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Review

Genotype-Phenotype Insights of Inherited Cardiomyopathies—A Review

Oana Raluca Voinescu [1], Adina Ionac [1,2,3], Raluca Sosdean [1,2,3], Ioana Ionac [1], Luca Silvia Ana [1,3], Nilima Rajpal Kundnani [1,2,*], Stelian Morariu [4,*], Maria Puiu [5,6] and Adela Chirita-Emandi [5,6]

1 Department of Cardiology, "Victor Babes" University of Medicine and Pharmacy, 300041 Timisoara, Romania
2 Research Centre of Timisoara Institute of Cardiovascular Diseases, "Victor Babes" University of Medicine and Pharmacy, 300041 Timisoara, Romania
3 Institute for Cardiovascular Diseases, Gheorghe Adam Street 13A, 300310 Timisoara, Romania
4 General Medicine Faculty, "Vasile Goldis" West University, 473223 Arad, Romania
5 Department of Microscopic Morphology, Genetics Discipline, Center of Genomic Medicine, University of Medicine and Pharmacy, "Victor Babeș" Eftimie Murgu Sq., 300041 Timisoara, Romania
6 Regional Center of Medical Genetics Timiș, Clinical Emergency Hospital for Children "Louis Țurcanu", Iosif Nemoianu Street N°2, 300011 Timisoara, Romania
* Correspondence: knilima@umft.ro (N.R.K.); morariu.stelian@uvvg.ro (S.M.)

Abstract: *Background*: Cardiomyopathies (CMs) represent a heterogeneous group of primary myocardial diseases characterized by structural and functional abnormalities. They represent one of the leading causes of cardiac transplantations and cardiac death in young individuals. Clinically they vary from asymptomatic to symptomatic heart failure, with a high risk of sudden cardiac death due to malignant arrhythmias. With the increasing availability of genetic testing, a significant number of affected people are found to have an underlying genetic etiology. However, the awareness of the benefits of incorporating genetic test results into the care of these patients is relatively low. *Aim*: The focus of this review is to summarize the current basis of genetic CMs, including the most encountered genes associated with the main types of cardiomyopathies: hypertrophic, dilated, restrictive arrhythmogenic, and non-compaction. *Materials and Methods*: For this narrative review, we performed a search of multiple electronic databases, to select and evaluate relevant manuscripts. *Results*: Advances in genetic diagnosis led to better diagnosis precision and prognosis prediction, especially with regard to the risk of developing arrhythmias in certain subtypes of cardiomyopathies. *Conclusions*: Implementing the genomic information to benefit future patient care, better risk stratification and management, promises a better future for genotype-based treatment.

Keywords: heritable cardiomyopathies; genetic testing; family screening; genetic counseling

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1. Introduction

Cardiomyopathies are defined as a group myocardial disorders in which the heart muscle becomes abnormal in structure and function leading to systolic and/or diastolic dysfunction and exhibits a higher risk of developing malignant arrhythmias [1]. The term cardiomyopathy was described for the first time in 1957, by Brigden, referring to patients with myocardial disease of unknown etiology, and some of them having familial aggregation [2]. The World Health Organization (WHO) and International Society and Federation of Cardiology (ISFC) presented the first classification of cardiomyopathies in 1980, based on the predominant structural and hemodynamic phenotype [3]. Five forms of the disease were formally classified at the beginning: hypertrophic cardiomyopathy (HCM; Figures 1 and 2), dilated cardiomyopathy (DCM; Figures 3 and 4), and restrictive cardiomyopathy (RCM; Figures 5 and 6), arrhythmogenic ventricular cardiomyopathy (AVC; Figures 7 and 8), and left ventricular non-compaction cardiomyopathy (LVNC). All cardiomyopathies initially were considered idiopathic, but later with the advancements in

genetic testing they were divided into genetic/inherited forms and acquired/secondary forms. According to recently published guidelines regarding cardiomyopathies, a reclassification was established, which divides the cardiomyopathies as dilated cardiomyopathy, non-dilated cardiomyopathy, hypetrophic cardiomyopathy, restrictive cardiomyopathy and arrhythmogenic ventricular cardiomyopathy. A complex classification, "MOGES", a comprehensive system which not only integrates the morphologic and functional characteristics but also includes the inheritance and genetic data including the: (M) from morpho-functional information, organ(s) involved (O), the genetic inheritance pattern (G), etiological annotation (E) and the functional status (S) of the patient, mostly based on heart failure symptoms [1,4].

Improvements in next-generation sequencing (NGS) technology for genetic clinical testing have provided access to larger gene panels, whole exome and whole genome sequencing over the years. Broader genetic testing increases the probability of identifying variants of incidental findings. All genetic testing can lead to discoveries of variants of uncertain significance (VUS) that represent a challenge for the clinical practice. Therefore, awareness of the benefits and hazards of genetic testing in order to choose the most suitable test, while also offering pretest genetic counselling, is valuable [5]. In the majority of cases, testing a small panel of specific genes in each type of cardiomyopathy offers good accuracy to detect single nucleotide substitutions for the identification of genetic defects such as: nonsense, missense or small deletion/insertion, while avoiding incidental discoveries. Specific cases, in which classic analyses turn out negative, might benefit from microarray tests in search of larger insertion/deletion variants > 25 nucleotides, but they represent < 1% of cases, as suggested by current studies, although these type of variants have been investigated less [4–6]. More recent advances in bioinformatics pipelines of NGS can provide information on copy number variants (CNV) from NGS [4,5].

Despite the rapid progress of molecular techniques over the past decades and that the increased genetic testing options have led to an improvement in understanding of the genetic complexity of these diseases, the actual global burden determined by genetic cardiomyopathies is still difficult to quantify, due to limited epidemiological studies [7]. In this review, we focus on the genetic background of the main primary cardiomyopathies, in order to improve medical management for the patients and their families.

2. Materials and Methods

We performed a search on the following electronic scientific resources: PubMed, Google Scholar, Web of Science, and Science Direct. Relevant open access articles employing the association between primary cardiomyopathies and genetic testing were identified. Key words used for the search included: "cardiomyopathy", "genetic testing", "next generation sequencing", "molecular testing", "genes". We selected 76 articles, based on a database search published between 2004 and 2023. Manually, we checked the reference lists of the selected literature in order to validate the inclusion of genetic cardiomyopathies and the molecular characterization of these cardiac diseases based on the genetic testing.

