Published in final edited form as:
Am J Med Genet C Semin Med Genet. 2013 August ; 163(3): 141–143. doi:10.1002/ajmg.c.31370.

Disorders of Left Ventricular Trabeculation/Compaction or Right Ventricular Wall Formation

Joseph T.C. Shieh[1,2,6], **John L. Jefferies**[3], and **Alvin J. Chin**[4,5,6]

[1]Division of Medical Genetics, Department of Pediatrics, University of California San Francisco, San Francisco, CA USA

[2]Institute for Human Genetics, University of California San Francisco, San Francisco, CA USA

[3]The Heart Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, 333 Burnet Avenue, MLC 2003, Cincinnati, OH USA

[4]Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania

[5]Division of Cardiology, Children's Hospital of Philadelphia, Philadelphia, PA USA

Abstract

Cardiomyopathies are remarkably variable in form. Although hearts may be dilated or hypertrophic, the spectrum of cardiomyopathies includes left ventricular noncompaction/ hypertrabeculation and right ventricular wall disorders. These conditions have been increasingly recognized in patients given advances in clinical diagnostics. Here we present information on cardiac pathophysiology, from ventricular wall formation and trabeculae in model organisms to pediatric and adult disease. Many genes to affect the ventricular phenotype, and this has implications for deciphering developmental and disease pathways and for applying testing for clinical care.

Keywords

Noncompaction; trabeculation; cardiomyopathy; genomic; testing; development; myosin; arrhythmogenic

INTRODUCTION

For many years, clinicians classified cardiomyopathies as dilated, hypertrophic, or restrictive; however, over the last two decades, an additional category has been increasingly recognized – "noncompaction." Although cases of deep trabeculations overlying the compact myocardium of the left ventricle date back nearly a century, acknowledgment of the importance of this family of disorders of trabeculation awaited three major events in the field of cardiovascular biology - the widespread availability of advanced cardiac imaging (leading to increased awareness), the generation of thousands of knockout model organisms to understand cardiovascular phenotypes, and powerful genetic sequencing technologies.

In cardiology, the tendency had been for practitioners to divide their patients into those with "Structural Heart Disease" (e.g., tetralogy of Fallot, truncus arteriosus, etc.) and those with

[6]Addresses for correspondence: Joseph Shieh MD PhD, Division of Medical Genetics, Department of Pediatrics, Institute for Human Genetics, University of California San Francisco, San Francisco, CA 94143-0793, Tel: 415-476-9347, Fax: 415-476-1356, shiehj2@humgen.ucsf.edu, Alvin J. Chin MD, Division of Cardiology, Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104, Tel: 215-738-9407, Fax: 215-590-5825, chinalvi@mail.med.upenn.edu.

"Functional Heart Disease" (i.e., cardiomyopathies) without considering the possibility that congenital morphological and functional abnormalities could coexist in the same patient. In mouse, homozygotes for the *pax3*^{Splotch} mutant allele display both truncus arteriosus and abnormally thin compact zone of myocardium [Conway et al., 1997]. Moreover, as cardiovascular developmental biologists have engineered more and more global and conditional (tissue-specific, stage-specific) knockouts, a plethora of embryonic and postnatal phenotypes involving the trabecular zone, the compact zone, or both, have been produced. Many of these models also phenocopy human congenital structural heart defects, e.g., outflow tract anomalies.

The accessibility of genomic technology facilitated two recent reports which solidified the importance of noncompaction in the practice of cardiology: (a) the finding that mutations in the same locus could produce several phenotypes with features of hypertrophic, dilated, and noncompaction cardiomyopathy in a single human kindred [Klaassen et al., 2008; Hoedemaekers et al., 2010]; and (b) the proof that mutations in one gene could produce both Ebstein anomaly of the tricuspid valve and left ventricular noncompaction in the same individual [Postma et al., 2011]. The former dispelled the myth that phenotypic sorting would correlate tightly with sorting by genomic sequence. The latter confirmed what mouse developmental biologists have known for at least 15 years, namely that morphological and functional abnormalities can coexist and result from a single gene defect.

Finally, the availability of magnetic resonance imaging which produces high-resolution, morphologic and functional images more reliably over a wider range of body sizes than does echocardiography has meant that phenotypic scoring can be done more completely and reproducibly than in past decades. This has given us the opportunity to further qualify noncompaction in the setting of concomitant cardiomyopathy phenotypes such as noncompaction in associated with a dilated phenotype. By doing so, we have insights into associated morbidity [Brescia et al., 2013], and this has facilitated medical and surgical management strategies.

Evolutionarily, cardiac trabeculae appear with the agnathans (e.g., lamprey), 500 million years ago. Since then, interspecies differences have mostly involved the thickness of the compact zone. In mouse development, reduced trabeculation is typically associated with a thin compact zone. However, abnormally numerous tall trabeculae can also be associated with a thin compact zone. The term "hypertrabeculation" refers to increased number and thickness of trabeculae in the mid-gestation embryo, while the term "noncompaction" refers to the lack of trabecular remodeling thereafter. In the clinical literature, the term noncompaction has been adopted for both processes.

