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Implications of Genetic Testing in Noncompaction/ Hypertrabeculation

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Abstract

Noncompaction/hypertrabeculation is increasingly being recognized in children and adults, yet we understand little about the causes of disease. Genes associated with noncompaction/ hypertrabeculation have been identified, but how can these assist in clinical management? Genomic technologies have also expanded tremendously, making testing more comprehensive, but they also present new questions given the tremendous diversity of phenotypes and variability of genomes. Here we present genetic evaluation strategies and assess clinical testing options for noncompaction/hypertrabeculation. We assess genes/gene panels offered by clinical laboratories and the potential for high-throughput sequencing to fuel further discovery. We discuss challenges in cardiovascular genetics, such as interpretation of genomic variants, prediction and disease penetrance.

Keywords

genomic medicine; genetic test; noncompaction; cardiomyopathy; genome; variant; interpretation; race

INTRODUCTION

Patients with cardiac noncompaction/hypertrabeculation cardiomyopathy are increasingly being recognized in clinical practice [Freedom et al., 2005; Nugent et al., 2003]. These patients may have relevant genetic variation identifiable via testing. By thoroughly screening family members, astute clinicians and researchers have revealed familial heart abnormalities and associated genetic changes [Budde et al., 2007; Hoedemaekers et al., 2010]. Now that laboratory testing options are more numerous, it is becoming possible to understand how the genome and its information lead to this cardiac condition. What clinical strategies in genetics are most helpful in managing patients with noncompaction/ hypertrabeculation? Gene testing and multi-gene panels are often considered for patients or their families for molecular diagnosis and risk management. High-throughput sequencing has tremendous capabilities, since the number of noncompaction-associated genes has expanded and these can be efficiently sequenced in parallel for clinical use. Variation data on these genes are still accumulating, however, and interpretation of sequencing can be challenging. In this article we address the utility of genetic evaluation in noncompaction/

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hypertrabeculation. Since technologies for testing are rapidly changing, we discuss evolving approaches to comprehensive patient and family care.

ELEMENTS OF GENETIC EVALUATION FOR NONCOMPACTION

Family History

The family history is important in providing care for patients in cardiovascular genetics. Pedigrees have been a cornerstone for evaluating families [Bennett et al., 2008], and they are essential in evaluation for cardiomyopathies [Morales et al., 2008]. Noncompaction/hypertrabeculation has been seen in concordant twins [Ali, 2008; Peters et al., 2012], in discordant twins [Ng et al., 2013], and in families with other cardiomyopathies or cardiac disease [Budde et al., 2007; Dellefave et al., 2009]. Evidence for familial disease, consanguinity [Shieh et al., 2012] or specific inheritance patterns should be examined thoroughly [Hoedemaekers et al., 2010]. Even in dominant disease, penetrance may be incomplete [Budde et al., 2007; Probst et al., 2011] or disease presentation may be different based on age or individual physiology. A three-generation pedigree with open-ended and specific questions is often elicited. Specific questions cover whether family members have had cardiac conditions, accidental or unexpected deaths, arrhythmia symptoms, thromboses, cardiac surgery or congenital heart disease. Family cardiac studies and records should be reviewed when available. Important information can be gained from skilled evaluation. In cardiovascular disease, for example, family histories have demonstrated added benefit in identifying at-risk patients beyond the Framingham-based risk criteria [Qureshi et al., 2012]. Electronic medical records, with further development, will also be able to provide more useful information.

Comorbid Genetic Conditions

A patient with noncompaction/hypertrabeculation can have primary “isolated” cardiac disease or can have a comorbid genetic condition. The heterogeneity in noncompaction/hypertrabeculation patients can be discerned by astute observation. Unusual physical features, other organ system abnormalities, or unexplained growth problems could herald a chromosomal abnormality. In patients with chromosome 1p36 deletion, noncompaction/hypertrabeculation is often present and can be a cause of significant morbidity. Findings in 1p36 deletion patients include certain facial physical features, developmental delay, seizures, or hearing loss [Battaglia et al., 2008]. One of the first well-defined genetic syndromes associated with noncompaction/hypertrabeculation was Barth syndrome [Bleyl et al., 1997; Ichida et al., 2001], a distinctive condition that should be recognized for multisystem management. Noncompaction/hypertrabeculation has also been reported in a large number of conditions including mitochondrial diseases [Finsterer et al., 2004; Scaglia et al., 2004; Yaplito-Lee et al., 2007], neuromuscular diseases [Stollberger et al., 2004], and other genetic syndromes (Table I). The clinical consequences of noncompaction/hypertrabeculation in these patients seem to vary tremendously, but more data is needed. For any of these conditions, prompt diagnosis and evaluation is important given potential comorbidities. If the heart is the primary or only organ involved, the term isolated ventricular noncompaction/hypertrabeculation has been used [Chin et al., 1990; Ritter et al., 1997]. Even in isolated ventricular noncompaction/hypertrabeculation, thromboses, arrhythmias, cardiac failure and other complications can occur, making it important to identify those individuals with susceptibility for cardiomyopathy.