2.1. Material Content

Basic Concepts of Clinical Genetics

Molecular genetics has shown that the classical Mendelian model of transmission might be more complex than previously thought. The model of inheritance should be determined in every case of genetic heart disease, which in daily busy clinical practice is difficult. Significant pitfalls need to be considered outside the Mendelian transmission. For example, diseases that were thought to be X linked recessive, for example Fabry disease, have shown that females may develop disease symptoms even with severe cardiac dysfunction, although the disease onset is later than for males. Moreover, an autosomal dominant cardiomyopathy may occur as an isolated case with a de novo variant [8]. The penetrance of a disease represents the proportion of variants carriers who develop the disease, irrespective of the presence of symptoms. For most autosomal recessive cardiac

diseases (such as: arrhythmogenic ventricular cardiomyopathy), the penetrance is often complete. Penetrance in autosomal dominant cardiac diseases has proven to be rather age-related than incomplete, as illustrated by studies of molecular analyses. In hypertrophic cardiomyopathy the penetrance is estimated to be incomplete by the age of 30 (P = 50–80%) but nearly complete (P = 90–95%) by the age of 60 [9]. The majority of the monogenic cardiomyopathies tend to follow an autosomal dominant inheritance pattern, but cardiac manifestations can be very different, sometimes related to the age of onset. Variability of disease expression has been observed even between members of a family, which carry the same genetic variant. This has been attributed to intervention of additional influencing factors. Lifestyle, environmental factors, pharmacological agents, modifier genes, coexistence of different genetic variants may influence the phenotype of the disease [10]. Mitochondrial cardiomyopathies however represent a specific group of disorders determined by defects in mitochondrial DNA (mtDNA)/nuclear DNA (nDNA) resulting in mitochondrial function defects thus leading to the inability to produce adequate energy for the body, including the heart. The clinical picture of these diseases range from isolated cardiac dysfunction to cardiac involvement in the context of multisystem disorders such as neuromuscular and/or metabolic disease. Mitochondrial DNA dysfunction may lead to various cardiac phenotypes: including hypertrophic, dilated or non-compaction cardiomyopathy. Promising therapeutic approaches that target cell therapy, gene therapy, mitochondrial therapy, pharmacological therapy for a patient with mitochondrial cardiomyopathy are emerging fast at the preclinical level but clinical translation is still lacking [11].

The ClinGen Gene Curation Working Group built a method to qualitatively define the "clinical validity" of the genes-disease relationship by creating a classification method based on the strength of evidence that supports this relationship. A gene which is interpreted as "definitive" in relation to a particular disease has been repeatedly demonstrated in both research and clinical settings and has been reported in at least two independent scored publications documenting human genetic evidence over time. Gene-disease relation with "strong" evidence is supported by numerous unrelated probands identified with variants with multiple evidence favoring disease causality. Gene-disease pair with "moderate" evidence imply some convincing genetic evidence and no data that contradicts the role of the gene in the noted disease has emerged. The "limited" association is considered when the variants have some support for pathogenic impact, but there is little to no functional evidence to prove it. When existing genetic evidence has been ruled out, leaving the gene with no valid evidence remaining after an initial claim, leads to a "refuted" association [12].

3. Genetic Testing? Whom, When and How

A methodical approach to the genetic diagnosis of a heritable cardiomyopathy should consist in obtaining a detailed history of the disease, physical examination with focus on syndromic cardiovascular disease and a complete family history incorporating a three-generation pedigree [6]. Genetic testing should be integrated in the work-out of any primary cardiomyopathy. It should be initiated with the patient having symptoms in the family or early onset of the disease, as this increases the probability of finding a genetic cause. There are no clear recommendations regarding the best timing for performing the genetic testing [11]. It is recommended to be performed at the moment of cardiomyopathy diagnosis because genetic results may guide the management [12]. The complexity of gene panels have improved over time, especially those for DCM [13]. For patients with negative or uncertain results at previous tests, reinterpretation of raw sequencing data or retesting may be an option. This indication is based on the fact that larger datasets become available with advanced research and gene variants can be reclassified over time [14,15]. This means that VUS can become likely pathogenic, or variants previously considered likely pathogenic can be downgraded to VUS. Next-generation sequencing using a multi-gene panel is the best option for these diseases with heterogeneous genetic background, as they are technically feasible and cost-efficient [16]. These large gene panels have the advantage of increasing the odds of identifying a genetic etiology, especially in patients with uncertain phenotypes

or without pathognomonic manifestations. With larger gene panels, the likelihood of identifying a variant of uncertain significance is higher and the overlap of genes responsible for different types of cardiomyopathies makes the interpretation harder. Family testing could be supported for reclassification of a VUS variant, if identified in multiple members of the family with a similar phenotype, or on the contrary if identified as de novo, from healthy parents and siblings. It is important that the ordering physician has a good knowledge of the advantages but also the limitations of specific test types in order to select the most appropriate test for their patient [17]. Once a pathogenic or likely pathogenic variant has been identified in the proband, Sanger sequencing and targeted gene analysis should be performed for the other family members. The rationale behind identifying family genetic risk is that those found to be at-risk can undergo periodic evaluation/systematic screening to detect the earliest manifestations of the disease. Thus, in such situations, the first symptom or imagistic sign would prompt early management, including lifestyle changes, cardio-protective treatment to slow down disease progression, and devices implantation for reducing the risk of sudden cardiac death. Identifying healthy carriers of the pathological gene may also have implications regarding family planning and reproductive decisions [18]. Combined medical education and genetic counseling provided by the cardiologist and genetic physician is crucial for achieving the best medical management.

4. Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is defined by the presence of inappropriate left ventricular hypertrophy unexplained by any cardiac or systemic abnormal loading condition. The diagnostic criteria is defined by maximum left ventricular wall thickness of $\geq$15 mm. For first-degree relatives, unexplained wall thickness of $\geq$13 mm in any segment is suggestive for the diagnosis [19]. It is the most frequently encountered inherited cardiomyopathy, with a prevalence in the general population of 1:500, or even higher [20,21].

As an example, we present in Figures 1 and 2, the images of the heart in a patient diagnosed with HOCM, carrier of a pathogenic gene variant in the *MYH7* gene (Courtesy: Prof. Dr. Adina Ionac-Institute of Cardiovascular Disease, Timisoara, Romania).

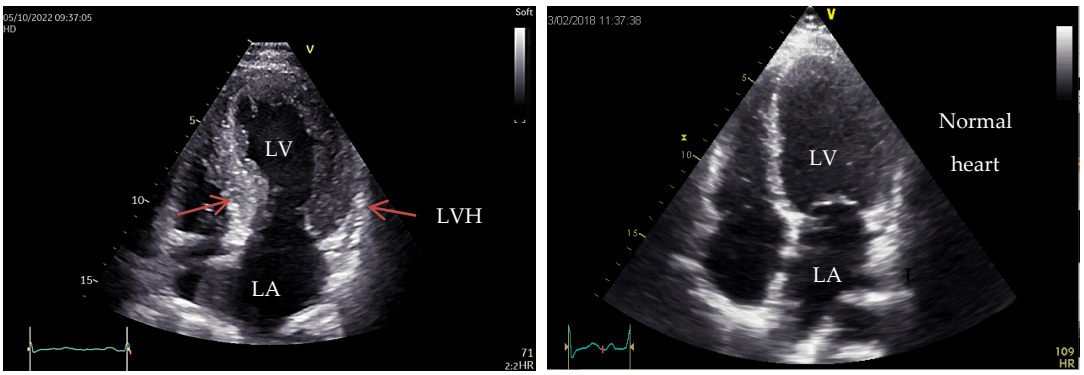

Figure 1. Two-dimensional echocardiography, apical four-chamber view showing important LV hypertrophy (LVH) and dilation of LA. Versus normal heart to the right side of the image.

