCM has higher mortality than autosomal dominant *JPH2*-mediated HCM. Transplant-free survival was significantly worse in probands with DCM than probands with HCM (Fisher Exact; $p = 0.004$). There was no significant difference between age of diagnosis between HCM, DCM and arrhythmia/SCD probands (one-way ANOVA; $p = 0.4$); however, the age at diagnosis of homozygous probands was significantly lower than heterozygous probands (one-way T-test; $p = 0.01$). There was no significant difference in age at diagnosis between the male and female probands (one-way T-test; $p = 0.3$). There was no significant difference between age at death or transplant between HCM, DCM, and arrhythmia/SCD patients (one-way ANOVA; $p = 0.4$). However, there was a younger age at death or transplant in homozygous compared to heterozygous patients (one-way T-test; $p = 0.005$). Interestingly, there was no difference in concomitant arrhythmia burden between patients with HCM and DCM (Fisher Exact; $p = 1$). There was no significant difference in the number of patients with HCM or DCM who received ICD, PM, or both. (Figure 3)

Variant location and disease phenotype

The localization of *JPH2* variants and their associated disease appear to loosely cluster around key functional domains of the protein (Figure 4). Notably, six of the eight HCM associated variants (P55A, S101R, Y141H, T161K, S165F, E169K) fall within the first six MORN motifs and linker region. All variants fall within the Nterminal domain following calpain cleavage. It is possible that even heterozygous dysfunction of such an important functional domain could create a dominant negative effect underlying the adaptive remodeling seen in HCM through impact on the ability of the Nterminal domain to trigger a stress response within the cell. In contrast, DCM variants, except for the heterozygous G85K variant, fall outside of the MORN motifs and are predicted loss-of-function. Given that heterozygous family members of DCM patients with homozygous variants are unaffected,

heterozygous variants in less critical functional domains may not cause a dominant negative effect. The heterozygous variants associated with arrhythmia also fall outside of the MORN motifs and affect the linker and alpha-helical domains, suggesting that heterozygous variants in these regions may be sufficient to alter Ca^{2+}-handling, but not cause significant structural remodeling (Figure 5).

Bias assessment and certainty of evidence

The Joanna Briggs Institute critical appraisal tool validated that all studies achieved sufficient quality for inclusion as assessed by two independent reviewers. Agreement between reviewers was 100%. The greatest source of bias arises surrounds variant classification, which is affected by the genetic testing modality used, availability of family genetic testing to clarify mode of inheritance and penetrance, and presence of concomitant variants in other cardiomyopathy-associated genes. Further, there were some studies that did not include information about age at diagnosis or concomitant arrhythmias, and this missing data could confound analysis.

Discussion

Proposed paradigm of JPH2-associated cardiomyopathy and arrhythmia

Our systematic review of patients with *JPH2*-associated cardiac pathology suggest a spectrum of disease presentation and severity that is influenced by mode of inheritance and variant location. Patients with autosomal dominant, heterozygous variants developed HCM (76%) and arrhythmia/SCD (24%). Patients with homozygous/compound heterozygous loss-of-function variants developed DCM and early onset heart failure. For the former, the majority of studies to date have identified heterozygous variants which were associated with the development of HCM which can occur at any age, including late adulthood. For the latter, DCM-associated loss of function variants appear to cause disease when there are biallelic variants, and predominantly cause DCM and early mortality in infancy and early childhood. This may be is akin to a genetic 'knockout' mechanism of genetic disease. Importantly, the published *JPH2*-associated DCM cases report that the clinical phenotype is that of true DCM, rather than burned-out HCM. While the numbers of individuals reported are small, all loss-of-function variants, when found heterozygously (*i.e.*, the parents of homozygous patients with DCM), do not seem to be sufficient to cause cardiac disease. Thus, heterozygous variants associated with AD HCM or arrhythmia are likely to have a dominant negative effect. In addition to these, the relatively high burden of concomitant arrhythmias, and separately AV nodal disease and conduction abnormalities, on both the DCM and HCM patients points towards the role of *JPH2* in E-C coupling and how dysregulation of Ca^{2+}-handling can predispose cardiac remodeling. This suggests that *JPH2* variants may be associated with four disease states with overlapping clinical phenotypes.

