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CONGENITAL CARDIOLOGY TODAY
9008 Copenhaver Drive, Ste. M
Potomac, MD 20854 USA
Tel: +1.301.279.2005
Fax: +1.240.465.0692

Editorial Offices:
16 Cove Road, Ste. 200
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MOLECULAR MARKERS OF CONGENITAL HEART DISEASE

By Mariam Arabi, MD; Marianne Majdalani,
MD; Georges Nemer, PhD and Fadi Bitar,
MD

INTRODUCTION

Cardiac abnormalities occur with an incidence of 1 per 100 live births represent 25% of all congenital malformations, and are the leading cause of death in the first year of life. The etiologies of Congenital Heart Disease (CHD) include consanguinity, environmental factors, teratogens and genetic mutations. Yet, 90% of all CHD cases do not have any known etiology. It has been reported that approximately 5 to 8% of patients with CHD have a gross chromosomal defect, usually trisomy 21, 13, 18 and Turner's Syndrome.

The complexity of heart formation, which integrates different structures and cell types, involves a network of genes regulated by transcription factors. The molecular causes of most CHDs remain unknown, although numerous cardiac regulatory factors have recently been described. Understandably, parents of patients, and increasingly patients themselves, are interested in the risk that future offspring will be affected. In this review, we pursue a discussion of the molecular markers for heart development and diseases that have been discovered during the last decade in numerous organisms.

I. HEART DEVELOPMENT

Studies in model organisms from the invertebrates and vertebrates have revealed an evolutionary conserved program of heart development, initiated by specific signaling molecules and mediated by tissue-specific transcription factors. The program, though still not complete due to lack of determination of all genes involved, details all steps

from cardiac-committed cells to the four-chambered heart (Figure 1).

Cells forming the heart originate from the lateral plate mesoderm in embryos: they migrate towards the middle and form two crescent-shaped primordia which subsequently fuse to form a beating heart tube. The subsequent patterning of this tube into the atria and ventricles is accompanied with a differential gene expression profile responsible for the morphogenesis of the heart into the well-known four chambered pump in the adults. These steps include cardiac looping, trabeculation, septation, and valve formation, in addition to the development of the conduction system from the pacemakers to the Pur-

