Review Article

Genetic Cardiomyopathies: An Overview of the Main Associated Pathogenic Mutations

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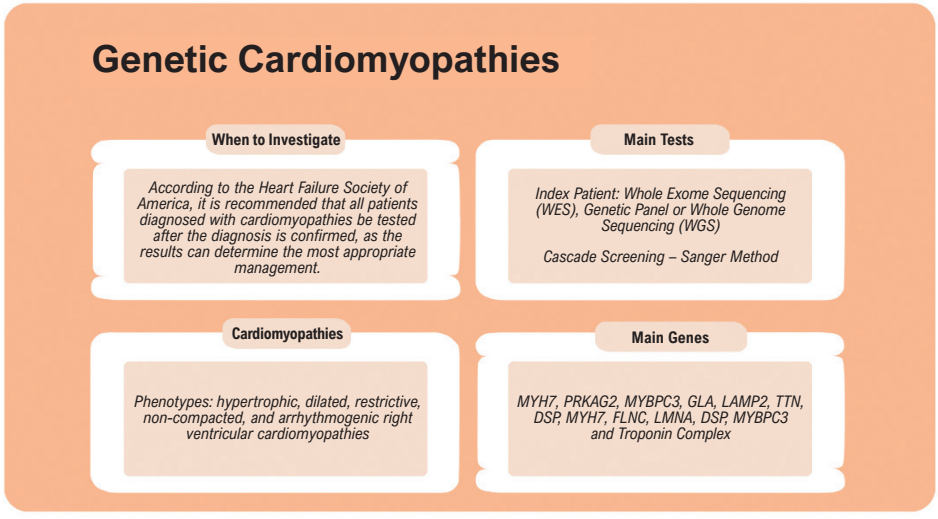
Central Illustration: Genetic Cardiomyopathies: An Overview of the Main Associated Pathogenic Mutations



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Abstract

Cardiomyopathies are pathological conditions associated with progressive dysfunction of cardiomyocytes, excluding situations in which other concomitant diseases may justify such progression. Their presentations can evolve with several phenotypes, the main ones being hypertrophic, dilated, restrictive, non-compacted, and arrhythmogenic phenotypes of the right ventricle (Table 1).

Regarding this topic's relevance, dilated and hypertrophic cardiomyopathies have a genetic origin in 30 to 50% of cases, evaluating these etiologies is a crucial tool in patient management. Assessing the risk of genetic transmission and the likelihood of phenotypic manifestation across generations requires identifying and classifying each gene's inheritance pattern and mutation type associated with structural cardiomyopathy. Additionally, determining the structural protein affected facilitates understanding the pathophysiological phenomenon and the phenotype manifested by the variant carrier.

Considering the growing advent of the genetic approach to cardiomyopathies, the Heart Failure Society of America, in collaboration with the American College of Medical Genetics and Genomics, developed a guide for the investigation and follow-up of these cases. However, in this study, the time to request the genetic tests was not evaluated. It is recommended that the tests be requested at any time after diagnosis confirmation since their results can contribute to guiding the most appropriate follow-up approach.

Despite the multitude of existing variants related to genetic cardiomyopathies, some are of greater clinical interest due to their impact on risk stratification and interest in family screening, namely: MYH7, PRKAG2, MYBPC3, GLA, LAMP2, TTN, DSP, MYH7, FLNC, LMNA, DSP, MYBPC3 and Troponin Complex (Table 2).

Keywords

Cardiomyopathies; Dilated Cardiomyopathy; Hypertrophic Cardiomyopathy

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Recognizing the main mutations associated with cardiomyopathies and the phenotypes related to them enables a more individualized medicine approach with early interventions and risk stratification. Genetic evaluation is essential for screening family members and optimizing patient management, which may vary depending on the identified mutation.

Introduction

Cardiomyopathies are pathological conditions associated with progressive cardiomyocyte dysfunction, in the absence of other diseases that justify the condition, such as coronary artery disease, hypertension, valve diseases, or congenital malformations. Cardiomyopathies can trigger multiple phenotypes, according to their etiology, the main ones hypertrophic, dilated, restrictive, non-compacted, and arrhythmogenic right ventricular cardiomyopathies. Thirty to fifty percent of dilated and hypertrophic cardiomyopathies are of genetic origin.[1]

From a classification point of view, these cardiomyopathies can follow autosomal dominant, recessive, or X-linked inheritance patterns and may involve single or multiple variants. These variants can lead to abnormal protein incorporation or nucleotide deletions, insertions, or substitutions, affecting the function of sarcomeric proteins, the Z disc, or intracellular calcium modulators.