In support of the possibility that *JPH2* variants cause disease through two distinct mechanisms, there is some suggestion that variant localization may play a role in altering the divergent functional roles of JPH2. HCM-associated *JPH2* variants tend to affect the N-terminal MORN motifs, while DCM and arrhythmia-associated variants tend to fall outside of this region. This suggests heterozygous perturbation of the N-terminal transcription

factor and MORN motifs is sufficient to perturb the cardiac stress response and accelerate cardiac hypertrophy, in a dominant negative effect. In contrast, homozygous loss of function variants or haploinsufficiency causes severe, early onset DCM suggesting the existence of a *JPH2*-knockout syndrome. This association between homozygous *JPH2* variants and DCM is supported by independent *in vivo* studies of *JPH2*. For example, *JPH2*-knockout mice are embryonic lethal by day 10.5 with disorganized junctional membrane complexes and altered Ca^{2+} transients.[17] Knockdown of *JPH2* in is associated with accelerated pressure-induced atrial dysfunction and heart failure.[18] Similarly, overexpression of *JPH2* can rescue the heart failure phenotype.[18] These *in vivo* studies support that loss of *JPH2* function, whether by knockdown or genetic defect, is sufficient to cause adverse cardiac remodeling and subsequent heart failure.[7] In addition, one study found that in mice with HCM or DCM without *JPH2* variants, *JPH2* expression was downregulated relative to unaffected hearts, suggesting JPH2 is perturbed in the pathogenesis of non-*JPH2* associated cardiomyopathy.[19] Importantly, only 25% of commercial gene panel tests for DCM include *JPH2*, and it is possible that some cases of DCM considered gene-negative may be mediated by undiscovered *JPH2* variants.[8]

Finally, the role of *JPH2* variants in arrhythmia, SCD, and conduction dysfunction is emerging. The role of *JPH2* at the inter-section of cardiac remodeling and electrical dysfunction is supported by existing *in vitro* studies and mouse models. In a model of the HCM and AF-associated E169K variant, pseudo-knockin mice subjected to atrial burst pacing recapitulated the atrial fibrillation observed in human patients.[20] Moreover, evidence of dysfunctional RyR2 stabilization as a direct result of the *JPH2* variant is thought to contribute to both electrical dysfunction and cardiac remodeling.[20] Many of the arrhythmia/SCD patients described in the literature were relatively young at the time of assessment, and it is unclear whether these patients will go on to develop adverse cardiac remodeling in the future. Given evidence that *JPH2* is downregulated in a canine model of premature ventricular contraction-induced cardiomyopathy, it is possible that arrhythmia directly precipitates development of cardiomyopathy.[21] Finally, studies described conduction and nodal dysfunction in patients with concomitant HCM or DCM; however, there were no reports of patients with isolated conduction dysfunction. It is possible that conduction dysfunction may be a common but under-reported consequence of *JPH2* variants. Further clinical studies and animal models are needed to evaluate this hypothesis.

Limitations and future directions

JPH2 variants associated with cardiac disease are rare, and there are only 62 total variant-positive individuals and 25 probands discussed in the literature to date. While meta-analysis provides evidence that homozygous *JPH2* variants are associated with early on-set DCM and younger age at death, and heterozygous variants are associated with HCM, additional patients are still needed to provide conclusive evidence for this association. Further, relying on published studies introduces reporting bias – those patients and families discussed in case reports and series are more likely to be severely impacted, and less penetrant variants may not be adequately represented. Finally, some variants were predicted benign via *in silico* pathogenicity modeling; however, were nevertheless associated with disease. While

this systematic review provides a novel framework to consider the phenotypic consequences of homozygous and heterozygous *JPH2* variants, additional *JPH2*-positive cases will help to clarify these associations and establish better genotype-phenotype correlations. In particular, the role of *JPH2* in conduction disease remains poorly understood, and further studies are needed to understand the difference between genetic predisposition to conduction disease versus age-related conduction defects.