GENETIC AND GENOMIC TESTING STRATEGIES

Individual Genes to Many Genes

A number of genetic tests are available for noncompaction/hypertrabeculation, and the utility of genetic testing is becoming increasingly apparent as it is for other cardiomyopathies [Ackerman et al., 2011; Green et al., 2013]. For the patient with noncompaction/hypertrabeculation, testing can yield a specific disease-associated molecular alteration or other variants. This has the potential to provide useful information for stratifying disease and tailoring therapies. Genetic testing results could also benefit the family, predicting who may be at increased risk. Familial genetic testing is recommended when a causal mutation is identified in an affected patient [Ackerman et al., 2011]. Several options are available for testing and a cardiovascular genetics provider can guide evaluation (Table II) based on the clinical scenario. While analysis of individual genes can be useful, multiple gene panels and high-throughput sequencing are increasingly used.

Genetic testing information can be incorporated to optimize patient care if there is availability and high-quality data. Multiple clinical laboratories offer testing of genes associated with noncompaction/hypertrabeculation. We examined gene testing offered by nine laboratories for noncompaction. *MYH7, TNNT2, MYBC3, LMNA, ACTC1*, and *TAZ* tests were offered the most often, followed by *LDB3* and *CASQ2*. Several other genes for sarcomeric proteins or arrhythmia-related phenotypes were also offered, including TPM1 [Chang et al., 2011; Hoedemaekers et al., 2010; Probst et al., 2011].

Multiple gene panels and high-throughput sequencing allow for analysis of many genes sequentially or simultaneously. This analysis is more comprehensive and potentially more efficient. This is particularly helpful since multiple genes have been associated with noncompaction/hypertrabeculation and discerning genetic alteration using cardiac phenotype is difficult. With exome and genome-based tests, a vast array of genes can be tested. Such testing has the potential to analyze all known noncompaction/hypertrabeculation or cardiomyopathy-associated genes. Broader exome/genome testing could yield additional beneficial information (e.g. pharmacogenetic-relevant variants) given that patients with noncompaction/hypertrabeculation cardiomyopathy may face new medications, hospitalizations, or sometimes cardiac transplantation [Zuckerman et al., 2011]. Data from the genome could be integrated into multiple aspects of patient care, given sufficient research. Genome-wide tests, however, will also reveal more variants and this will require interpretative expertise (Table III) and correlation with individual clinical data.

Gene Variants and Patient Diversity

Cardiomyopathies affect patients of all races and ethnicities, but important clinical differences are seen in individual physiology. Several groups have reported increased hypertrabeculation in patients of African descent and suggest that racial differences in ventricular trabeculation may exist [Kohli et al., 2008; Luijkx et al., 2012]. However, information on race/ethnicity is sometimes missing in published reports of noncompaction/hypertrabeculation and cardiomyopathy, and such information may be important for interpreting clinical phenotypes and genomic variation. Since genomic variants differ by race/ethnicity, clinical test interpretation may need to be tailored to each patient.

FUTURE DIRECTIONS

Although clinical criteria exist for noncompaction/hypertrabeculation, translational research will need continuing development to inform clinical care. It is unclear whether a neonate with noncompaction cardiomyopathy has a similar underlying ventricular pathophysiology as a child with congenital heart malformation and hypertrabeculation. How does this relate

to ventricular function and response to treatment? How does pediatric noncompacted/hypertrabeculated physiology compare to adult disease? Noncompaction/hypertrabeculation, ultimately, may be a recognizable phenotype in a heterogeneous group of patients [Oechslin et al., 2011]. These patients will require our attention to identify forms of disease amenable to different therapies. Genetic testing provides powerful tools for this, and the challenge is how to leverage the full capabilities of genomics for clinical care. With further clinical and scientific progress, we can drive further advances in patient care.

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Biography

Joseph Shieh, M.D. Ph.D. is a physician in the Department of Pediatrics and an investigator in the Institute for Human Genetics at the University of California San Francisco. Dr. Shieh practices genomic medicine and received his degrees from Stanford University and the University of Pennsylvania. He trained at the University of Washington and Seattle Children's Hospital in genetics at Stanford and UCSF. His research focuses on the genomics of birth defects, undiagnosed diseases, and cardiovascular biology.