There are several phenotypes described. The symmetrical form of HCM accounts for 33% of cases having concentric thickening of the left ventricle with a small ventricular cavity diameter. The obstructive form of HCM (HOCM) involves predominant thickening of the basal septum, narrowing the left ventricular outflow tract. Anterior displacement of the papillary muscles is common and anterior mitral leaflet systolic motion (SAM) into the left ventricle outflow tract obstruction (LVOT) during systole is responsible for LVOT (Figure 2). This pattern has been considered in past as pathognomonic for HCM, but it has been described also in non-sarcomeric HCM. HCM may involve any segment of the left ventricle and there have been variants described that involve mid-ventricular or apical LV hypertrophy.

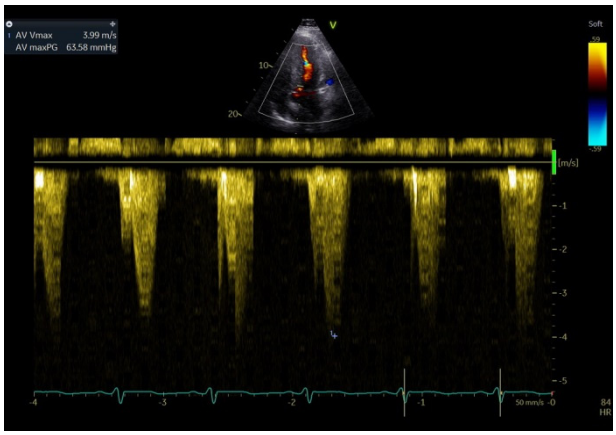

Figure 2. Continuous Wave Doppler in LV outflow tract measures a maximum gradient pressure of 63 mmHg.

Symptoms may vary a great deal, related to the severity of hypertrophy and grade of fibrosis. Patients may be asymptomatic or complain about heart failure symptoms due to diastolic dysfunction. Angina is common and can be explained by microvascular dysfunction and relative myocardial ischemia. Narrowing of the small intramural coronary arteries due to wall media thickening by muscle cell hyperplasia may lead to fibrosis and the development of the systolic dysfunction in advanced stages. Furthermore, myocardial fibrosis has been correlated to the risk of sudden cardiac death through malignant arrhythmias. Patients with asymmetric hypertrophy in particular have the risk of developing syncope during physical exertion due to dynamic LVOT obstruction [22].

HCM is an autosomal dominant disease in most of cases, commonly caused by variants in genes encoding sarcomere proteins [20,23]. In patients fulfilling diagnostic criteria for HCM, genetic testing is positive in 30–60% of cases and even higher in cases of familial aggregation. About 70% of these variants are localized in sarcomere genes encoding cardiac β-myosin heavy chain (*MYH7*) and cardiac myosin binding protein C (*MYBPC3*) [24]. It is estimated that 50–60% of patients who have a family member with HCM carry a pathogenic gene variant [25,26]. To date, there have been multiple gene variants responsible for HCM described [Table 1]. The most frequent genes involved are *MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, *ACTN2*, and *TPM1*. Different variants of the same gene have been related to different grades of disease severity and prognosis. For example, pathogenic variants in the cardiac β-myosin heavy chain gene are related to severe forms of HCM with onset at early age and high risk of sudden cardiac death. Disease-causing variants in Troponin T despite inducing only mild hypertrophy are associated with poor outcomes and high risk of malignant arrhythmias. On the other hand, myosin-binding protein C variants are associated with late clinical onset and a more benign clinical course. Expression variability is emphasized by different clinical response and evolution between members of the same family carriers of an identical genetic variant. In a study published in 2019 by Maurizi et al., it was stated that only 10% of the asymptomatic HCM-carriers of pathogenic variants developed cardiac disease during a clinical follow-up of 6 ± 2 years [27]. According to 2104 ESC Guidelines for diagnosis and management of HCM, genetic testing is recommended in patients who fulfill diagnostic criteria to confirm the diagnosis (indication class I, level B), especially where familial aggregation is present [19,28].

Etiological diagnosis is challenging when HCM is represented by multiple phenocopies. These include physiological transitory changes found in athletes, metabolic and other hereditary diseases such as Fabry disease or cardiac amyloidosis. A correct diagnosis is crucial since these diseases have a different evolution and benefit from specific treatment further influencing the prognosis [29]. For example, in patients with sarcomeric hypertrophic obstructive cardiomyopathy, mavacamten treatment, an inhibitor a cardiac myosin ATPase, was found to be associated with favorable remodeling of myocardium and

improvement in functional capacity of these patients (EXPLORER HCM Trial) [30]. Invasive treatment to reduce gradient form the left ventricle outflow tract may be considered in patients with a maximum gradient $\geq$ 50 mmHg, with heart failure severe symptoms and syncope despite maximum tolerated medical therapy. This therapeutic approach include alcohol septal ablation or surgical procedure for ventricular septal myectomy. Patients with HCM express an annual incidence for death of 1–2%, SCD, heart failure, and thrombo-embolism events being the major causes of death. Calculation of SCD risk score is indicated in these patients and ICD implantation in primary prevention of SCD in recommended according to the score value [4].

Table 1. List of common genes and patterns of inheritance in cardiomyopathies (alphabetical), curated by ClinGen [31] and literature review.

Gene Symbol	Disease OMIM #	Gene Name	Mode of Inheritance	HCM	DCM	RCM	ACM	LVNC
ABCC9	601439	ATP-binding cassette	AD	-	Limited	-	-	-
ACTC1	102540	Actin alpha	AD	Definitive	Moderate	-	-	-
ACTN2	102573	Actinin alpha 2	AD	Definitive	Definitive	Definitive	Definitive	Definitive
ALMS1	606844	Centrosome and basal body associated protein	AR	-	Definitive			
ALPK3	617608	Alpha kinase 3	AR	Definitive	-	-	-	-
ANKRD1	609599	Ankyrin repeat domain-containing protein 1	AD	Disputed	Limited	-	-	-
ARVD3	602086	Arrhythmogenic right ventricular dysplasia, familial, 3	AD	-	-	-	Limited evidence	-
ARVD4	602087	Arrhythmogenic right ventricular dysplasia, familial, 4	AD	-	-	-	Limited evidence	-
ARVD6	604401	Arrhythmogenic right ventricular dysplasia, familial, 6	AD	-	-	-	Limited evidence	-
BAG3	603883	Bcl2-associated athanogene 3	AD	-	Definitive	-	-	-
BRAF	164757	B-Raf proto-oncogene serine/threonine kinase	AD	Definitive	-	-	-	-
CASQ2	114251	Calsequestrin 2	AR, AD	Disputed	-	-	-	-
CAV3	601253	Caveolin 3	AD	Definitive	-	-	-	-
CRYAB	123590	Crystallin	AD	Limited evidence	Limited evidence	-	-	-
CSRP3	600824	Cysteine and glycine rich protein 3	AD	Definitive	Limited			
CTF1	600435	Cardiotrophin 1	AR, AD	-	Limited			
CTNNA3	607667	Catenin alpha 3	AD	-	-	-	Limited	-
DES	125660	Desmin	AD, AR	-	Definitive	-	Moderate	-
DMD	300377	Dystrophin	XLR	-	Definitive * Duchenne muscular dystrophy Becker muscular dystrophy	-	-	-
DOLK	610746	Dolichol kinase	AR	-	Limited	-	-	-
DSC2	600271	Desmocollin 2	AD, AR	-	Limited	-	Definitive	-

