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Genetics and Hypertrophic Cardiomyopathy

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Abstract While there are some similarities with adult hypertrophic cardiomyopathy (HCM), pediatric HCM has many differences. Although sarcomere protein mutations affecting only the heart explain the majority of pediatric HCM, many young pediatric patients have HCM as part of a larger syndrome, neuromuscular disease, or metabolic disorder. Current HCM genetic testing panels are useful to identify a mutation in some affected children; however, the yield for pediatric patients is lower than that for adults. The yield improves when the panel of genes involved in the RASopathies is also included. Future genetic testing strategies may rely more on whole-exome sequencing as a reflex after negative panel results or even as an initial first step. Furthermore, while there is currently no known intervention that prevents the development of HCM in mutation-positive individuals, various pharmacologic and molecular treatment strategies are now focused on efforts to correct the underlying genetic defect.

Keywords Hypertrophic cardiomyopathy · Genetics · Sarcomere · RASopathy · Genetic testing · Whole-exome sequencing

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Introduction

Hypertrophic cardiomyopathy (HCM) is characterized by the abnormal development of left ventricular hypertrophy and cardiac myocyte disarray [1]. It affects 1:500 individuals, making it one of the most common cardiac genetic diseases [2] with recent studies suggesting that HCM may even be 2.5-fold more common [2, 3]. Clinically, the disease is extremely variable. Affected individuals can present with a murmur or abnormal electrocardiogram, or more seriously with syncope, heart failure, or sudden cardiac death [4].

Just as the disease is clinically heterogeneous, there is also marked genetic heterogeneity for HCM. Adult-onset HCM is generally considered an autosomal dominant disease with reduced penetrance. Linkage studies in the 1980s led to the discovery that HCM was caused by mutations in the genes encoding sarcomere proteins [5]. To date, over 1500 mutations have been identified with the majority in the genes *MYH7* (OMIM 160760) and *MYBPC3* (OMIM 600958) which encode for β-myosin heavy chain and cardiac myosin-binding protein C, respectively [6, 7]. Most mutations are individually rare and family specific, making larger genotype–phenotype correlations difficult.

While there are some similarities to adult HCM, pediatric HCM has many differences. The Pediatric Cardiomyopathy Registry found that the annual incidence of HCM in the pediatric population was 4.7 per one million [8]. As opposed to the isolated cardiac disease seen in the adult population, 25.2 % of pediatric patients have HCM as part of a larger syndrome, neuromuscular disease, or metabolic disorder [8]. Furthermore, children with inherited sarcomere protein mutations rarely develop clinical disease before the age of 14 [9], which suggests that infantile and early pediatric cases represent a unique

disease entity with a different genetic etiology. Underlying etiology is an important correlate with clinical outcomes, and infants with extracardiac disease have lower rates of survival [10].

In this review, we summarize the current knowledge about the genetics of HCM, focusing on the pediatric age group. We will discuss genetic testing recommendations and testing strategies for both inherited cardiomyopathy and suspected cases of de novo disease. We conclude with potential therapeutic strategies and future directions in the field. The goal of this review is to provide the general practitioner with an up-to-date summary of current knowledge while highlighting potential new developments on the horizon.

Genetics

In the majority of patients, HCM is inherited in an autosomal dominant fashion meaning that an affected individual has a 50 % chance of passing on the disease gene in each pregnancy. However, in children, autosomal recessive and de novo mutations are increasingly becoming recognized as important contributors to disease. There is growing evidence that older adolescents and young adults with isolated HCM are similar in etiology to adult-onset disease, while infants and younger children often have a very different type of HCM associated with extracardiac features. In particular, knowing about noncardiac features is important as additional surveillance or intervention may be required for syndromic, neuromuscular, and metabolic cardiomyopathies. Furthermore, knowing about systemic disease is important as it can impact medical management decisions particularly when considering cardiac transplantation.

