Genetic Screening of Hypertrophic Cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is a common inherited heart disease with an estimated prevalence of up to 1 in 200 individuals. In the majority of cases, HCM is considered a Mendelian disease, with mainly autosomal dominant inheritance. Most pathogenic variants are usually detected in genes for sarcomeric proteins.

hypertrophic cardiomyopathy genetics molecular genetic testing

1. Introduction

Hypertrophic cardiomyopathy (HCM) is an inherited cardiac disorder, defined by the presence of increased left ventricular (LV) wall thickness that is not solely explained by abnormal loading conditions [1][2]. In the majority of cases, HCM is considered a Mendelian disease with autosomal dominant inheritance, incomplete penetrance, and variable expressivity [3]. It is one of the most frequent inherited heart diseases with an estimated prevalence of up to 1 in 200 individuals and together with arrhythmogenic right ventricular cardiomyopathy (ARVC) among the most common cause of sudden cardiac death (SCD) in young athletes [4][5][6], who are often unaware of their underlying condition.

2. History of Finding the Cause of HCM

HCM was first described more than 60 years ago as asymmetrical myocardial hypertrophy with an increased risk of sudden cardiac death [7]. Although considered familial disease, the exact cause of HCM remained unknown for two subsequent decades.

Genetic studies in the 1980s and 1990s led to landmark discoveries that sarcomeric mutations cause both hypertrophic and dilated cardiomyopathies (DCM). In 1989, a mutation in the beta-myosin heavy chain (*MYH7*) gene was first identified as responsible for causing HCM [8][9]. During the next decade, numerous genes were reported to be associated with disease (**Table 1**) [10]. These eight sarcomeric genes (*ACTC1, MYBPC3, MYH7, MYL2, MYL3, TNNI3, TNNT2,* and *TPM1*) are commonly called core genes, with the most robust evidence to be causative of HCM (**Table 1**) [10][11]. This spectrum of sarcomeric genes has been gradually extended to non-sarcomeric genes encoding, for example, desmosomal proteins or ion channels [12][13]. However, a systematic evaluation of the investigation panels shows that the strongest evidence of causality remains in the eight core genes [11]. There is also strong evidence of causality in three genes—*PLN, FLNC* [11][14][15], and recently *ALPK3* [16] and moderate evidence of causality in five genes—*CSRP3, TNNC1, ACTN2*, *JPH2*, and *FHOD3* [17][18]. For the

other genes, evidence is weak or almost non-existent [11][13][19]. Variants in genes encoding non-sarcomeric proteins account for a small percentage of patients with HCM. In light of recently published analyses, they seem to be the presumed causal genes at several genome-wide association study loci [17][20], and their role in cardiomyopathy genetics is gradually expanding. Currently published data demonstrate that common genetic variants and modifiable risk factors have important roles in the HCM phenotype [17].

Table 1. Main sarcomeric genes associated with HCM.

Gene	Protein	Year of Discovery	Frequency (%) *	Inheritance	Most Common Pathogenic Variant
	Thick filament				
MYH7	Beta-myosin heavy chain	1989	20–30	AD	c.1988G>A
MYL2	Regulatory myosin light chain	1998	2–4	AD	c.173G>A
MYL3	Essential myosin light chain	1996	1–2	AD	c.281G>A
	Thin filament				
TNNT2	Cardiac troponin T	1993	10	AD	c.236T>A
TNNI3	Cardiac troponin I	1997	7	AD	c.433C>T
TPM1	Alpha tropomyosin	1993	<1	AD	c.574G>A
ACTC1	Alpha cardiac actin	1999	<1	AD	c.301G>A
	Intermediate filament				
MYBPC3	Myosin-binding protein C	1993	30–40	AD	c.1504C>T

AD—autosomal dominant, * Indicates relative frequency in HCM population.

Nowadays, more than 30 years after the publication of the first causal mutation in the MYH7 gene, thousands of mutations have been described and the numbers of identified HCM-associated genes are gradually increasing [21][22][23][24]. The Online Mendelian Inheritance in Man (OMIM) database currently lists 26 associated genes [25]. However, associations in at least 33 genes have already been reported [11] and 67 candidate genes are part of investigation panels at some expert sites [14].

It is clear, that genetic studies continue to demonstrate that HCM is predominantly a disease of the sarcomere, although the genetic basis of HCM is more diverse. Additionally, sarcomere mutations have been identified in association with other disorders of cardiac structure and function, apart from the above-mentioned DCM including

restrictive cardiomyopathy and left ventricular non-compaction [26][27][28]. Moreover, recently published data suggest that shared genetic pathways contribute to HCM and DCM development with opposite directions of effect [20].