Table 1. *Cont.*

Gene Symbol	Disease OMIM #	Gene Name	Mode of Inheritance	HCM	DCM	RCM	ACM	LVNC
DSG2	125671	Desmoglein 2	AD	-	Limited	-	Definitive	-
DSP	125485	Desmoplakin	AD, AR	Disputed	Definitive	-	Definitive-	-
DTNA	601239	Dystrobrevin, alpha	AD	-	Limited	-	-	Limited Evidence
EMD	300384	Emerin	XLR1	- Definitive * Emery-Dreifuss Muscular Dystrophy	Definitive * Emery-Dreifuss Muscular Dystrophy	-	-	-
EYA4	603550	Eyes absent Drosophila homolog 4	AD	-	Limited			
FHL1	300163	Four and a half LIM domain 1	XL	Definitive * Emery-Dreifuss Muscular Dystrophy and related phenotypes	Definitive * Emery-Dreifuss Muscular Dystrophy and related phenotypes	-	-	-
FKRP	606596	Fukutin-related protein	AR	-	Definitive * Limb Girdle Muscular Dystrophy			
FKTN	607440	Fukutin	AR	-	Definitive * Limb Girdle Muscular Dystrophy			
FLNC	102565	Filamin C	AD	Definitive	Definitive	Limited evidence	Limited evidence	-
GAA	606800	Glucosidase alpha	AR	Definitive	-	-	-	-
GATA4	600576	Gata-binding protein 4	AD	-	Limited	-	-	-
GATAD1	614518	Gata zinc finger domain-containing protein 1	AR	-	Limited	-	-	-
GLA	300644	Galactosidase alpha	XL	-	-	Definitive	-	-
HCN4	605206	Hyperpolarization-Activated. Cyclic nucleotide-gated. Potassium Channel 4	AD	-	-	-	-	Limited
HRAS	190020	HRas proto-oncogene, GTPase	AD	Definitive	-	-	-	-
ILK	602366	Integrin-linked kinase	AD	-	Limited	-	-	-
JPH2	605267	Junctophilin 2	AD	Moderate	Moderate	-	-	-
JUP	173325	Junction plakoglobin	AD, AR	-	-	-	-	Definitive * Naxos Disease
LAMA4	600133	Laminin alpha-4	AD	-	Limited			
LAMP2	309060	Lysosome-associated membrane protein 2	XLD	Definitive	Limited			
LDB3	605906	LJm domain-binding 3	AD	Limited evidence	Limited		Disputed	Limited evidence

Table 1. *Cont.*

Gene Symbol	Disease OMIM #	Gene Name	Mode of Inheritance	HCM	DCM	RCM	ACM	LVNC
LMNA	150330	Lamin A/C	AD, AR	Limited evidence	Definitive		Limited	Limited evidence
MAP2K1	176872	Mitogen activated protein kinase 1	AD	Definitive * Cardiofaciocutaneous syndrome	-	-	-	-
MAP2K2	601263	Mitogen activated protein kinase 2	AD	Definitive * Cardiofaciocutaneous syndrome	-	-	-	-
MYBPC3	600958	Myosin-binding protein C, cardiac	AD	Definitive	Limited	-	Limited	Limited evidence
MYH6	160710	Myosin heavy chain 6	AD	Limited	Limited	-	-	-
MYH7	160760	Myosin, heavy chain 7, cardiac muscle, beta	AD	Definitive	Definitive	Limited evidence	Limited	Limited evidence
MYL2	160781	Myosin light chain 2	AD	Definitive	Limited	-	-	-
MYL3	160790	Myosin light chain 3	AD, AR	Definitive	Disputed	Limited evidence	Limited	-
MYLK2	606566	Myosin light chain kinase 2	AD	Disputed	Limited	-	-	-
MYOM1	603508	Myomesin 1	AD	Disputed	-	-	-	-
MYOT	604103	Myotilin	AD	-	Limited	-	-	-
MYOZ2	605602	Myozenin 2	AD	Disputed	Limited	Limited evidence	-	-
MYPN	608517	Myopalladin	AD	Disputed	Limited	Limited evidence	-	-
NEBL	605491	Nebulette	AD	-	Limited	-	-	-
NEXN	613121	Nexilin	AD	Limited	Moderate	-	-	-
NKX2-5	600584	Nk2 homeobox 5	AD	-	Limited	-	-	-
NRAS	164790	Neuroblastoma Ras viral oncogene homolog	AD	Definitive * Noonan syndrome	-	-	-	-
PDLIM3	605899	Pdz and lim domain protein 3	AD	Limited	Disputed	-	-	-
PKP2	602861	Plakophilin 2	AD	-	Disputed	-	Definitive	-
PLN	172405	Phospholamban	AD	Definitive	-	-	Moderate	-
PRDM16	605557	Pr domain-containing protein 16	AD	-	Limited-	-	-	Limited
PRKAG2	602743	Protein kinase amp-activated non-catalytic	AD	Definitive	Limited evidence	-	-	-
PTPN11	176876	Protein tyrosine phosphatase non-receptor type 11	AD	Definitive * Noonan Syndrome	-	-	-	-
RAF1	164760	V-Raf-1 murine leukemia viral oncogene homolog 1	AD	Definitive * Noonan Syndrome	-	-	-	-