Sarcomeric Cardiomyopathy

Even though there are differences between adult and pediatric HCM, sarcomere protein mutations explain the majority of cases for both (Table 1). In one study examining 84 children with isolated HCM, sequencing of eight sarcomere proteins [*MYH7*, *MYBPC3*, *TNNT2* (OMIM 191045), *TNNI3* (OMIM 191044), *TPM1* (OMIM 191010), *MYL3* (OMIM 160790), *MYL2* (OMIM 160781), and *ACTC* (OMIM 102540)] and two metabolic proteins [*PRKAG2* (OMIM 602743) and *LAMP2* (OMIM 309060] revealed that 55 % of children, regardless of family history, had an identifiable mutation [9]. Specifically, 75 % of children with an identifiable mutation had at least one mutation in *MYBPC3* or *MYH7* with an increased number of *MYBPC3* missense mutations compared to adult-onset cases. Only one of the 46 mutation-positive children had a mutation which was not in a sarcomeric gene which led the authors to conclude that the genetic architecture was similar in children with isolated cardiomyopathy.

Some recent studies have suggested that digenic or multigenic sarcomere protein mutations may lead to a more severe phenotype [11, 12]. Early-onset disease development may partially be explained by multiple mutations with additive or synergistic effects. In unpublished work, we have observed that infants less than 1 year of age and pediatric patients one to 18 years of age were more likely to have two or more mutations compared to adults (11.1 and 12.6 %, respectively, vs. 5.6 % for adults; $p = 0.0001$ for both in comparison to adults).

Syndromic Cardiomyopathy

Genetic syndromes comprise approximately 10 % of pediatric HCM cases [13•]. RASopathies (Noonan syndrome, Noonan syndrome with multiple lentigines, Costello syndrome, and cardiofaciocutaneous syndrome) account for the majority of these cases [14]. These autosomal dominant disorders affect the RAS signaling pathway. HCM has been observed in all these conditions with varying frequencies.

Up to 90 % of Noonan patients have cardiovascular involvement [15••] which includes HCM in 20 % of the cases [16]. As opposed to sarcomere protein mutations, HCM associated with Noonan syndrome has a much earlier age of presentation, with a median age of 5 months [15••]. Furthermore, individuals with Noonan syndrome are more likely to present with signs and symptoms of heart failure and significant left ventricular outflow tract obstruction [15••], and outcomes are poorer with earlier mortality, particularly during infancy [17]. Other clinical manifestations include neurocognitive delays, bleeding disorders, myeloproliferative disorders such as juvenile myelomonocytic leukemia, and abnormal lymphatics [18].

PTPN11 (OMIM 176876) gain-of-function mutations account for 50 % of Noonan diagnoses [19] with additional genes that alter RAS signal transduction such as *SOS1* (11 %, OMIM 182530), *RAF1* (5 %, OMIM 164760), *SHOC2* (2 %, OMIM 602775), *KRAS* (1.5 %, OMIM 190070), *NRAS* (0.2 %, OMIM 164790), *BRAF* (OMIM 164757), *CBL* (OMIM 165360), and *RIT1* (OMIM 609591) accounting for other known genetic causes [18, 20]. Recent molecular technology advances have allowed for the identification of additional novel genes such as *A2ML1* (OMIM 610627), *LZTR1* (OMIM 600574), *RASA2* (OMIM 601589), *RRAS* (OMIM 165090), and *SOC2* (OMIM 233700) which may also be implicated [18]. However, at this time about 30 % of RASopathies remain without a genetic diagnosis [18].

Multiple other RASopathies have also been described with features that overlap with Noonan syndrome. Noonan

Table 1 Common genetic causes of pediatric hypertrophic cardiomyopathy [13•, 58]