Genetic testing was initially possible only in research laboratories capable of performing linkage analysis and candidate gene sequencing in large, well-characterized families with obviously inherited diseases. The genetic and allelic heterogeneity of HCM makes molecular analysis by conventional methods time consuming and expensive [29][30]. Advances in contemporary DNA-sequencing methodology have made gene-based diagnosis increasingly feasible in routine clinical practice. Next-generation sequencing (NGS)-based genomic testing allows rapid analysis of a large number of genes or even a whole genome at similar cost and accuracy to conventional sequencing methods [30][31]. NGS is a high-throughput method that, in comparison with classical sequencing methods (Sanger), evaluates a large amount of genetic material quickly and is cheaper. NGS uses the principle of parallelization of the sequencing process, allowing the sequencing of thousands to millions of sequences simultaneously. In addition to classical examinations of genetic variability, mutation analysis of specific genes, and quantification of individual alleles, it is possible to examine the whole exome (WES) or to perform whole-genome sequencing (WGS).

Faster and more affordable genetic testing provides opportunities to improve diagnostic certainty when evaluating patients and families with relatively non-specific phenotypes of cardiac hypertrophy. With a molecular-level diagnosis, we can differentiate genetic sarcomeric HCM from phenocopies, such as hypertensive heart disease, athlete's heart, and storage or metabolic disorders [32][33][34][35][36].

Nevertheless, screening large numbers of genes results in the identification of many genetic variants of uncertain significance (VUS) [30][31] and makes the interpretation of the results more difficult. The results of NGS produce a huge amount of output data with the subsequent need to sort and further analyze.

3. Identification of a Causative Mutation

For the clinical use of molecular genetic testing, the classification of the identified variants is essential. Due to a large amount of output data, a combined approach is currently used, based on the following rules:

-Frequency of variants in the control population, using international databases (e.g., 1000Genomes Project, Exome Sequencing Project, Exome Aggregation Consortium) [37][38][39]

-Published disease-associated variants (e.g., ClinVar, Human Gene Mutation Database) [40][41]

-In silico classification using software (e.g., Polyphen2, Sorting Intolerant From Tolerant) predicting the possible impact of the mutation on the structure and function of the final protein

-Mutations in the so-called evolutionarily highly conserved functional domains of the target protein

-Segregation analyses of genotype with phenotype in affected families (strong evidence)

-Functional studies on animal models or in vitro (expensive, complex)

In 2015, recommendations for the classification of genetic variants were published by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) [42], which is based on the above-listed principles. This classification divides the found variants into five following classes: (1) benign, (2) likely benign, (3) VUS—variant of unknown significance, (4) likely pathogenic (LP), and (5) pathogenic (P).

4. Genetic Screening

Genetic screening plays an important role in the management of patients with HCM and their relatives. The standard procedure is to obtain a detailed family history (at least three generations) and molecular genetic examination of the proband with a focus on at least all eight „core" sarcomeric genes associated with HCM (**Table 1**). If there is a clinical suspicion of a specific cause or HCM within the complex syndrome, then it is appropriate to expand the panel to other non-sarcomeric genes (**Table 2**).

Table 2. Non-sarcomeric genes associated with HCM.

Gene	Protein	Phenotype	Prevalence *	Inheritance	Frequency (%) **
PRKAG2	Protein kinase, AMP-activated, gamma 2 subunit	Wolff–Parkinson–White syndrome	1/4000	AD	0.2–1.0
LAMP2	Protein kinase, AMP-activated, gamma 2 subunit	Danon disease	1/100,000	X	0.1–0.2
GLA	Galactosidase, alpha	Fabry disease	1/40,000	X	0.5–1.0
FHL1	Four and a half LIM domains 1	Emery–Dreifuss myopathy	1/100,000	X	0.1–0.5
TTR	Transthyretin	Amyloidosis ***	1/100,000	AD	0.8–5
GAA	Glucosidase, alpha	Pompe disease	1/40,000	AR	0.01–0.1
PTPN11	Protein tyrosine phosphatase, non-receptor type 11	Noonan syndrome LEOPARD	1/2000	AD	1–5
FXN	Frataxin	Friedreich ataxia	1/20,000	AR	0.05–0.2

AR—autosomal recessive, X-X linked, * Indicates prevalence in the general population, ** Indicates relative frequency among HCM cases, may differ from the expected prevalence in the general population due to the selection bias of HCM genotyped cohorts, *** hereditary, not wild-type (senile).