Table 1. *Cont.*

Gene Symbol	Disease OMIM #	Gene Name	Mode of Inheritance	HCM	DCM	RCM	ACM	LVNC
RBM20	613171	RNA-binding motif protein 20	AD	Limited	Definitive	-	-	-
RIT1	609591	Ras-like without Caax 1	AD	Definitive * Noonan Syndrome	-	-	-	-
SCN5A	600163	Sodium channel, voltage-gated, type V, alpha subunit	AD	-	Definitive	-	Limited	-
SGCA	600119	Sarcoglycan alpha	AR	-	Definitive * Limb Girdle Muscular Dystrophy	-	-	-
SGCB	600900	Sarcoglycan beta	AR	-	Definitive * Limb Girdle Muscular Dystrophy	-	-	-
SGCD	601411	Sarcoglycan delta	AD, AR	-	Limited Definitive * Limb Girdle Muscular Dystrophy	-	-	-
SHOC2	602775	Soc-2 homolog	AD	Definitive * Noonan Syndrome	-	-	-	-
SLC25A4	103220	Solute carrier family 25	AD, AR	Definitive	Limited * Leigh Syndrome			
SOS1	182530	Son of sevenless Drosophila homolog 1	AD	Definitive * Noonan Syndrome	-	-	-	-
TAZ	300394	Tafazzin	XL R	-	Definitive * Barth Syndrome	-	-	Limited Evidence
TBX20	606061	T-box 20	AD	-	Limited	-	-	Limited Evidence
TCAP	604488	Titin-Cap	AR	Disputed	Limited	-	-	-
TGFB3	190230	Transforming growth factor beta 3	AD	-	-	-	Limited	-
TMEM43	612048	Transmembrane protein 43	AD	-	-	-	Definitive	-
TNNI3	191044	Troponin I type 3 (cardiac)	AD	Definitive	Moderate	Limited evidence	-	-
TNNC1	191040	Troponin C type 1	AD	Definitive	Definitive	-	-	-
TNNT2	191045	Troponin T type 2 (cardiac)	AD	Definitive	Definitive	Limited evidence	-	Limited evidence
TOR1AIP1	614512	Torsin-1a-interacting protein 1	AR	-	Limited evidence	-	-	-
TPM1	191010	Tropomyosin 1 (alpha)	AD	Definitive	Moderate	Limited evidence	-	-
TTN	188840	Titin	AD, AR	Limited	Definitive	-	Limited	-
TTR	176300	Transthyretin	AD	Definitive	-	Definitive	-	-
TXNRD2	606448	Thioredoxin reductase 2	AD, AR	-	Limited evidence	-	-	-
VCL	193065	Vinculin	AD	Disputed	Moderate	-	-	Limited evidence

* Syndromic cardiomyopathy, ACM: arrhythmogenic cardiomyopathy, AD: autosomal dominant, AR: autosomal recessive, XL: X linked, HCM: hypertrophic cardiomyopathy, DCM: dilated cardiomyopathy, RCM: restrictive cardiomyopathy, LVNC: left ventricular non-compaction.

5. Dilated Cardiomyopathy (DCM)

Dilated cardiomyopathy is a disease of the heart muscle characterized by ventricular dilatation and systolic dysfunction, in the absence of abnormal loading conditions such as: coronary artery disease, significant valvulopathies, or viral infections such as COVID-19 [30,32]. The clinical picture is represented by heart failure (HF), arrhythmias, conduction system disorders or SCD. Globally, DCM represents the main cause of HF, reaching almost half of the patients in HF registries and represents a leading cause of heart transplant [33].

The prevalence of DCM has varied a lot over time and it is difficult to establish; recent studies have reached to a prevalence 1:400 [17]. About 30–50% of cases have positive family history, with autosomal dominant pattern of transmission but with variable penetrance. Autosomal recessive, X-linked, and mitochondrial inheritance patterns have been described but they are more frequently diagnosed during childhood [1,34,35]. DCM has been classified into non-syndromic forms, when the defect is localized only to the heart, and syndromic forms which involves systemic disease manifestations.

As an example, we present in Figures 3 and 4, the images of the heart in a patient diagnosed with dilated cardiomyopathy, carrier of the pathogenic variant in the *TTN* gene (Courtesy: Dr Raluca Sosdean).

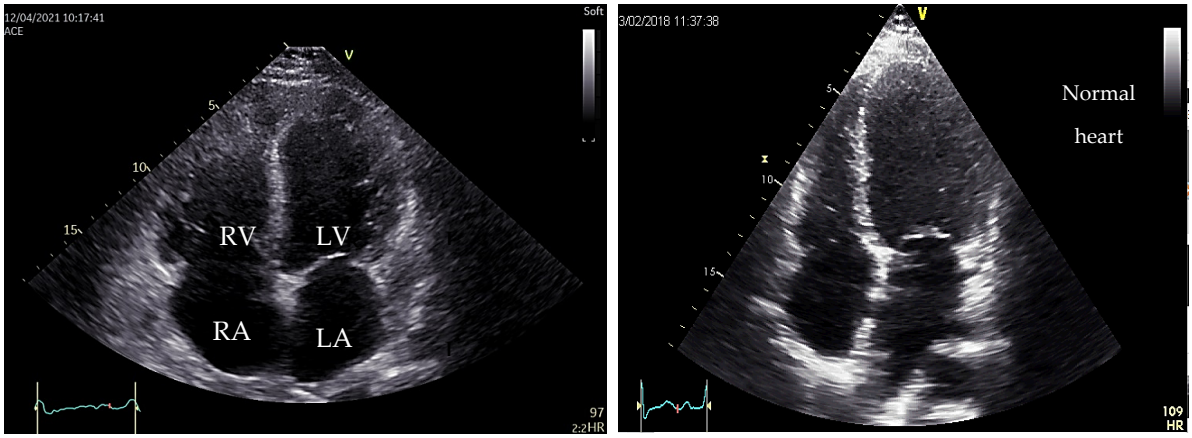

Figure 3. Two-dimensional echocardiography, apical four-chamber view showing biventricular dilation with spherical geometry and bilateral atrial enlargement, versus normal heart to the right side of the image.

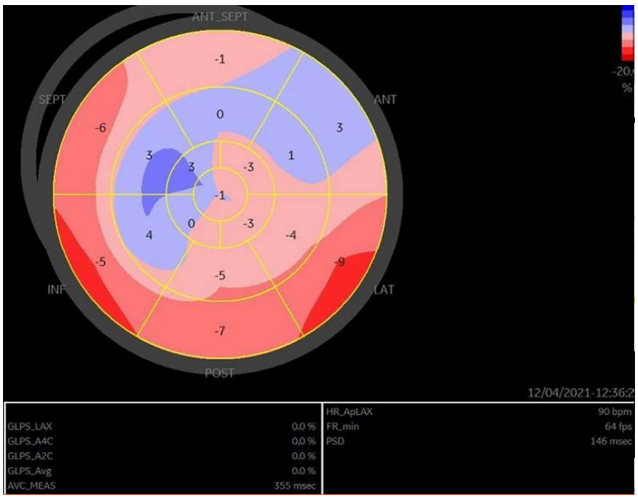

Figure 4. Speckle tracking emphasizes a left ventricle with reduced Global Longitudinal Strain (GLS) of −0%.