According to the Heart Failure Society of America, genetic testing is recommended at any time after the diagnosis of cardiomyopathy, with a systematic approach, assessing family history, phenotype, and screening of relatives at risk.[2] Therefore, the aim is to confirm the diagnosis, request the most appropriate genetic test (Whole Exome Sequencing (WES), Genetic Panel, or Whole Genome Sequencing (WGS)), and classify the variant based on the criteria proposed by the American College of Medical Genetics and Genomics (ACMG).[3]

According to the American College of Cardiology's guidelines, in the case of a positive result – pathogenic variant, possibly pathogenic – cascade screening should be conducted,[4] through the study of co-segregation and genetic screening of family members using the Sanger Method.[5]

Methods

This systematic review was conducted using a comprehensive search in major scientific databases, including PubMed and OMIM (Online Mendelian Inheritance in Man), to identify relevant articles on the topic.

PubMed search was performed using combinations of keywords related to the topic, using Boolean operators ("AND", "OR", "NOT") to refine the results. The selected keywords were "cardiomyopathy", "hypertrophic", "dilated", "genetic" and the gene in question. The OMIM search was conducted using the identification numbers (MIM) and keywords associated with the diseases or syndromes of interest. The OMIM database was consulted to ensure complete coverage of genetic diseases and their respective clinical manifestations.

Articles published in English or Portuguese, addressing changes associated with the mutation were included, with an emphasis on case reports, and clinical, genetic, and molecular studies associated with cardiomyopathy.

Once searches were completed, the articles were selected based on their titles and abstracts. The articles that met the inclusion criteria were analyzed in full to verify the quality and relevance of the information. The data synthesis was performed qualitatively, summarizing the main findings of each study.

A key limitation of this study was its reliance on publications in English and Portuguese, potentially excluding relevant studies in other languages.

ALPK3

The ALPK3 gene is responsible for encoding an alpha-protein kinase, a protein responsible for cardiomyocyte differentiation, acting as a regulator of cardiac transcription factors. Loss-of-function variants in this gene are related to the early development of hypertrophic cardiomyopathy.[6] Studies have shown that homozygous variants lead to the development of dilated cardiomyopathy (DCM) in childhood with subsequent progression to the hypertrophic phenotype.[7] Despite its typically recessive nature, it has been shown that heterozygous variants in ALPK3 are also associated with the development of the disease, with cases showing late-onset hypertrophic cardiomyopathy.[8]

Syndromic presentations are possible, with the association of musculoskeletal alterations such as facial dysmorphisms, skeletal abnormalities, and *pectus excavatum*. The development of the phenotype can occur from childhood to the fourth decade of life with gradual progression of the disease.[9]

BAG3

BCL2-associated Athanogene 3 (BAG3) is part of a family of proteins that regulate chaperones of the Hsp70 family, assisting in the folding and transport of other proteins.[10] Thus, the impacts of BAG3 variants are related to changes in its expression, considering that its expressivity is high in normal cardiac tissue.[11]

Among the pathological associations of this gene's variants, DCM was correlated with an autosomal dominant inheritance, in which variations in the number of copies and deletions in affected limbs were identified.[12] Regarding the manifestations in the assessed probands, results varied. The age at diagnosis of DCM was 21 to 64 years and severity was high in approximately half of the patients (need for transplant or severe heart failure (HF)), while in others the disease was minimal or absent.[12]

One of the theories for the pathophysiology of diseases caused by BAG3 variants is a binding impairment between proteins essential for the integrity and functionality of cells, such as Bcl-2, which inhibits cell death by apoptosis. Another theory is that binding between BAG3 and Hsc70 would be necessary to maintain cardiac myofibrillar integrity during cardiac contractile activity.[13]

Troponin complex

The troponin complex is composed of three subunits (TnC, TnI, and TnT) that, together with calcium, mediate muscle contraction. Changes in genes related to this complex are associated with the development of hypertrophic, restrictive, and DCM. The pathophysiological mechanism is related to changes in calcium sensitivity in the process of muscle contraction and relaxation.[14]