Etiology	Genes	Extracardiac features	Treatments
Isolated cardiomyopathy			
Sarcomere disease [59]	*ACTC* (*ACTC1*), *MYBPC3*, *MYH6*, *MYH7*, *MYL2*, *MYL3*, *TNNC1*, *TNNI3*, *TNNT1*, *TNNT2*, *TPM1*, *TTN*		
Z-disk	*ACTN2*, *ANKRD1*, *CSRP3*, *LBD3*, *MYOZ2*, *NEXN*, *TCAP*, *VCL*		
Calcium handling	*JPH2*, *PLN*		
Cardiomyopathy with extracardiac features			
Genetic syndromes			
RASopathies [18]			
Noonan syndrome	*BRAF*, *CBL*, *KRAS*, *NRAS*, *PTPN11, RAF1*, *RIT1*, *SHOC2*, *SOS1*	Neurocognitive delay, bleeding disorders, myeloproliferative disorders, abnormal lymphatics	
Noonan syndrome with multiple lentigines (previously LEOPARD syndrome)	*BRAF, PTPN11*, *RAF1*	Sensorineural deafness	
Costello syndrome	*HRAS*	Neurocognitive delay, failure to thrive, increased risk of malignant tumors	
Cardiofaciocutaneous syndrome	*BRAF*, *KRAS*, *MAPK21*, *MAP2K2*	Severe neurocognitive delay, failure to thrive, hypotonia	
Neuromuscular disorders [26]		Muscular dystrophy or myopathy is the common feature in this group of disorders	
Becker muscular dystrophy	*DMD*		
Facioscapulohumeral muscular dystrophy	Contraction mutation of number of D4Z4 repeats in 4q35 region, *SMCHD1*		
Emery–Dreifuss muscular dystrophy	*EMD*, *FHL1, LMNA*		
Limb-girdle muscular dystrophy	*ANO5*, *CAPN3*, *CAV3*, *DES*, *DNAJB6*, *DYSE*, *FKRP*, *FKTN*, *GMPPB*, *LMNA*, *MYOT*, *PLEC*, *POMGNTI*, *POMT1*, *POMT2*, *SGCA*, *SGCB*, *SGCD*, *SGCG*, *TCAP*, *TRIM32*, *TTN*		
Myofibrillar myopathy	*BAG3*, *CRYAB*, *DES*, *DNAJB6*, *FHL1*, *FLNC*, *LDB3*, *MYOT*		
Glycogen storage disease			
Pompe disease (GSD II)	*GAA*	Failure to thrive, hypotonia	ERT
GSD III	*AGL*	Liver and muscle involvement	
AMP kinase disease *PRKAG2*	*PRKAG2*		
Danon disease	*LAMP2*		
Lysosomal storage disease			
Fabry disease	*GLA*	Renal disease, vascular cutaneous lesions, sweating abnormalities, corneal and lenticular opacities, pain crises	ERT
Hurler syndrome (MPS I)	*IDUA*	Neurocognitive delay, growth failure, skeletal dysplasia, retinal degeneration, corneal clouding, hearing loss	ERT HSCT
Hunter syndrome (MPS II)	*IDS*	Neurocognitive delay, growth failure, progressive airway disease, skeletal dysplasia	ERT

Table 1 continued

Etiology	Genes	Extracardiac features	Treatments
Sanfilippo syndrome (MPS III)	*GNS*, *HGSNAT*, *NAGLU*, *SGSH*	Progressive neurologic degeneration, seizures	
Morquio syndrome (MPS IV)	*GALNS*	Progressive skeletal disease, visual and hearing impairment	ERT
Maroteaux–Lamy syndrome (MPS VI)	*ARSB*	Skeletal dysplasia	ERT HSCT
Sly syndrome (MPS VII)	*GUSB*	Neurocognitive delay, hydrocephalus, skeletal dysplasia, corneal clouding	HSCT
Disorders of fatty acid metabolism			
Carnitine deficiency	*SLC22A5*	Hypoketotic hypoglycemia, hypotonia	Carnitine supplementation
Long-chain 3-hydroxyacyl-CoA deficiency	*HADHA*	Hypoglycemia, hepatomegaly, hypotonia	Dietary management
Very long-chain acyl-CoA dehydrogenase deficiency	*ACADVL*	Hypoglycemia, hepatomegaly, hypotonia	Dietary management
Other metabolic disease			
Barth syndrome	*TAZ*	Growth delay, muscular myopathy, neutropenia	
Mitochondrial disorders			
Kearns–Sayre	Mitochondrial DNA deletions	Cerebellar ataxia, progressive external ophthalmoplegia, pigmentary retinopathy, deafness	
MELAS	*MT-CO1, MT-CO2, MT-CO3*, *MT-CYB*, *MT-ND1*, *MT-ND3*, *MT-ND5, MT-ND6, MT-TC, MT-TF, MT-TK*, *MT-TL1, MT-TQ*, *MT-TS1, MT-TS2*, *MT-TV, MT-TW*	Seizures, muscle, weakness, visual impairment, sensorineural hearing loss	
MERRF	*MT-TF*, *MT-TI, MT-TK*, *MT-TL1*, *MT-TP*	Epilepsy, ataxia, myoclonus, optic atrophy, hearing loss	