According to Human Gene Mutation Database and the Online Mendelian Inheritance in Man [36], initially more than 100 genes have been linked to DCM, some of them being refuted after advanced data analysis. They are involved in coding proteins of the different cell structures such as: cytoskeleton, sarcomere, nuclear membrane and ion channels, with an important overlap with other types of cardiomyopathies [37]. The majority of disease-causing variants are specific to a family and about 10% of patients seem to have at least two variants involved [35,38]. Non-syndromic DCM are most common determined by truncating variants of the Titin gene (*TTN*) [39,40]. Associated neuromuscular symptoms in the patient or relatives is an important criterion for gene analysis since variants in *LMNA* are involved in DCM associated with neuromuscular disease (limb girdle muscular dystrophy). Laminopathies are frequently associated with prolonged PR interval on the ECG, indicator of cardiac conduction disorder [41,42].

Recent data indicates that sarcomere genes *MYH7*, *TNNT2* and *TPM1*, usually involved in HCM etiology, represent 2–4% of the variants identified in DCM, while *MYBPC3* variants are rare [43]. Phospholamban (*PLN*) variants, which encodes a transmembrane protein that inhibits sarcoplasmic reticulum Ca^{2+}-ATPase, have been associated with DCM. Variable phenotypes have been described, with different phenotypes from mild cases to early onset disease associated with lethal ventricular arrhythmias [44,45]. In centers with cardiovascular genetic expertise, the rate of genetic diagnosis in non-syndromic DCM is about 46–73% [46]. Acquiring more information about the genotype–phenotype associations could improve the specificity of genetic testing and lead to cost efficient analysis.

HF medication has proved to have benefic effect on LV remodeling in symptomatic patients that associate LV dysfunction, first-line heart failure therapy: angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics, and aldosterone antagonists should be considered in these patients to prevent LV dilatation and dysfunction progression. An ICD is recommended in DCM patients with purpose of increasing the survival; arrhythmic risk calculators may be useful tools to predict the risk of SCD, where available. Progression towards end-staged heart failure despite maximally tolerated drug therapy or intractable ventricular arrhythmia leads to indication of cardiac transplantation [4].

6. Non-Dilated Cardiomyopathy

A phenomenon characterized by intermediate phenotypes that do not meet standard disease criteria despite the identification of myocardial disease on cardiac imaging or tissue evaluation has been described [46]. Therefore, 2023 ESC Guidelines for the management of cardiomyopathies proposed the introduction of a new term "non-dilated left ventricular cardiomyopathy" (NDLVC). This phenotype defined by the existence of non-ischemic LV scar or fatty tissue replacement on MRI scans, without cardiac chamber dilation, regardless of the presence of global or regional contractility dysfunction. Isolated global LV hypokinesia without fibrosis is also included in this category. The NDLVC phenotype includes patients that previously been considered as having DCM without LV dilatation, left dominant arrhythmogenic left ventricular cardiomyopathy but often without having complete diagnostic criteria for ARVC. The diagnosis of an NDLVC phenotype should initiate a multi-variable approach including clinical examination, family history, cardiac imaging, myocardial tissue characterization, Holter ECG monitoring for arrhythmic burden and genetic testing. These entire tests can lead to a specific etiological diagnosis with implications for medical/interventional treatment and follow-up [4].

7. Restrictive Cardiomyopathy (RCM)

Restrictive cardiomyopathy is characterized by diastolic dysfunction of a non-dilated LV with normal systolic function. The clinical presentation is heterogeneous and it is correlated with high cardiac filling pressures due to a non-compliant left ventricle [46]. Patients may present signs and symptoms of heart failure, tachyarrhythmia's, or sudden cardiac death. Echocardiography together with electrocardiography is the most important tool

for the diagnosis, revealing normal ventricular volumes with normal/mild hypertrophic walls, restrictive diastolic dysfunction and bi-atrial dilation and hence and also of their arrhythmic complications including atrial fibrillation and ventricular tachycardia, that can be complicated by sudden death or stoke [47]. These changes can be augmented by the association of other cardiovascular risk factors such as obesity, dyslipidemia, diabetes isolated or grouped as in the diagnosis of metabolic syndrome [48,49].

As an example, we present in Figures 5 and 6, the echocardiographic images of a patient diagnosed with restrictive cardiomyopathy secondary to cardiac amyloidosis, carrier of a pathogenic variant in the transtiretin (*TTR*) gene (Courtesy: Prof. Dr. Adina Ionac).

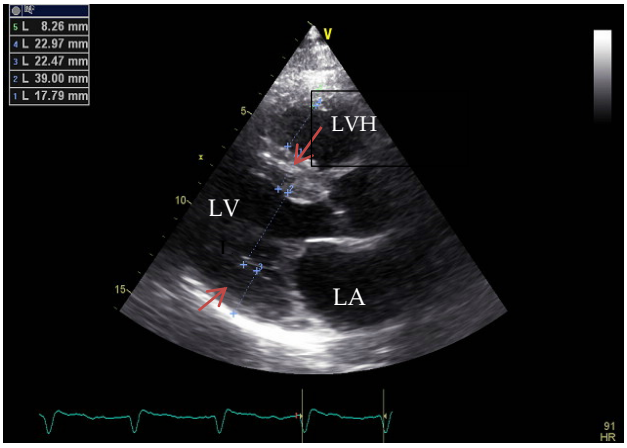

Figure 5. Two-dimensional echocardiography, parasternal long axis view showing an LV with concentric hypertrophy (LVH) and LA enlargement.

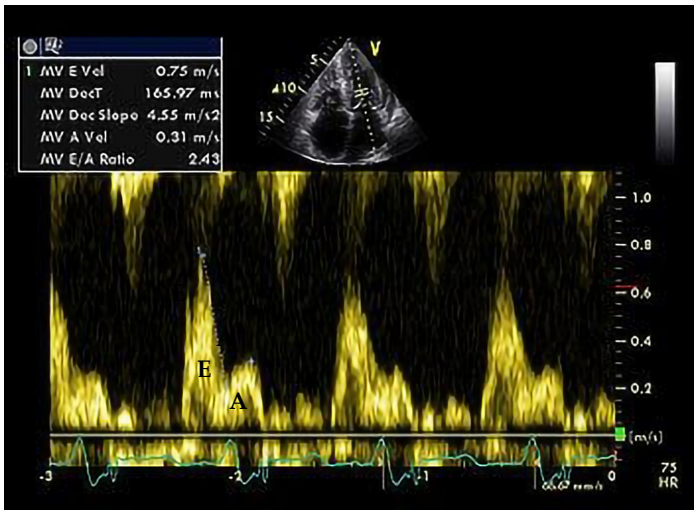

Figure 6. Pulsed Wave Doppler (PWD) at the mitral valve (MV) level, with E/A ratio of 2.4—suggestive for restrictive diastolic dysfunction.