Additional functional studies are needed to better understand the mechanisms of how variants in *JPH2* drive divergent disease presentation, including the potential role of nonsense mediated decay in patients with loss-of-funciton variants and dilated cardiomyopathy.

Conclusion

In conclusion, current evidence suggests autosomal recessive loss-of-function variants in *JPH2* are associated with early onset, severe DCM, while autosomal dominant pathologic variants are associated with HCM through a dominant negative effect. There is emerging evidence that *JPH2* variants carry a predisposition to arrhythmogenesis and conduction disease. As *JPH2* is incorporated into cardiomyopathy panels, developing better tools to distinguish between pathogenic and non-pathogenic is critical to cascade family screening and development of novel therapeutic targets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations:

AD	autosomal dominant
AR	autosomal recessive
AVB	atrioventricular block
CICR	calcium-induced calcium release
DCM	dilated cardiomyopathy
E-C	excitation-contraction coupling
HCM	hypertrophic cardiomyopathy
ICD	implantable cardiac defibrillator
LAFB	left anterior fascicular block

| LBBB | left bundle branch block |
MORN	membrane occupation recognition motif
PVC	premature ventricular contraction
RBBB	right bundle branch block
SCD	sudden cardiac death
SA	sinoatrial
SR	sarcoplasmic reticulum.