In the case of a positive finding, molecular genetic testing of the first-degree relative for a specific gene and mutation already found in the proband is performed. If a pathogenic mutation is detected in a relative, a cascade examination of other relatives is possible (due to the predominant AD inheritance). Detailed family history and

pedigree will help us to identify the probable hereditary cause of the disease and usually determine the type of heredity. Genetic analysis of post-mortem tissue samples with cascade screening of relatives is feasible [43]. The main clinical advantage is the situation where a specific causal mutation in the proband is not found in the first-degree relative. The relative can then be excluded from the dispensary, the probability of the disease is low, however, de novo mutations are possible. Therefore, we always warn patients about the need to seek a specialist in case of symptomatology. According to current recommendations, the examination of children is appropriate around the age of 6–10 [1][44]. The threshold was established based on pediatric studies, which showed a rare incidence of serious complications of HCM before the onset of puberty [45][46].

If the molecular genetic examination of the proband is negative (no P/LP variant is found), we continue the established regular clinical monitoring of first-degree relatives. It includes clinical and echocardiographic examination, 12-lead ECG, Holter ECG monitoring (**Figure 1**). In selected patients (usually with insufficient echocardiographic window), cardiac magnetic resonance imaging (MRI) is performed. MRI can be useful in young patients with an early-onset screening of metabolic diseases [44][47] and its role in SCD risk stratification is increasing [44][48].

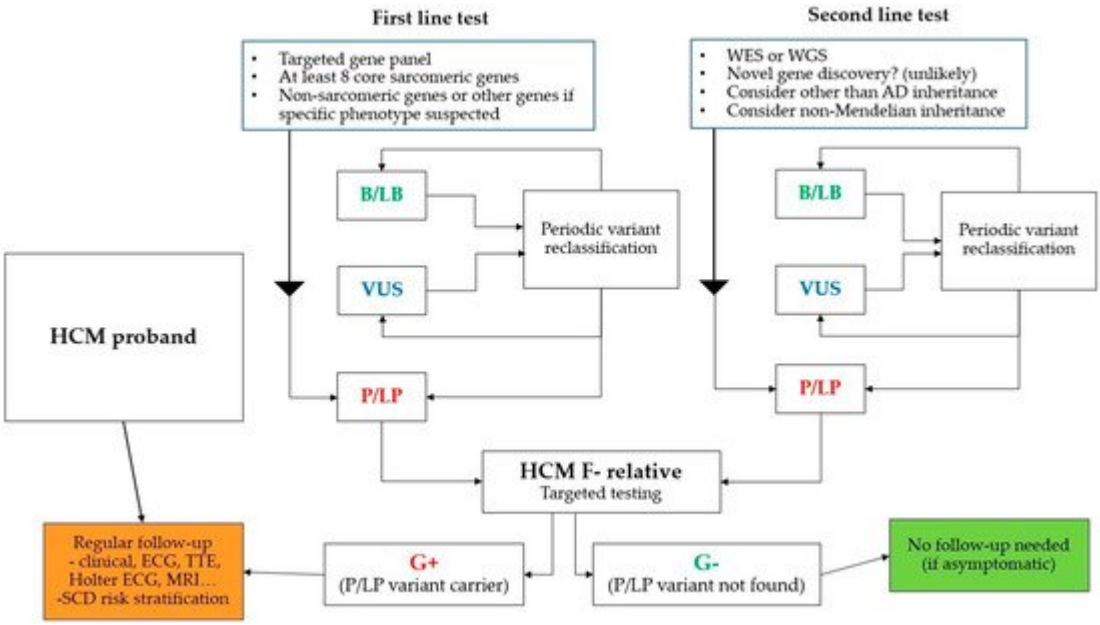

Figure 1. Cascade genetic testing. B/LB—benign or likely benign, P/LP—pathogenic or likely pathogenic, VUS—variant of unknown significance, WES—whole exome sequencing, WGS—whole genome sequencing, ECG—electrocardiography, MRI—magnetic resonance imaging.

The opposite clinical situation is a clinically negative phenotype (F-) with the finding of P/LP mutation (genotype positive, G+). In contrast to DCM, where, for example, a mutation in the LMNA gene is associated with an unfavorable prognosis and is even part of the indication for ICD (implantable cardioverter-defibrillator) implantation according to ESC guidelines [49], the risk of SCD is generally low in individuals without expressed hypertrophy. Mutations in TNNT2 may be an exception, as suggested by some publications [50][51], but this is not strong evidence. It is not clear whether to make specific recommendations and propose restrictions, e.g., for professional

athletes [21][52][53], based on a positive genotype without an expressed phenotype (G+/F-). It has been repeatedly reported that most G+/F- patients probably have a favorable prognosis [52][54]. However, due to age-related variable penetrance (55% to 30 years of age, up to 95% over 50 years of age [55], regular clinical monitoring of these individuals should be continued.

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