RCM is mainly classified as primary and secondary. The primary RCM are histologically characterized by interstitial fibrosis and include the endomyocardial fibrosis (EMF), Loeffler's endocarditis, and idiopathic forms. Secondary forms of RCM are more common and are subclassified as infiltrative (amyloidosis, sarcoidosis) or as storage disorders (haemochromatosis, glycogenosis, Fabry disease) and non-infiltrative (anthracycline induced toxicity carcinoid syndrome) [50]. The most frequent genetic variants found in RCM cases are in sarcomeric genes, such as *TNNI3* (most common), *TNNT2*, *MYH7*, *ACTC1*, *TPM1*, *MYL3*, and *MYL2* also known to cause HCM [51,52]. Therefore, genetic testing for RCM should include HCM genes [53]. Most variants are localized in genes encoding

sarcomeric proteins, some in sarcomere-associated proteins like small heatshock protein: crystallin αB, or their binding partners *LBAG3*—proteins whose dysfunction potentially leads to the accumulation of aggregated proteins. There have also been variants described in genes whose proteins are not directly involved in contractile function such as: desmin, filamin C and crystallin αB [54,55]. Desmin variants have been usually associated with DCM, however, a p.*E413K* variant has been described in a family with a history of SCD, in which three family members were diagnosed with RCM [56]. Familial aggregation is identified in up to 30% of cases in RCM.

Infiltrative causes of RCM are mainly represented by cardiac amyloidosis—a disorder characterized by deposition of insoluble fibrillar protein-like filaments between the muscle fibers, small arteries media, and peripheral nervous system. It is classifies into two main types: light chain (AL) and the transthyretin amyloidosis (ATTR). The latter type includes a hereditary sub-type caused by variants of the transthyretin protein (genetic), and a more common wild-type ATTR (ATTRwt) which is age-related (senile) [57]. If ATTR cardiomyopathy is identified, then genetic sequencing of the *TTR* gene is necessary. Differentiating ATTRv from ATTRwt is critical because confirmation of ATTRv should trigger genetic counseling and potential screening of family members. Furthermore, identification of Val122Ile variant involves a more aggressive progression with median survival after diagnosis in untreated patients of 2.5 years [58]. Hemochromatosis is a disorder which involves abnormal systemic deposition of iron. This disease has been associated with low-penetrance autosomal dominance of pathogenic variants identified in the *HFE* gene [59]. A pathogenic variant of *BTNL2* gene has been associated with sarcoidosis, a granulomatous systemic disease characterized by restrictive cardiomyopathy, pulmonary and skin infiltration [60]. The importance of a correct etiological diagnosis the disease benefit from specific treatment. According to the results of ATTR-ACT randomized trial (Safety and Efficacy of Tafamidis in Patients wth Transthyretin Cardiomyopathy), Tafamidis treatment was associated with a significantly lower mortality and cardiovascular hospitalization [61].

8. Arrhythmogenic Cardiomyopathy (ACM)

Arrhythmogenic ventricular cardiomyopathy (AVC) is characterized by the progressive loss of myocytes due to the replacement of myocardium by fibro-adipose tissue. Groups of myocytes are surrounded by fatty-fibrous tissue creating an electrical pathway for malignant ventricular arrhythmias [62]. Sudden cardiac death is more frequent in young individuals and is commonly precipitated by exercise. Though it was firstly thought to be a disease isolated to the right ventricle, now it is known that it can affect both ventricles or predominantly LV. Subsequently, the initially name of right ventricular dysplasia was replaced by "arrhythmogenic cardiomyopathy".

As an example, we present in Figures 7 and 8 the images of the heart in a patient with right ventricle arrhythmogenic cardiomyopathy, a carrier of a pathogenic variant in the *PLN* gene. (Courtesy: Dr Raluca Sosdean, Institute of Cardiovascular Disease Timisoara).

In 2020, Padua criteria for positive diagnosis were proposed, focused on the most affected ventricle. They include morpho-functional changes, tissue characterization, ECG disorders, ventricular arrhythmias and family history/genetic variants [63]. Up to 50% of AVC cases have positive family history [46]. AVC frequently has an autosomal dominant transmission with incomplete penetrance, although two autosomal recessive forms have been described (Naxos disease and Carvajal syndrome) [64]. ACM has a heterogeneous genetic background, mainly involving variants in genes encoding structural proteins as desmosome proteins: plakoglobin, desmoplakin, plakophillin, accounting for up to 60% of affected patients [65]. Variants in *PLN* encoding phospholamban have been identified to cause 10–15% of all ACM patients in Netherlands. Loss of desmosomal integrity affect myocytes gap junctions and electrical propagation leading to ventricular arrhythmias in the absence of extensive structural changes. Other ACM target genes encode the cardiac sodium channel, titin, lamin A/C transmembrane protein 43, and filamin C [66]. Overall,

the most commonly mutated gene is plakophilin, which accounted for 46–61% of patients from two registries [67].

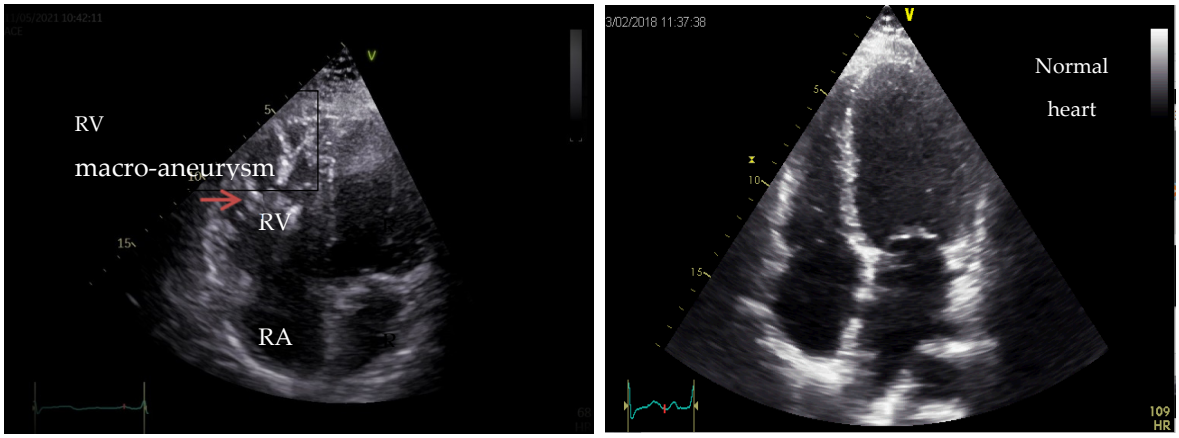

Figure 7. Two-dimensional echocardiography, apical four-chamber view showing right ventricular (RV) dilation with multiple macro-aneurysms and reduced systolic function versus normal heart to the right side of the image.