Mutations in troponin C (TNNC1) are associated with the development of dilated and hypertrophic cardiomyopathy.[15] In turn, troponin T (TNNT2) variants are associated with dilated, restrictive, and familial hypertrophic cardiomyopathy, and left ventricular non-compaction.[16] Finally, troponin I (TNNI3) alterations are associated with the development of dilated, familial restrictive, and hypertrophic cardiomyopathies.[17]

DSP

Desmosomes are the most common intracellular junctions in vertebrate epithelial cells and are essential for tissue strength and resilience during traction. Among the proteins in this system, desmoplakin functions as a force transducer between cardiac desmosomes and intermediate filaments.[18]

Cardiomyopathies associated with DSP variants include arrhythmogenic right ventricular cardiomyopathy (ARVC), an autosomal dominant condition, and DCM, which can follow either an autosomal dominant or recessive inheritance pattern. Depending on the specific variant, the latter may also present as a syndrome with capillary, dermal, and dental abnormalities.[19]

ARVC is characterized by progressive myocardial degeneration, followed by fibrofatty tissue deposition. The clinical presentation usually includes arrhythmias originating in the right ventricle, which can progress to ventricular tachycardia and fibrillation and, in more extreme cases, even cause sudden death.[20]

In variants related to DCM, the desmoplakin gene can cause capillary changes, palmoplantar epidermis changes, as well as dilation of the left ventricle (LV) associated with HF and early morbidity.[21]

FLNC

Filamin C is a FLNC-encoded protein, responsible for cross-linking actin filaments, which are essential for cardiac muscle contraction.[22] FLNC gene variants correlate with myopathies and cardiomyopathies with varied phenotypes, including hypertrophic, dilated, restrictive, and arrhythmogenic dysplasia of the right ventricle, all with autosomal dominant inheritance.[22]

In familial DCM, although the mechanism remains unclear, haploinsufficiency and reduced filamin C levels are believed to contribute to disease development. This would occur due to impaired stability and fixation of cardiomyocytes, deficiency in sarcomeres organization, and the formation of Z discs.[23]

Among the hypertrophic cardiomyopathies associated with filamin C variants, despite the similar phenotype, the manifestations and prognosis are distinct depending on the mutation. The missense variant p.A1539T, for example, was correlated with sarcomeric disorder and aggregates. In the family analyzed here, an early manifestation of ventricular hypertrophy and a history of sudden death in a first-degree relative were identified.[24]

GLA

The GLA gene is present on the X chromosome and encodes the enzyme alpha-galactosidase, a lysosomal hydrolase. Variants in this gene lead to reduced production of this enzyme, resulting in Fabry disease, infiltrative cardiomyopathy that causes myocardial wall thickening due to the accumulation of globotriaosylceramide.[25]

Fabry disease typically presents two phenotypes - classical and non-classical - affecting both sexes. However, the condition onset is earlier in men, who also experience more neurological and renal manifestations. Women, on the other hand, have more cardiovascular manifestations, with later onset.[26] Other disease manifestations include typical skin lesions (angiokeratomas), acroparesthesias, corneal opacity, and recurrent febrile episodes.

The typical cardiological picture is the development of left ventricular hypertrophy, in addition to valvular heart disease, systolic or diastolic dysfunction and defects in the conduction system.[27] Left ventricular hypertrophy is present in both forms of Fabry disease, but the left ventricular mass index is higher in the classic presentation.[28] In addition, hypertrophy is commonly concentric, but may also present an apical, septal, and eccentric pattern.[25]

In such cases, the treatment of choice is enzyme replacement therapy,[25] with genetic diagnosis being essential for the management of these patients.

LAMP2

Lysosome-associated Membrane Protein 2 (LAMP2) is one of the main glycoprotein components of the lysosomal membrane. LAMP2 variants play a role in organelle integrity and are commonly associated with Danon disease, which disrupts glycogen storage, leading to neurological, hepatic, cardiac, and skeletal muscle manifestations.[29] As an X-linked disorder, Danon disease primarily affects males, accounting for 1-3% of primary cardiac hypertrophies in adolescents and young men.[30]

The cardiomyopathy presented in Danon Disease is characterized by marked cardiac hypertrophy, conduction system abnormalities, and ventricular arrhythmias. During the analysis of the LAMP2 variant's impact on cardiomyocyte function, Alcalai et al.[30] concluded that autophagic impairment interferes with calcium homeostasis, metabolic pathways, and cell survival. Such modifications contribute to the hypertrophy and cardiac electrical abnormalities of this condition.