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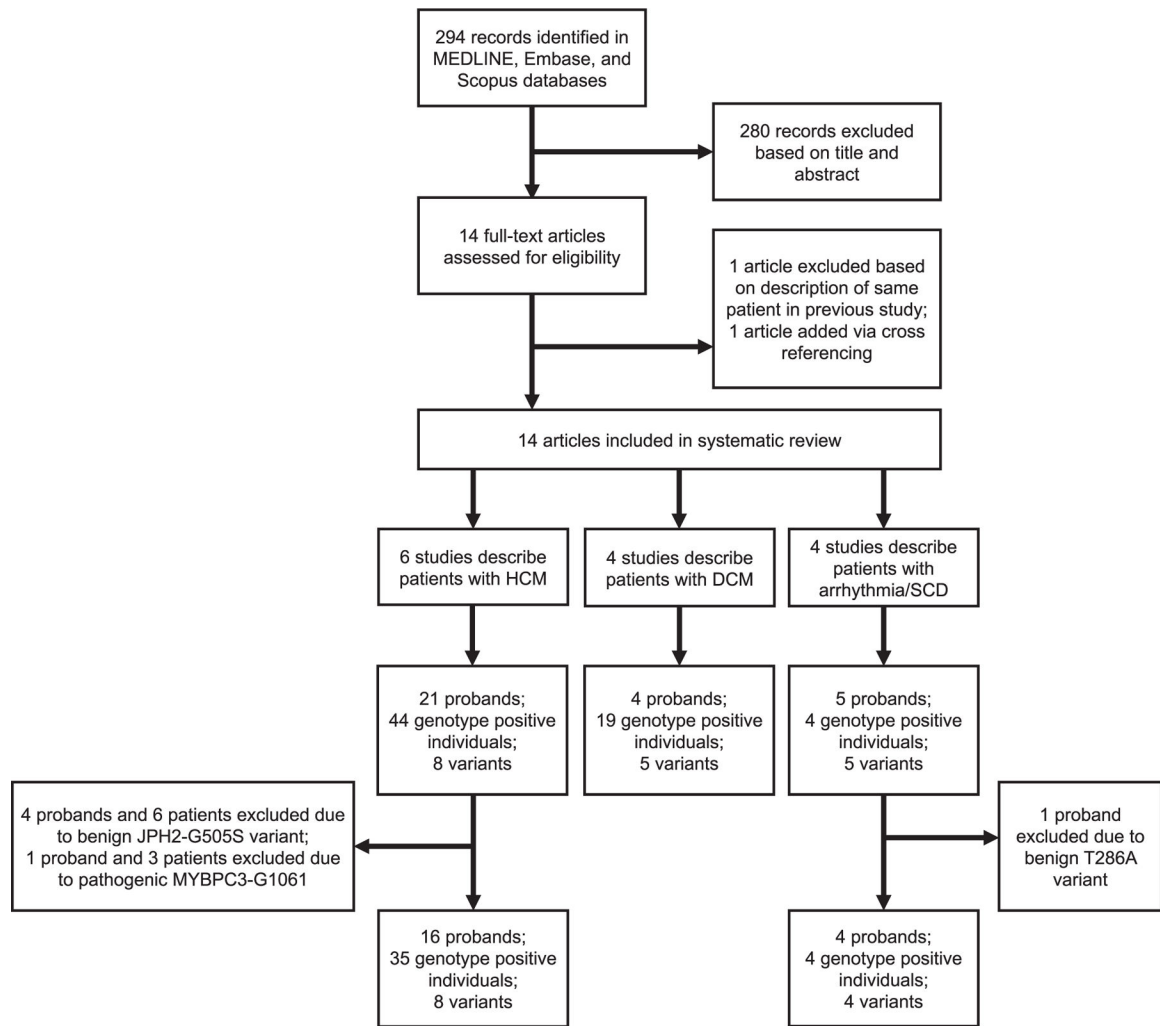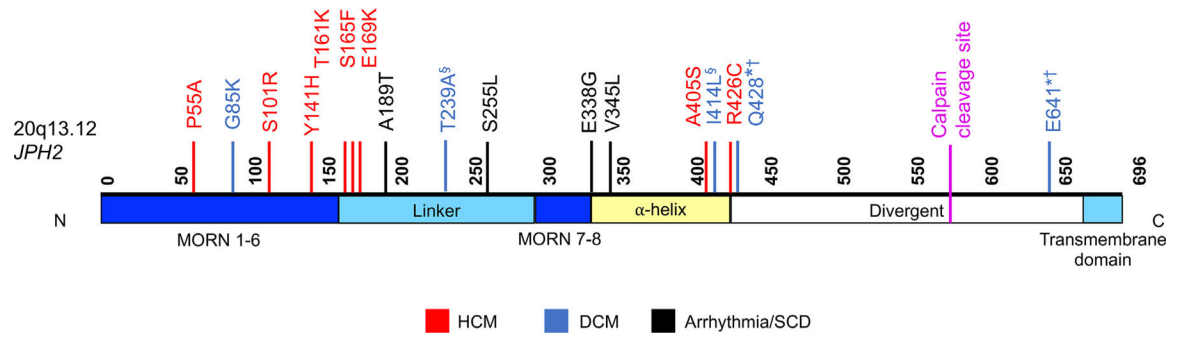
Fig. 1.
Identification of studies included in the review of cardiac manifestations of *JPH2* variants.
HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; SCD, sudden cardiac
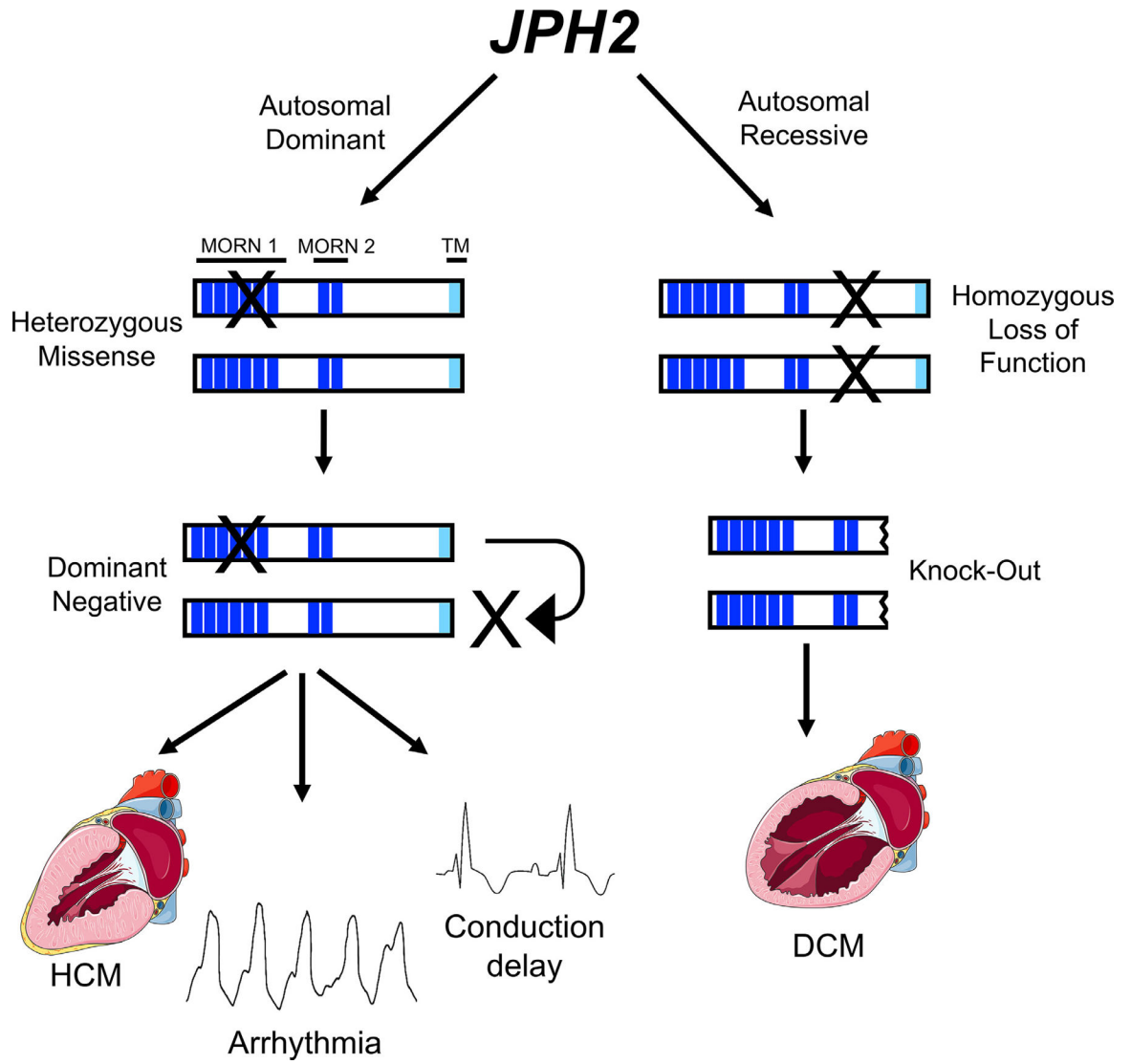death.