ERT enzyme replacement, *GSD* glycogen storage disease, *HSCT* hematopoietic stem cell transplantation, *MELAS* mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, *MERRF* myoclonic epilepsy with ragged red fibers, *MPS* mucopolysaccharidosis

syndrome with multiple lentigines (previously LEOPARD syndrome) is the RASopathy most frequently associated with HCM which is found in 80 % of patients [21]. This disorder is also associated with *PTPN11* mutations; however, these mutations tend to decreased protein function. *RAF1* and *BRAF* variants have also been implicated [22, 23]. Costello syndrome, caused by mutations in *HRAS*, is also associated with HCM and 65 % of patients have hypertrophy which tends to be asymmetric [24]. Cardiac disease can be rapidly progressive in 40 % of those affected [15••]. Additionally, individuals with Costello syndrome have a 10–15 % increased risk for malignant tumors [18]. Lastly, 40 % of patients with cardiofaciocutaneous syndrome have HCM [25]. Phenotypically, there is a great deal of overlap with Costello syndrome, and cardiofaciocutaneous individuals have growth failure, development delay, hypotonia, as well as skin abnormalities. There is genetic overlap and *KRAS* and *BRAF* are associated with both Noonan syndrome and cardiofaciocutaneous syndrome. Additionally, *MAP2K1* (OMIM 176872) and *MAP2K2* (OMIM 601263) are implicated in cardiofaciocutaneous syndrome.

Neuromuscular Cardiomyopathy

Cardiomyopathy can be due to a systemic myopathy or neuromuscular disease. In some instances, cardiomyopathy can be the initial manifestation. Overall, neuromuscular disorders account for almost 10 % of pediatric HCM cases [8]. Friedreich ataxia, which is an autosomal recessive disorder due to mutations in the *FXN* (OMIM 606829) gene, is the most common neuromuscular cause of HCM. Patients commonly develop concentric hypertrophy without outflow tract obstruction after developing other symptoms of ataxia and/or muscle weakness [13•]. Other common neuromuscular diseases associated with HCM include Emery–Dreifuss muscular dystrophy, limb-girdle muscular dystrophy, and myofibrillar myopathy [26]. In addition, HCM has increasingly been described in many other different types of neuromuscular disease although

with lower frequency. Modes of inheritance can include autosomal dominant, autosomal recessive, and X-linked.

Metabolic Cardiomyopathy

Metabolic causes of cardiomyopathy can include storage diseases, such as glycogen and lysosomal storage diseases, and disorders of lipid metabolism. Collectively, this group accounts for about 10 % of pediatric HCM cases [8].

Most cases of HCM related to a metabolic disorder are secondary to a glycogen storage disease (GSD) [8]. Pompe disease, or GSD II, is an autosomal recessive disorder due to mutations in *GLA* (OMIM 300644) which leads to a deficiency in the enzyme acid maltase. The infantile form can present in the first few months of life with hypotonia and massive cardiac hypertrophy secondary to glycogen deposition in the heart. Many states now include population-based screening for Pompe disease in their newborn screening programs since enzyme replacement therapy is now available. Cardiac muscle generally responds well to enzyme replacement, and better outcomes have been demonstrated when treatment is initiated as early as possible [27].

Another type, GSD III, has four subtypes with varying liver, muscle, and heart involvement. Childhood development of HCM can occur in the majority of those with the IIIa subtype [28]. Treatment for GSDs is focused on high-protein diet with cornstarch supplementation to maintain normal glucose levels. While liver transplantation is recommended in some GSDs, in type III liver transplant is generally reserved for cases with severe liver disease as the cardiac and muscle disease persists after transplant [29].

Danon disease is an X-linked disorder, sometimes referred to as lysosomal glycogen storage disease with normal acid maltase, which can affect both males and females. It is caused by defects in the *LAMP2* (OMIM 309060) gene, and males usually present in childhood while females tend to develop disease in adulthood. HCM and dilated cardiomyopathy (DCM) have both been associated. Prognosis is usually poor due to the high incidence of arrhythmias and sudden cardiac death [30].