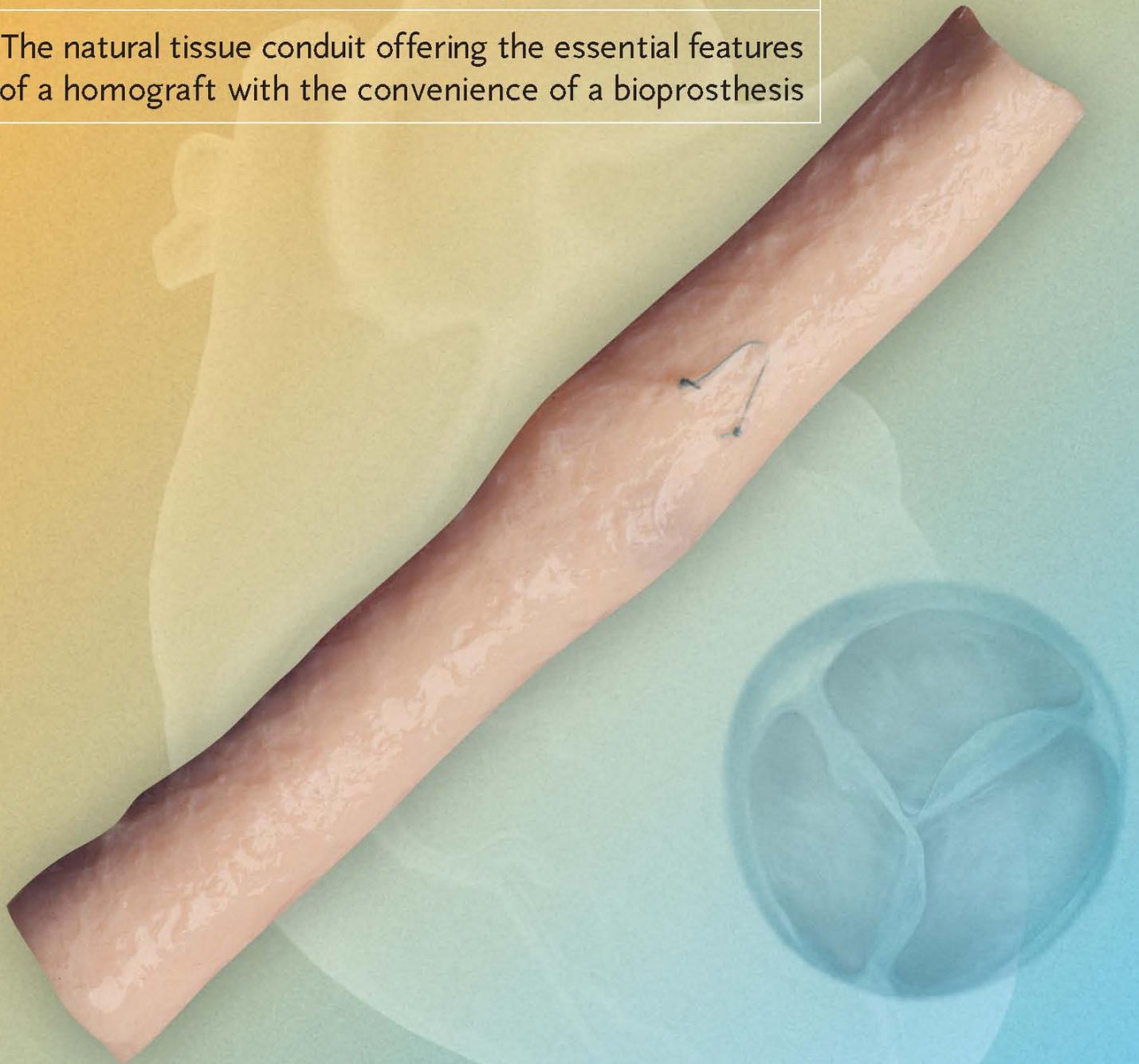
“Heart development processes including gradient-like expression of some genes, as well as the chamber-specific expression of others, are tightly regulated by combinational interactions of several transcription factors and their cofactors.”

kinje fibers. On the other hand, the vascularization of the heart requires the migration of cells from the neural crest and their differentiation into smooth muscle cells and endothelial cells which will make up the great arteries and veins. Moreover, the coronaries are formed from precursor cells migrating from the epicardium. Any mistake in any step from cell-commitment to valve formation can have a major impact on heart morphogenesis and function and may lead to CHDs.

Factors affecting heart tube formation have been described. In *Drosophila*, the mutant