LMNA

The LMNA gene encodes lamin A and lamin C, which are intermediate filaments forming the nuclear lamina. This structure lines the inner nuclear membrane, determining the size and shape of cell nuclei. Alterations in this gene are associated with DCM, as well as other diseases such

as Charcot-Marie-Tooth, Emery-Dreifuss dystrophy, Holt-Oram syndrome, Malouf syndrome, and Hutchinson-Gilford syndrome.[31] LMNA variants are the second most common genetic cause of nonsyndromic DCM, with a 5% to 13% incidence of idiopathic dilated cardiomyopathies.[32] Studies demonstrate a penetrance of 90 to 95% up to the seventh decade of life, without a genotype-phenotype correlation.[33]

DCM follows an autosomal dominant inheritance pattern and is characterized by left ventricular dilation and/or reduced systolic function, typically manifesting in young adults. Cardiomyopathy is commonly preceded or accompanied by a defect in the electrical conduction system and arrhythmias,[33] which may manifest years or even a decade before other cardiac changes. The most common conduction alterations are symptomatic bradyarrhythmias; supraventricular arrhythmias such as atrial flutter, atrial fibrillation, tachycardia-bradycardia syndrome; and ventricular arrhythmias, which may even lead to sudden death.[33]

Targeted therapies against the MAP kinase protein are still under investigation but have potential as a treatment option for dilated cardiomyopathies caused by LMNA variants.[34]

MYBPC3

Myosin-binding protein C (MYBPC3) is located in the A bands of the myocardial sarcomere, where it connects to the myosin-heavy chain and titin to fulfill its function. Although it does not directly participate in cardiac muscle contraction, MYBPC3 plays a fundamental role in modulating contraction speed in response to adrenergic stimulation.[35]

The phenotype most correlated with MYBPC3 variants is Hypertrophic Cardiomyopathy (HCM), with this protein being associated with 15% of familial cases of HCM.[36] This phenotype has multiple variants, autosomal dominant and recessive inheritance, and heterogeneous clinical presentations. Among the families studied, 58% of adults over 50 years of age presented cardiac hypertrophy. Penetrance remained incomplete until age 60.[36] Furthermore, it is worth noting that the overall survival of MYBPC3 variant carriers with hypertrophic cardiomyopathy was higher when compared to other sarcomeric protein mutations.[35]

Although MYBPC3 variants have a more frequent correlation with HCM, some studies have identified DCM phenotypes and isolated left ventricular noncompaction associated with alterations in this same gene. However, regarding the investigated DCM phenotypes, the presence of confounding factors made some analyses inconclusive. This was the case of the publications by Konno et al[37] and Shimizu et al.,[38] who were not able to prove the association of the presented variant with the DCM condition, due to the impossibility of ruling out a progression of Hypertrophic Cardiomyopathy.

Thus, the strongest established correlation currently links MYBPC3 variants to hypertrophic cardiomyopathy,[36] a frequent cause of familial cases. This association enables improved screening strategies based on the index case.

MYH7

The MH7 gene is responsible for encoding the myosin-heavy chain in skeletal muscles, being expressed mainly in the cardiac ventricles and slow-twitch fibers. By causing an alteration in the sarcomeres, the contractile function of the muscle becomes impaired. In this sense, variants in this gene are related to cardiomyopathies and myopathies. Among the cardiomyopathies, the associated phenotypes are dilated, hypertrophic, restrictive, non-compacted LV, and other variations of congenital cardiomyopathies with predominantly autosomal dominant inheritance.[39]

Regarding hypertrophic cardiomyopathy, studies show that alterations in this gene are present in 10% to 30% of cases,[40,41] with a predominance of missense variants. Moreover, it is possible to establish a genotype-phenotype relationship depending on the affected functional domain. MYH7 variants are strongly associated with systolic dysfunction and worse prognosis,[26] particularly for alterations in the conversion domains.[42]

Compound variants (those with more than one mutated allele) are associated with the development of more complex conditions and worse prognoses.[43] Given this scenario, studies indicate that the presence of multiple genetic alterations has a cumulative effect, leading to earlier disease onset, a higher risk of sudden death, and increased severity.[43]

Variants in MYH7 are associated with diverse phenotypic presentations, with coexisting mutations further increasing case complexity.