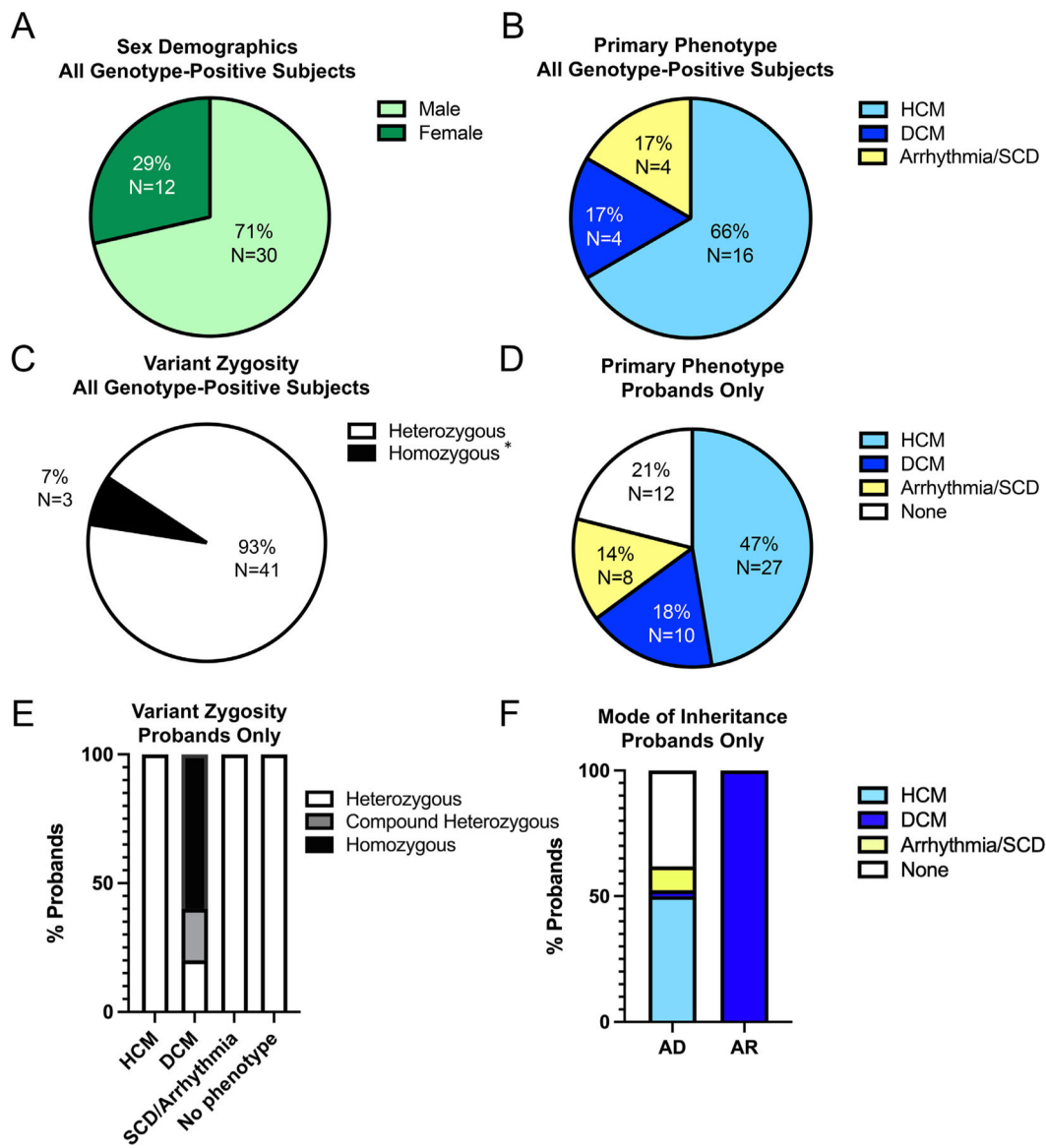
Fig. 2.
Descriptive statistics of genotype positive subjects, including sex (A), cardiac phenotypes (B), and variant zygosity (C). Descriptive statistics of probands, including cardiac phenotype (D), variant zygosity among probands with different cardiac phenotypes (E), and cardiac phenotypes among probands with