Mutations in *PRKAG2* (OMIM 602743), which encodes for the γ-subunit of AMP kinase, have been observed in infants with severe HCM [31]. Hypertrophy is caused by the accumulation of glycogen-filled vacuoles. Conduction disease and pre-excitation can also be seen with *PRKAG2* mutations.

Fabry is a lysosomal storage disease caused by X-linked mutations in the *GLA* (OMIM 300644) gene which affects multiple organs including the kidneys and peripheral nerves. Myocardial deposition may lead to cardiac hypertrophy but for the classic form of the disease this is usually not evident until later adulthood and predominantly in males [32]. Enzyme replacement therapy is available and is maximally beneficial if initiated before the onset of severe cardiac disease.

Mucopolysaccharidoses (MPSs) are also classified as lysosomal storage diseases and characterized by deficient breakdown of glycosaminoglycans. Valvular disease is most commonly observed, but HCM is another manifestation. Examples of diseases in this category include Hurler (MPS I), Hunter (MPS II), Sanfilippo (MPS III), Morquio (MPS IV), Maroteaux–Lamy (MPS VI), and Sly (MPS VII) syndrome [13•]. Enzyme replacement therapy is available for MPS types I, II, IV, and VI. Bone marrow transplantation is another treatment alternative and has been most successful for MPS I, VI, and VII. Treatment response can be variable, and timing of initiation of therapy likely has some influence on the clinical response.

Other metabolic disorders can involve fatty acid oxidation. Very long-chain acyl-CoA dehydrogenase deficiency and long-chain 3-hydroxyacyl-CoA deficiency can present with severe HCM early in life. Diet modification with low-fat formula and treatment with medium-chain triglycerides can lead to dramatic reversal of cardiac hypertrophy [33]. Similarly, levocarnitine supplementation in carnitine deficiency can produce striking improvement [32]. Newborn screening has been particularly impactful on these forms of metabolic cardiomyopathy with significant reductions in morbidity and mortality [34].

Barth syndrome, or 3-methylglutaconic aciduria type II, is an X-linked disease that can present with DCM, noncompaction cardiomyopathy, endocardial fibroelastosis, and occasionally HCM generally before the age of five [35]. Prolonged QTc interval, ventricular arrhythmia, and sudden cardiac death have also been described. Cardiac disease is generally responsive to standard heart failure treatment regimens, but cardiac transplantation has been necessary in some cases [36, 37]. Barth syndrome is also associated with growth delay, skeletal myopathy, and neutropenia.

Mitochondrial Cardiomyopathy

Mitochondrial disorders disrupt the normal oxidative phosphorylation process and lead to decreased activity of mitochondrial enzymes. This class of disorders can be inherited via maternal mitochondrial DNA and also from nuclear DNA generally in an autosomal recessive manner. HCM and DCM have both been associated, and cardiac involvement is observed in 40 % of cases [38]. Concentric hypertrophy is generally observed and can rapidly progress to DCM with heart failure. Examples include MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes) and MERRF (myoclonic epilepsy with ragged red fibers). Kearns–Sayre syndrome is a

mitochondrial disease that has also been associated with progressive heart block and ophthalmologic involvement.

Congenital Disorders of Glycosylation

HCM is a rare but reported feature in congenital disorders of glycosylation [39]. This group of disorders is characterized by abnormalities in the pathways involved in the glycosylation of proteins or lipids. Most cases present during infancy. The clinical picture is variable but at the severe end of the spectrum can be associated with profound development delay and multiorgan involvement. There are many different subtypes, each with a different associated gene. Initial screening for all congenital disorders of glycosylation starts with transferrin isoform analysis.

Clinical Genetic Testing

Clinical genetic testing has been available for HCM since 2003 [6] and is useful to identify a mutation in an affected individual. Current clinical panels have a yield of about 60 % across all ages [40]. The yield in children is lower with only 30.8 % of infants under 12 months of age and 49.9 % of children ages 1–18 years having an identified genetic etiology (unpublished data).

Once a familial mutation has been identified, cascade genetic testing can be offered to first-degree family members to identify relatives at risk for disease and/or provide parents information about risk of recurrence in future pregnancies. Genetic testing is commonly covered by insurance and can be performed on blood or saliva. The 2011 American College of Cardiology Foundation/American Heart Association and the 2014 European Society of Cardiology guidelines provide detailed recommendations regarding genetic testing [41•, 42].