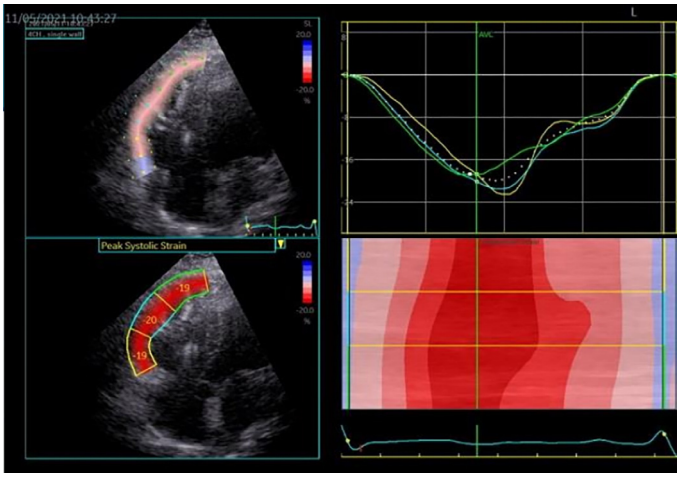

Figure 8. Speckle tracking analysis revealed reduced RV free wall longitudinal strain of −20% in a patient diagnosed with ACM predominantly affecting the RV.

To control arrhythmia-related symptoms in patients with ARVC, beta-blockers represent the first option of treatment by reduction of adrenergic tone, particularly during exercise. Amiodarone is often used when other beta-blockers fail to control arrhythmias. Sotalol has been used for many years, but data regarding the efficacy is limited or conflicting. Flecainide should be considered when single-agent treatment has failed. Experience with other antiarrhythmic medications is limited to very small case series. A proportion of patients with high arrhythmic burden require invasive procedures for ablation useful in reducing the risk of electrical storm. Patients with increased risk of SCD will require ICD implantation. Discontinuation of intense physical exercise has proven to be effective against disease progression and reducing the ventricular arrhythmia burden [4].

9. Left Ventricular Non-Compaction

Left ventricular non-compaction is morphologically characterized by a thinned, compact myocardial layer and a thickened trabecular myocardial layer composed of excessive trabeculations and deep recesses [68]. Abnormal intrauterine myocardial compaction occurs in the final phase of myocardial morphogenesis, during the first trimester of preg-

nancy [69]. Imagistic diagnostic criteria are based on echocardiography or cardiac magnetic resonance imaging. The most widely used CMR indicator in clinical studies is a non-compacted-to-compacted (NC/C) ratio > 2.3, according to criteria established by Petersen et al. associated with LV dysfunction and dilation [70,71]. LVNC primarily involves the LV, although cases of biventricular or isolated RV non-compaction have been described [72]. Clinical manifestations in patients with LVNC vary from asymptomatic patients to congestive heart failure symptoms, arrhythmias, thromboembolic complications, or sudden cardiac death. Diagnostic testing in patients with LVNC appear to have a detection rate of clinically significant variants in 35–40% of individuals, with sarcomere-encoding genes most commonly found to be mutated [73]. Physiologic hyper trabeculation may be present also in individuals without a cardiomyopathy with increased incidence in certain situations, such as pregnancy and intense physical exercise [74,75]. For this reason, recently it has been proposed to replace the term of LVNC cardiomyopathy by hyper-trabeculation. The Task Force does not consider LVNC to be a specific type of cardiomyopathy but a phenotypic feature that can be associated with other structural abnormalities, such as: ventricular hypertrophy, dilatation, and/or systolic impairment. The term 'hypertrabeculation' if preferred for this phenotype, rather than LVNC, as recommended by the Guideline of Cardiomyopathies published in August 2023 [4], due to the fact that this structural feature can be transitory or developed during adulthood. LVNC may be associated with congenital heart disease (CHD), including septal defects (ASD, VSD), hypoplastic left heart syndrome (HLHS), pulmonic stenosis (PS) and Ebstein's disease [71]. Variants in sarcomere-encoding genes (*MYH7*, *ACTC*, *TNNT2*, *MYBPC3*, *TMP1*, and *TNNI3*) and the Z-line protein-encoding *ZASP/LDB3* gene account for 20% or more of isolated LVNC, especially diagnosed during childhood [76]. Other variants described in the development of LVNC are affecting ion channels (*SCN5A*, *HCN4*, and *RYR2*) and mitochondria (*NNT*, *TAZ*). Pathogenic variants of the *SCN5A*, *LMNA*, *RBM20*, *TTN*, and *DES* genes have been associated with LVNC and increased risk of arrhythmias [77].

10. Conclusions

Inherited cardiomyopathies represent a heterogeneous group of genetic myocardial diseases with high risk of morbidity and mortality. In recent years, the number of patients diagnosed with hereditary CMs has grown, due to increased awareness and advances in cardiac imaging modalities. Next-generation sequencing methods have revolutionized genetic testing, providing identification of genetic cause of inherited cardiac diseases. Increasing numbers of rare genetic variants have been validated, new genetic markers for cardiomyopathy risk have been identified and a new pathway for future personalized care in cardiomyopathies is now available. However, diagnostic precision and potential therapeutic implications of genetic testing are still limited due to wide genetic heterogeneity, new identified variants and multiple genetic variants association. Influencing factors such as: incomplete penetrance, variable expression, impact of modifier genes, the environmental factors and furthermore the incomplete understanding of VUS, still represent significant challenges. Studying early manifestations of CMs can help identify genotype-phenotype correlations and potentially find disease-modifying treatments. Pleiotropy is a crucial aspect of genotype-phenotype relationships in the context of cardiomyopathies. Single genetic variants may contribute to the development of different forms of cardiomyopathies or even affect non-cardiac phenotypes [78,79]. Integrating genetic testing into diagnostic calculation of inheritable cardiomyopathies and cascade screening have been shown to be cost-effective. Early identification of genetic involvement in high-risk family members implies systematic follow-up and for better prognostic outcomes. The implementation of genetic-based medicine in a multidisciplinary approach of heritable CMs will hopefully shift the paradigm from a disease-based treatment to a preventive and individualized medical management.

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Abbreviations

CMs	Cardiomyopathies
ACC	American College of Cardiology
ACM	Arrhythmogenic cardiomyopathy
AHA	American Heart Association
AL	Light chain amyloidosis
ASD	Atrial septal defect
ATPase	Adenozin triphosphate-ase
ATTR	Transthyretin amiloidosis
ATTR-ACT	Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy
ATTRwt	Transthyretin amyloidosis wild-type
AVC	Arrhythmogenic ventricular cardiomyopathy
CHD	Congenital heart disease
CMs	Cardiomyopathies
CWD	Continuous Wave Doppler
DCM	Dilated cardiomyopathy
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EMF	Endomyocardial fibrosis
GLS	Global Longitudinal strain
HCM	Hypertrophic cardiomyopathy
HLHS	Hypoplastic left heart syndrome
HOCM	Hypertrophic obstructive cardiomyopathy
ISFC	International Society and Federation of Cardiology
LA	Left atrium
LV	Left ventricle
LVNC	Left ventricular noncompaction
MRI	Magnetic resonance imaging
NGS	Next-Generation Sequencing
NYHA	New York Heart Association
PLN	Phospholamban
PS	Pulmonic stenosis
PWD	Pulsed Wave Doppler
RV	Right ventricle
SCD	Sudden cardiac death
VSD	Ventricular septal defect
VUS	Variant of uncertain significance
WHO	World Health Organization

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