AR and AD modes of inheritance. AD, autosomal dominant; AR, autosomal recessive, HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; SCD, sudden cardiac death. * - Homozygous includes compound heterozygous.
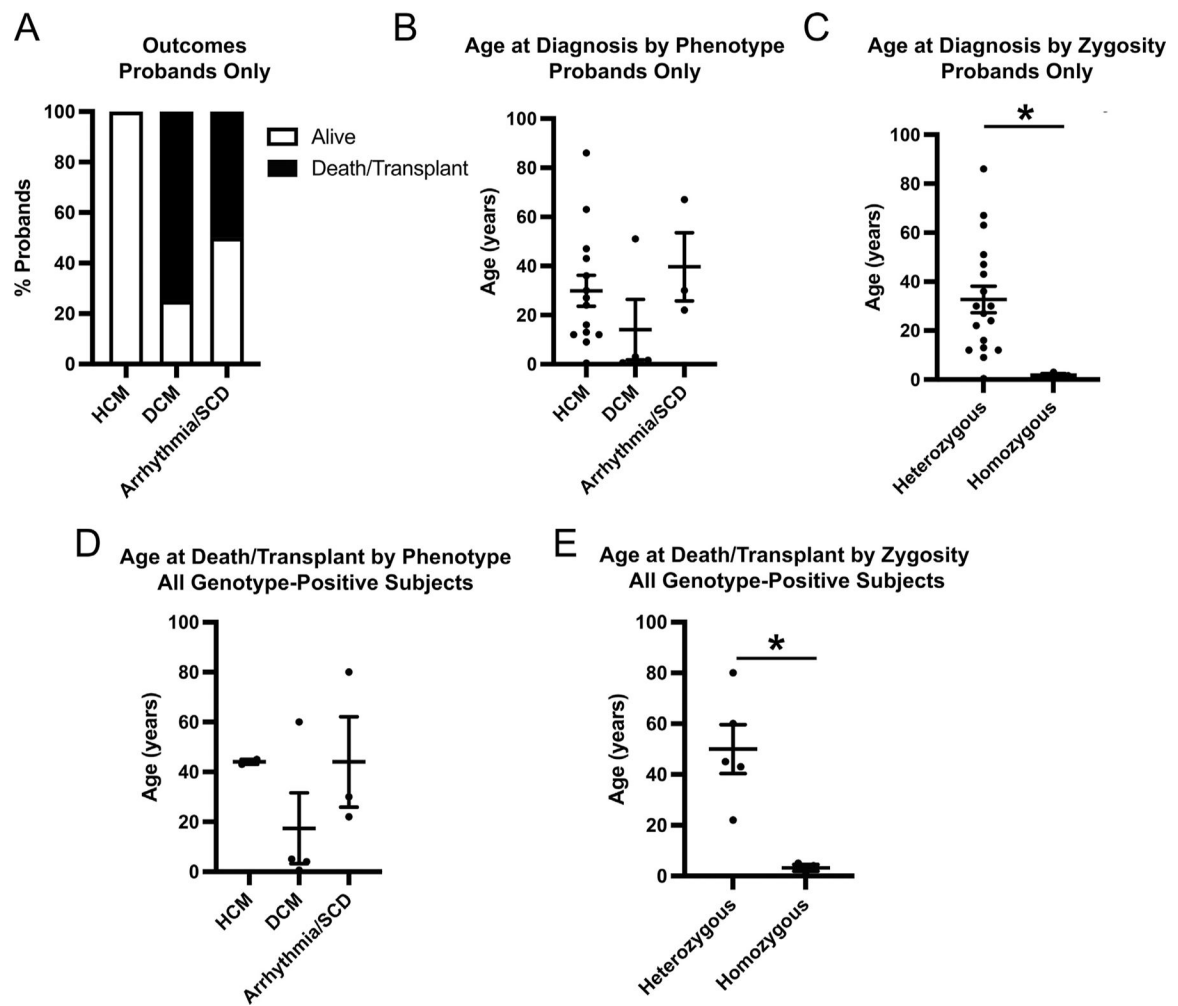
Fig. 3.
Association between proband cardiac phenotype and major outcomes such as death or transplant (A) and age at diagnosis (B). Association between proband variant zygosity and age at diagnosis (C) (p = 0.01, Fisher Exact). Association between age at death or transplant among all genotype positive patients and cardiac phenotype (D) and zygosity (E) (p = 0.005, Fisher Exact). HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; SCD, sudden cardiac death.