Noonan-RASopathies

RASopathies are a group of syndromes with similar clinical presentations resulting from the same pathogenesis. This group of diseases presents alterations in genes of the Ras/MAPK (mitogen-activated protein kinase) cellular signaling pathway, leading to cardiac and cutaneous alterations and intellectual deficit. Examples of syndromes linked to MYH7 variants include Noonan syndrome, Costello syndrome, and cardio-facio-cutaneous syndrome. The genes associated with RASopathies are BRAF, HRAS, KRAS, LZTR1, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RASA2, RRAS2, RIT1, SOS1, SOS2.[44]

In Noonan Syndrome, congenital heart disease is present in 50% to 80% of patients,[45] being manifested as pulmonary valve stenosis, septal defects, and Tetralogy of Fallot. Hypertrophic cardiomyopathy is present in 20% to 30% of individuals and may manifest at birth or even in childhood,[45] with half diagnosed by 6 years of age. The genes most closely correlated with the development of hypertrophic cardiomyopathy are LZTR1, MRAS, RAF1, and RIT1.[45-47]

Costello Syndrome presents a broad phenotypic spectrum. In cardiological terms, the most common alterations are hypertrophic cardiomyopathy, congenital heart disease (pulmonary stenosis), and arrhythmias. Regarding hypertrophic cardiomyopathy, approximately 60% of patients have this alteration,[48] with a typically mild to moderate presentation. The diagnosis of Costello Syndrome can be made through genetic testing and the identification of a heterozygous variant in the HRAS gene.[49]

Cardiofaciocutaneous syndrome is characterized by cardiac, facial, and cutaneous alterations. Cardiac alterations include congenital heart disease (pulmonary stenosis, valvular heart disease, septal defects), arrhythmias, and hypertrophic cardiomyopathy. The genes most associated with this syndrome are BRAF, KRAS, MAP2K1, and MAP2K2.[50]

PRKAG2

The PRKAG2 gene is responsible for encoding the non-catalytic gamma subunit of AMP-activated protein kinase (AMPK). This protein is activated in situations of stress, in which there is increased cellular AMP and decreased ATP levels. Variants in this gene are associated with the development of hypertrophic cardiomyopathy, fatal congenital glucose storage cardiomyopathy, and Wolff-Parkinson-White syndrome.[51]

PRKAG2 hypertrophic cardiomyopathy is inherited in an autosomal dominant manner. Individuals carrying this variant often present with concurrent conduction disorders, particularly Wolff-Parkinson-White syndrome, atrial fibrillation, ventricular pre-excitation, and progressive atrioventricular block.[52]

Individuals with missense variants, which result in a gain of AMPK function, may develop the formation and accumulation of glycogen granules in myocytes. This metabolic alteration culminates in the development of ventricular hypertrophy and electrical conduction system defects.[53]

Differentiating PRKAG2 cardiomyopathy from other sarcomeric hypertrophic cardiomyopathies is crucial, as differences in clinical presentation, prognosis, and disease course exist. Sudden death occurs more frequently in patients with PRKAG2 variants.[54]

TTN

Titin is a key protein in cardiac muscle, spanning from the Z line to the M line. It is essential for cardiomyocyte contraction and tension during cardiac activity.[55] The TTN gene encodes titin, with variants including nonsense, frameshift, splicing, and large tandem insertions.

These variants follow an autosomal dominant inheritance pattern with high penetrance, reaching up to 95% after the age of 40.[56] Additionally, they are frequently associated with DCM, accounting for approximately 25% of familial cases and 18% of sporadic cases.[56]

In terms of clinical presentation, no significant differences were observed in age at diagnosis, ejection fraction, transplantation need, or mortality between cardiomyopathies with or without titin variants. However, among patients with this mutation, sex influenced cardiac outcomes, with HF occurring earlier in male participants.[56]

As the most common genetic cause of DCM,[56-60] early identification of TTN variants may allow for a more timely therapeutic approach.