Genetic Testing

Genetic counseling and genetic testing for individuals with HCM is recommended. Genetic testing is strongly recommended when there is atypical HCM or signs or symptoms of disease beyond the heart. A specific genetic diagnosis often clarifies prognosis and identifies other noncardiac disease for monitoring, as well as identifies treatment options for metabolic cardiomyopathies. Identification of a genetic cause of the HCM allows for cascade genetic testing of family members which can help identify at-risk individuals within the family. Moreover, knowing the genetic cause of HCM in one child can help parents plan for future pregnancies, as the risk to have another affected child can be as high as 50 % in autosomal dominant and 25 % in autosomal recessive and X-linked cases.

Gene panels are available for HCM genetic testing with the actual number of genes ranging from as few as five to over 30 genes for the different laboratories in the United States. We believe that when testing children, the panel of genes involved in the RASopathies should be included as one study showed that 28.8 % of children with HCM had clinical phenotypic features consistent with Noonan syndrome [10].

Whole-Exome Sequencing (WES)

WES sequences the protein-coding portion of the genome. It is useful in diseases that are genetically heterogeneous and when all the genes for a disease may not have yet been identified. At this time, the yield of WES in children with HCM is not known. It remains to be determined if children, particularly infants, should first have HCM panel testing and then reflex to WES if the results are negative versus just starting with WES. Given that the cost of WES has dramatically declined and is now covered by some insurances, WES should be considered in the diagnostic evaluation. WES is particularly useful in diseases for which de novo mutations account for a significant fraction of the disease burden as the child's DNA sequence can be directly compared to the parents' in a trio analysis to determine if there are pathogenic variants in the child that were not inherited. WES may also be useful in families with consanguinity or suspected autosomal recessive inheritance.

Variants of Unknown Significance and Uninformative Negative Results

Genetic testing is more useful when parents and other family members are available for comparison. Testing can sometimes identify variants of uncertain significance. Testing additional affected and unaffected family members to determine if the variant segregates with disease can be helpful. Variants in known cardiomyopathy genes that are de novo in the child are almost always pathogenic. As the knowledge about the underlying genetics of HCM continues to grow and additional data become available for differing ethnic groups, classification of variants will improve with decreasing frequency of variants of uncertain significance.

Genetic testing in children using a gene panel can often yield a negative result which is considered uninformative. Failing to identify a mutation does not exclude a genetic disease in the family, and it is important that patients understand this distinction and that cardiac surveillance of first-degree relatives is still necessary in this scenario. In particular, although genetic testing is not officially recommended in the evaluation of athlete's heart [42], should genetic testing be used in an attempt to distinguish between

athlete's heart versus HCM, and a negative test greatly reduces the probability but does not exclude the diagnosis of HCM [43].

Familial or Cascade Testing

Currently, the most immediate clinical utility of HCM genetic testing is to identify at-risk family members [44]. When genetic testing of the proband identifies a pathogenic mutation, cascade testing can be performed in first-degree relatives. This allows identification of relatives who may have subclinical disease or be predisposed to develop disease in the future. Moreover, family members who test negative no longer require serial cardiac surveillance. This use of predictive genetic testing has been shown to be highly cost effective [45].

Surveillance clinical screening is recommended for family members who are mutation positive or in families in which an underlying genetic diagnosis is not made. Cardiac surveillance for familial disease is performed annually during adolescence and early adulthood [6]. After age 25, screening is recommended at least once every 5 years although more frequent screening, including annual screening, is advocated by some. Earlier screening during childhood is recommended if early-onset disease has been observed in the family.

Prenatal Genetic Testing

The genetic testing strategies described above can also be performed prenatally on a fetus by obtaining fetal DNA via chorionic villus sampling or amniocentesis. Prevention of genetic transmission to offspring is currently available through preimplantation genetic diagnosis which involves in vitro fertilization and testing embryos to select those without the mutation prior to embryo transfer. Particularly in families with early lethality, this may be a desired option.