ARTICLES

In this Issue of Seminars, Weinian Shou and colleagues lead off by reviewing the morphogenetic events which occur to form the ventricular wall in the mammalian embryo. All three cell layers – endocardium, myocardium, and the interposed cardiac jelly – have essential roles. They discuss in detail the *FKBP12* null, which is abnormal in both trabeculation and compaction (trabecular remodeling). As this was the first mouse model of human noncompaction, it has been particularly well studied and has illuminated at least four signaling pathways (BMP10; p57^{Kip2}; Notch1; and non-canonical Wnt) in addition to the neuregulin-ErbB pathway which had been previously implicated in the process of trabeculation.

To this, Jiandong Liu and colleagues add the insights from the study of chick and zebrafish embryos. The development of the cardiac conduction system is affected by the processes of trabeculation and compaction, which affords us a window into the underlying basis of

arrhythmias which are frequently seen in human ventricular noncompaction. In addition, they review the evidence that fluid flow also plays an important role in trabeculation, cardiomyocyte proliferation, and establishment of the conduction system.

Ursell present an autopsy series of three fetuses and five neonates with noncompaction pointing out that all eight showed biventricular endocardial fibroelastosis (presence or absence of right ventricular noncompaction could not be evaluated because there are no consensus standards for noncompaction in that chamber).

Mulder, Keavney and colleagues discuss the connection between noncompaction, Ebstein anomaly, and myosin heavy chain 7 gene mutations. This combination points out that genetic alterations can lead to important overlaps in phenotype, here in a form of congenital heart disease and a type of cardiomyopathy. They propose that noncompaction with Ebstein could represent a particular subtype of Ebstein anomaly, which would be important for management and counseling.

Iyer and Chin report on arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), a phenotype caused by mutations in any of 12 chromosomal loci, and distinguish these entities from other syndromes affecting the right ventricular myocardium. They review clinical phases of ARVC/D and conduction system abnormalities, risk of sudden death and cardiomyopathy. The authors provide clinical insights via cardiac magnetic resonance imaging and discuss differential diagnosis and patient management. The article also highlights important aspects of disease mechanism: desmosomal proteins, other genomic loci, proposed pathogenesis, and modeling disease.

Jefferies describes Barth syndrome and associated cardiomyopathy phenotypes, most importantly left ventricular noncompaction. They provide a review of the pertinent molecular and clinical reports on this disease as well as some novel management approaches for those with end-stage heart failure. The article also highlights ongoing clinical investigations into the disease.

Shieh presents strategies for evaluation for noncompaction/hypertrabeculation using a genomic medicine approach and by covering clinical testing options. The classical family history has always been essential and gene sequencing has been available, but new modes of multiple gene testing can be very powerful as diagnostic or predictive tools. Shieh points out that next-generation sequencing can transform testing given the ability to interrogate multiple genes and boost risk stratification in patients and families. The technology also brings new challenges, as the article demonstrates.

In all, we hope this collection on ventricular disease and development provides genetic and physiologic pathways and human phenotypes that spark further investigation.

Acknowledgments

JS receives support from the National Institutes of Health, National Heart, Lung, and Blood Institute, Grant HL092970.

Biographies

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.

John Jefferies MD, MPH, FACC, FAAP is Director of Advanced Heart Failure and Cardiomyopathy and Co-Director, Cardiovascular Genetics, Associate Professor, Pediatric Cardiology and Adult Cardiovascular Diseases and Associate Professor, in the Division of Human Genetics at The Heart Institute of Cincinnati Children's Hospital Medical Center.

Alvin Chin is Professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania and Senior Cardiologist at the Children's Hospital of Philadelphia. His clinical and research interests have centered on the management of single ventricle disorders and the developmental biology of the cardiovascular system, respectively.

REFERENCES

Brescia ST, Rossano JW, Pignatelli R, Jefferies JL, Price JF, Decker JA, Denfield SW, Dreyer WJ, Smith O, Towbin JA, Kim JJ. Mortality and Sudden Death in Pediatric Left Ventricular Noncompaction in a Tertiary Referral Center. Circulation. 2013

Conway SJ, Henderson DJ, Kirby ML, Anderson RH, Copp AJ. Development of a lethal congenital heart defect in the *splotch* (*Pax3*) mutant mouse. Cardiovasc Res. 1997; 36:163–173. [PubMed: 9463628]

Hoedemaekers YM, Caliskan K, Michels M, Frohn-Mulder I, van der Smagt JJ, Phefferkorn JE, Wessels MW, ten Cate FJ, Sijbrands EJ, Dooijes D, Majoor-Krakauer DF. The importance of genetic counseling, DNA diagnostics, and cardiologic family screening in left ventricular noncompaction cardiomyopathy. Circ Cardiovasc Genet. 2010; 3:232–239. [PubMed: 20530761]

Klaassen S, Probst S, Oechslin E, Gerull B, Krings G, Schuler P, Greutmann M, Hürlimann D, Yegitbasi M, Pons L, Gramlich M, Drenckhahn JD, Heuser A, Berger F, Jenni R, Thierfelder L. Mutations in sarcomere protein genes in left ventricular noncompaction. Circulation. 2008; 117:2893–2901. [PubMed: 18506004]

Postma AV, van Engelen K, van de Meerakker J, Rahman T, Probst S, Baars MJ, Bauer U, Pickardt T, Sperling SR, Berger F, Moorman AF, Mulder BJ, Thierfelder L, Keavney B, Goodship J, Klaassen S. Mutations in the sarcomere gene MYH7 in Ebstein anomaly. Circ Cardiovasc Genet. 2011; 4:43–50. [PubMed: 21127202]