Fig. 4.

Protein map of *JPH2* functional domains and disease-causing variants described in published studies. § - Variants were inherited in a compound heterozygous fashion; † - Variants were homozygous. HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; SCD, sudden cardiac death.

Fig. 5.
Flowchart demonstrating how differential modes of inheritance of *JPH2* variants lead to different cardiac phenotypes. AR, loss-of-function variants lead to severe, early onset DCM, often resulting in death or heart transplant. AD, missense variants lead to a wider range of cardiac phenotypes, including HCM, arrhythmia, and conduction delay. We hypothesize that AD variants cause disease via a dominant negative mechanism. This figure was created using images modified from Servier Medical Art Commons, licensed under a Creative Commons Attribution 3.0 Unported License (http://smart.servier.com). HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; SCD, sudden cardiac death.

Table 1.

Characteristics of studies that met inclusion criteria for systematic review. DCM, dilated cardiomyopathy; ES, exome sequencing; F, female; HCM, hypertrophic cardiomyopathy; M, male; U, unknown; VUS, variant of uncertain significance.

StudyName	Year	Study Type	Type of Genetic Testing (# total patients)	# JPH2 positive patients	# alive/# dead	Phenotype	Variant(s) described/ ACMG classification/ gnomAD allele frequency	Patient ancestry	Zygosity	Functional Characterization?	Ref.
Landstrom et. al.	2007	Case series	Targeted sequencing (3)	2M/1F	3/0	HCM	S101R/VUS/0 Y141H/VUS/8.72e-6 S165F/VUS/0	Caucasian Caucasian Caucasian	Heterozygous	Yes – all damaging *in vitro*	[17]
Matsushita et. al.	2007	Case series	Targeted (8)	4M/2F/2U	8/0	HCM	G505S /LB/1.04e-2 R426C /VUS/0	Japanese Japanese	Heterozygous	No	[22]
Beavers et. al.	2013	Case report	Targeted sequencing (2)	2M/0F	2/0	HCM	E169K/VUS/0	Unknown	Heterozygous	Yes - damaging *in vivo*	[20]
Ramirez et. al.	2013	Case series	Panel (2)	1M/1F	2/0	Drug-induced torsades de pointes	V345L/VUS/5.67e-5 T286A/LB/1.12e-3	Caucasian Caucasian	Heterozygous	No	[23]
Narula et. al.	2015	Case series	ES (1)	1M/0F	0/1	SCD	A189T/VUS/8.00e-4	Caucasian	Heterozygous	No	[24]
Sabater-Molina et. al.	2016	Case series	Panel (1), targeted (8)	9M/0F	9/0	DCM	G85K/LP/0	Unknown	Heterozygous	No	[25]
Quick et. al.	2017	Case report	Targeted sequencing (1)	1M/0F	1/0	HCM	A405S/VUS/1.78e-5	Caucasian	Heterozygous	Yes - damaging *in vivo*	[26]
Vasilescu et. al.	2018	Case series	Panel (1)	0M/1F	1/0	HCM	Q428* /VUS/0	Finland	Homozygous	No	[27]
Vanninen et. al.	2018	Case series	Targeted (28)	18M/10F	25/3	HCM	T161K/LP/0	Finland	Heterozygous	No	[28]
Doñate Puertas et. al.	2018	Case series	Panel (1)	0M/0F/1U	1/0	Atrial fibrillation	S255L/VUS/0		Heterozygous	No	[29]
Jones et. al.	2019	Case series	ES (56)	4M/2F	5/1	DCM	E614* /VUS/0	Iranian	Homozygous (1), heterozygous (5)	No	[30]
De Bruijn et. al.	2019	Case report	Panel (1)	1M/0F	1/0	HCM	P55A/VUS/0	Unknown	Heterozygous	No	[31]
Miura et. al.	2020	Case report	ES (1)	0M/1F	0/1	DCM	T239A/I414L/VUS/0	Japanese	Compound Heterozygous	No	[32]