Genotype Positive–Phenotype Negative Patients

Currently, the American and European guidelines differ on the exercise restriction policy in preclinical mutation carriers. In the United States, guidelines stipulate that there is insufficient evidence to exercise restriction in genotype positive–phenotype negative individuals, while the European guidelines prohibit competitive athletics [41•, 42]. This reluctance to allow competitive athletic participation is in part due to evidence that even those with preclinical disease can have molecular abnormalities related to myocardial relaxation [46]. However, this is countered by the psychological impact of sport restriction and the maladaptive effects of a sedentary lifestyle such as obesity, metabolic syndrome, and other cardiovascular diseases [47].

Psychosocial Impact of Genetic Testing in Children

Genetic testing in minors must be guided by the best interests of each child in accordance with international standards for good practice [48]. Genetic testing can help reduce uncertainty, allow for adjustment, and facilitate realistic life planning. However, testing can negatively increase anxiety and distort self-image. These challenges are even more evident when the patients are adolescents in the process of forming identities, planning futures, and developing family and peer relationships. Focused studies are needed in this vulnerable age group to determine the impact that genetic testing results can have on psychosocial well-being and quality of life.

Potential Therapeutic Approaches

Currently, there is no known intervention that prevents the development of HCM in mutation-positive individuals with sarcomere protein mutations. Animal studies have suggested that abnormal calcium handling may be one of the key inciting events, and a randomized controlled clinical trial comparing the calcium channel blocker diltiazem to placebo was recently completed, which showed that treatment with diltiazem may improve left ventricular remodeling [49]. Other studies using angiotensin II receptor blockers, like valsartan, are currently ongoing (https://clinicaltrials.gov/ct2/show/NCT01912534?term=VANISH&rank=1).

Treatment Strategies for RASopathies

Since RASopathies involve dysregulation of the RAS/mitogen-activated protein kinase pathway, unique therapeutic targets that inhibit this signaling cascade have been suggested for this group of disorders [50]. Mouse studies have shown that blocking this pathway can ameliorate the associated phenotypic findings [51, 52] and potential application for humans is currently being explored.

Molecular Strategies

Various molecular treatment strategies are now focused on efforts to correct the underlying genetic defect. Gene therapy strategies have been attempted in animal models and include methods of genetic manipulation such as gene replacement, gene overexpression, and gene inhibition [53]. One study in mice showed that the introduction of the normal gene could prevent development of cardiac disease and also suppress expression of the abnormal gene product [54]. This method, in particular, seems promising for sarcomeric HCM caused by autosomal dominant missense

mutations. For frameshift mutations or mutations which truncate the protein, studies have shown that antisense oligonucleotides can be used to mediate exon skipping over a mutated exon and as a result restore sarcomeric formation [55]. Mutation silencing by RNA interference cassettes may also be a possible strategy for dominant mutations [56]. While these studies are promising, the near-term applicability for treating patients with HCM remains to be determined.

Future Directions

Current research is directed at identifying additional genes for HCM in children as well as genetic modifiers to explain the reduced penetrance and variable expressivity of the known HCM genes. Advances in cellular technology and programming have now made it possible to generate induced pluripotent stem cell-derived cardiomyocyte models of disease that can be used to study HCM in vitro. Patient-specific cell lines can be generated that recapitulate clinically observed phenotypes. Known and novel drugs can be studied for potential side effects and efficacy [57]. Moreover, genetic variants can be studied to determine potential pathogenicity and to elucidate underlying molecular mechanisms for disease pathogenesis. It is anticipated that cellular models of disease will aid in the development of novel therapeutics and facilitate personalized medical treatments.

Conclusion

Increased understanding of the genetic etiology of HCM has led to progress within the field. While sarcomere protein mutations still account for the majority of pediatric cases, RASopathies and other metabolic or multisystemic diseases are increasingly recognized, particularly in early-onset disease. Genetic heterogeneity makes genetic diagnosis and clinical management challenging as extracardiac involvement must be considered. Genetic testing can help clarify diagnosis, but current testing panels have a lower yield in pediatric patients as compared to adults. As technology improves and cost declines, WES may represent a feasible first test, particularly in infants.

Identification of a genetic cause of the HCM allows for cascade genetic testing of family members which can help identify at-risk individuals within the family and help parents plan for future pregnancies. Genetic testing has allowed for the identification of mutation carriers who may not have clinical disease. Research focused on this preclinical cohort may lead to better understanding of disease progression and potentially novel therapeutic interventions to halt disease development.

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Compliance with Ethics Guidelines

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