Conclusion

The analysis of genetic cardiomyopathies highlights the importance of early case identification. To this end, genetic sequencing should be requested for patients diagnosed with cardiomyopathies to facilitate early screening of at-risk family members.

Given the specific characteristics of each variant and the genotype-phenotype correlation, genetic research enables targeted early intervention, maximizing the prevention of adverse outcomes and complications. Therefore, advancing Precision Medicine is essential to achieving more individualized management for patients with cardiomyopathies.

Author Contributions

Conception and design of the research and Analysis and interpretation of the data: Hama FM, Rocha EG, Azeka E; Acquisition of data and Writing of the manuscript: Hama FM, Rocha EG; Critical revision of the manuscript for content: Azeka E.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Table 1 – Genotype-phenotype correlation

Phenotype	Genotype
Hypertrophic	MYH7, PRKAG2, MYBPC3, GLA, LAMP2
Dilated	TTN, DSP, MYH7, FLNC, LMNA
RV arrhythmogenic	DSP
Restrictive	MYBPC3, Troponin complex

Adapted from Vogiatzi et al.[61]

Table 2 – Summary of each of the mutation's main characteristics

Gene	Key Information
ALPK3	• Hypertrophic cardiomyopathy • Typically recessive inheritance • Associations with musculoskeletal alterations (facial dysmorphisms, skeletal abnormalities, and pectus excavatum)
BAG3	• DCM • Autosomal dominant inheritance (copy number variation and deletions) • Age at diagnosis between 21 and 64 years, with variable severity (asymptomatic to severe heart failure)
Troponin complex	• Troponin C (TNNC1): dilated and hypertrophic cardiomyopathy • Troponin T (TNNT2): dilated, restrictive, familial hypertrophic cardiomyopathy and left ventricular noncompaction • Troponin I (TNNI3): dilated, familial restrictive and hypertrophic cardiomyopathy
DSP	• Arrhythmogenic right ventricular cardiomyopathy – autosomal dominant inheritance • DCM – autosomal dominant and recessive inheritances – syndromes with capillary, dermal, and dental alterations
FLNC	• Hypertrophic, dilated, restrictive, and arrhythmogenic right ventricular dysplasia • Autosomal dominant inheritance • Variants associated with hypertrophic cardiomyopathy have different prognoses, depending on the mutation. Such differentiation helps in risk stratification
GLA	• Hypertrophic cardiomyopathy • X-linked inheritance • Associated with Fabry disease • Treatment with enzyme replacement therapy
LAMP2	• Hypertrophic cardiomyopathy • Associated with Danon disease: – X-linked – Defect in glycogen storage – Neurological, hepatic, skeletal and cardiac striated muscle manifestations
LMNA	• DCM (second most common genetic cause of nonsyndromic DCM) • Autosomal dominant inheritance • Associated with the following diseases and syndromes: – Charcot-Marie-Tooth – Emery-Dreifuss dystrophy – Holt-Oram syndrome – Malouf syndrome – Hutchinson-Gilford syndrome • Targeted therapies against MAP protein kinase are being studied for the treatment of LMNA-associated dilated cardiomyopathies
MYBPC3	• Hypertrophic cardiomyopathy (most frequent and most strongly correlated), DCM, and isolated left ventricular noncompaction • Autosomal dominant and recessive Inheritance • Clinically heterogeneous

MYH7	• Hypertrophic cardiomyopathy • Associated with skeletal muscle myopathies
Noonan RASopathies	• Hypertrophic cardiomyopathy • Genes: – BRAF, HRAS, KRAS, LZTR1, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RASA2, RRAS2, RIT1, SOS1, SOS2 • Associated syndromes – Noonan syndrome – Costello syndrome – Cardiofaciocutaneous syndrome
PRKAG2	• Hypertrophic cardiomyopathy • Autosomal dominant inheritance • Other associated cardiac conduction disorders: – Wolff-Parkinson-White syndrome – Atrial fibrillation – Ventricular pre-excitation – Atrioventricular block
TTN	• DCM • Autosomal dominant inheritance • Nonsense, frameshift, splicing, and large tandem insertion variants

DCM: dilated cardiomyopathy.

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