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Table 1

Noncompaction/Hypertrabeculation (NC-HT) in Genetic Syndromes

Syndrome[1]	Reference	Findings	Cardiac
Beals	[Matsumoto et al., 2006]	Contractures, arachnodactyly, crumpled antihelices, family history, clinical diagnosis	NC-HT, LV dilation, membranous VSD
CHARGE	[Digilio et al., 2012]	*CHD7* mutation, coloboma, hearing impairment	NC-HT, ASD
Coffin-Lowry	[Martinez et al., 2011b]	*RPS6KA3* mutation	NC-HT, restrictive physiology, abnormal mitral valve
Cornelia-de Lange	[Digilio et al., 2012]	Growth abnormality, array negative	NC-HT, aortic coarctation
Marfan	[Digilio et al., 2012]	Array negative	NC-HT, aortic dilation, bicuspid aortic valve
	[Kwiatkowski et al., 2010]	*FBN1* mutation	NC-HT, min enlarged aortic root, MVP, PVC
Myotonic dystrophy I	[Finsterer et al., 2003]	Father and daughter, *DMPK* repeat increase	NC-HT
	[Finsterer et al., 2009]	Cataracts, *DMPK* repeat increase	NC-HT apex and septum, not present previously
Nail-Patella	[Finsterer et al., 2007]	Dysplastic nails and patellae, glomerulonephritis, *LMX1B* mutation, mitochondrial 3243A>G	NC-HT, thickening of apical myocardium, heart block
Noonan	[Digilio et al., 2012]	No positive mutation identified	NC-HT
Noonan-Multiple Lentigines (Leopard)	[Limongelli et al., 2007] [Digilio et al., 2012]	*PTPN11* mutation	NC-HT, no hypertrophy
Roifman	[Mandel et al., 2001]	Immunodeficiency, epiphyseal abnormalities, growth abnormality	NC-HT, LV dilation, LA thrombus
Sotos	[Martinez et al., 2011a]	Two unrelated patients with *NSD1* mutations	NC-HT, LV dilation in one patient
	[Saccucci et al., 2011]	One patient	NC-HT
Toriello-Carey	[Lacombe et al., 1992]	Agenesis of the corpus callosum, facial features, cryptorchidism, growth abnormality;	NC-HT, “primitive cardiomyopathy”
	[Paladini et al., 2002]	Agenesis of the corpus callosum prenatal, sibling similar findings	NC-HT, “spongious cardiomyopathy”
Trisomy 13	[McMahon et al., 2005]	11 year old	NC-HT free wall and septal wall
	[Yukifumi et al., 2011]	9 year old	NC-HT free wall
Trisomy 18	[Beken et al., 2011]	Neonate	NC-HT
22q11.2 deletion	[Pignatelli et al., 2003],	Deletion on FISH	NC-HT, no other congenital heart disease
	[Digilio et al., 2012]	Deletion on FISH	NC-HT, laryngeal web
	[Branton et al., 2011]	Deletion on FISH, hypoparathyroidism, low CD4 T cells	NC-HT, heavy trabeculations at apex, coronary artery fistula

Syndrome[1]	Reference	Findings	Cardiac
22q11.2 distal deletion	[Madan et al., 2012]	Growth abnormality, scoliosis, calf asymmetry	NC-HT, bicuspid aortic valve, dilated aorta, PDA, VSD
	[Digilio et al., 2012]	Growth abnormality, microcephaly, hypotonia, umbilical hernia, single umbilical artery	NC-HT, bicuspid aortic valve, VSD, persistent LSVC

[1]Multiple reports have noted NC-HT in patients with 1p36 deletion, Barth syndrome, mitochondrial disease, or neuromuscular disease

Table II

Genetic Testing Strategies

Test	Result[†]	Comment
Microarray, FISH, karyotype	Deletions and duplications, Contiguous gene syndromes	Often used for diagnosing multiple congenital anomaly conditions (e.g. 1p36 deletion)
Sequencing (Sanger)	Individual gene variants, Variants in several genes (sequential testing)	Has been the standard methodology for years (e.g. familial *MYH7* mutation testing)
Deletion/duplication testing (MLPA, qPCR)	Smaller deletions and duplications, often intragenic	This testing may need to be specifically requested
Focused high-throughput sequencing	Variants in targeted genes (e.g. cardiomyopathy gene panels)	High depth of coverage in known noncompaction genes or targeted loci
Exome/genome high-throughput sequencing	Exome or genome variants	Comprehensive, More incidental findings

[†]Testing varies by laboratory, test methodology, and interpretation expertise. Further test information is available from testing resources (Genetests and the NCBI genetic testing registry)

Table III

Challenges in Genomic Test Interpretation

Variation	Challenge	Comments
Missense variants	Unclear clinical significance	Dependent on variation in controls, functional prediction, or experimental data
Indels	May be missed in high-throughput analyses	Should be specifically assessed in sequencing analysis [Genomes Project et al., 2012; Lescai et al., 2012]
Deletions/duplications, large	May be missed in standard sequencing or in exome studies	Should be specifically assessed
Noncoding or uncaptured genomic regions	Variation may be in under-explored regions of the genome	[Liu et al., 2013]
Pseudogenes	Determining true from false positive variation in gene	Multigene families [Karakoc et al., 2012]
Genotype-phenotype	Variable penetrance	[Hoedemaekers et al., 2010; Probst et al., 2011]