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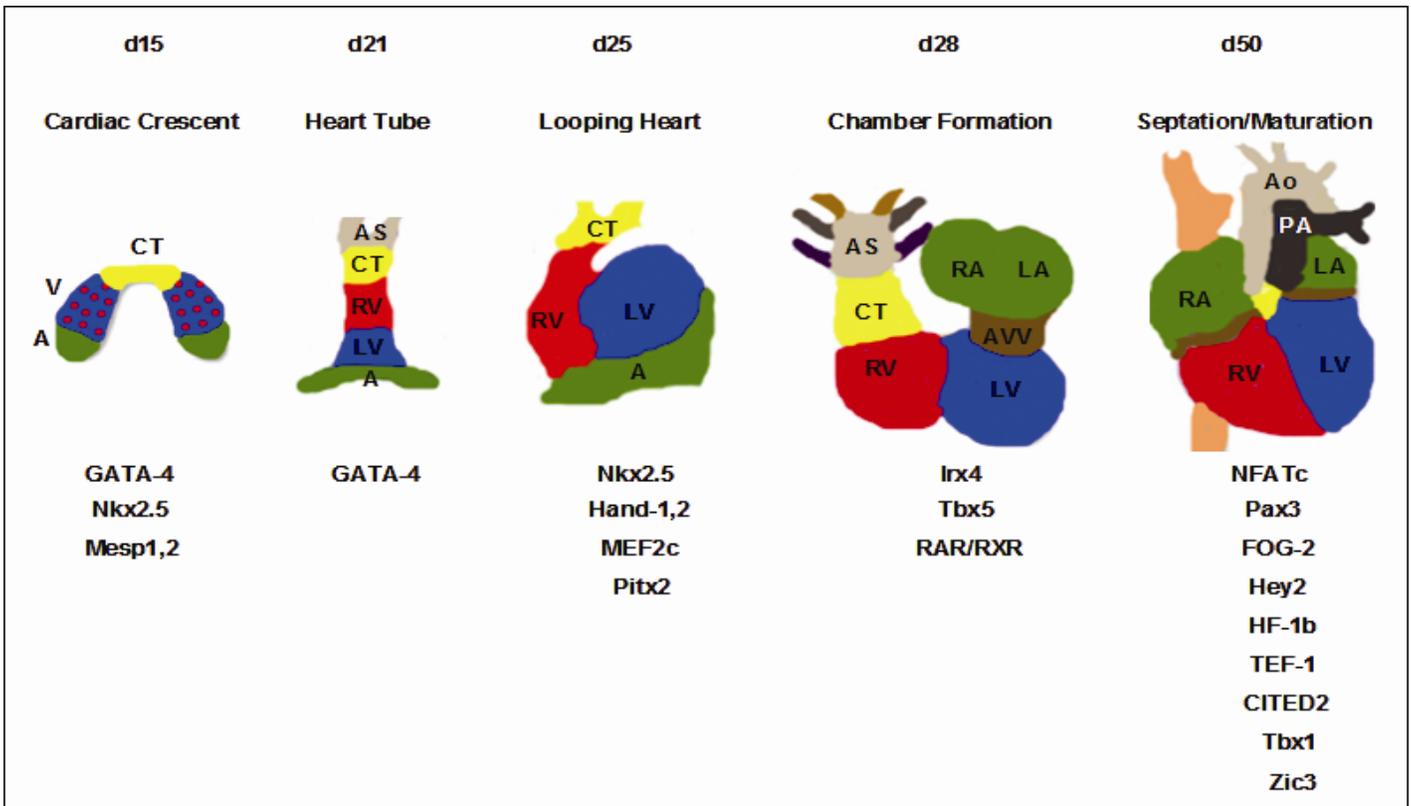


Figure 1. Schematic representation of the main stages of embryonic heart development in humans.

heartless has permitted the identification of a fibroblast growth factor (FGF) receptor as being essential for the migration of the pre-cardiac cells. In this mutant, the heart is not formed since the pre-cardiac cells do not migrate to the center of the embryo. In mice, the inactivation of the genes encoding Bone Morphogenetic Protein 2 (BMP-2) or BMP-4, the fibronectin, and the GATA-4 transcription factor, causes a phenotype resembling the heartless mutant.

The mechanisms implicated in the looping, and the forces causing it are not yet clarified. The asymmetry at the level of the organs, named situs

solitus is inverted in 1 per 7000 of humans (situs inversus), and causes many physiological abnormalities, as well as an increasing predisposition to develop congenital diseases notably at the atrial and ventricular septations. Recent studies have shown that it is caused by mutations in the gene encoding the zinc finger transcription factor Zic3. Retinoic acid (RA) affects cardiac folding in many species. This is the reason why in chicks and in mice, an excess of retinoic acid causes situs inversus.

Myocyte differentiation into two subtypes, atrial and ventricular, will form the different chambers of the mature

heart. Members of the basic/helix-loop-helix (bHLH) family of transcription factors have been implicated in regulation of cell fate specification and differentiation in different organisms. In the heart, the two subfamilies which are expressed are the hand proteins (dHand and eHand), and the Hairy protein (Hey 1,2, and 3). dHand and eHand are asymmetrically expressed in the heart: dHand being in the right ventricle and eHand being in the left. This differential expression implies a role in chamber specification and function.

Dissections of the molecular pathways implicated in valve formations have revealed two pathways govern-



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ing the epithelial-mesenchymal transformation the endocardial cells undergo to form the mature valves. These pathways involve the calcineurin/NFATc pathway whereby the dephosphorylation of the transcription factor NFATc (nuclear factor for activated T-cells) is essential for the transformation, and the Ras proto-oncogene pathways essential for the proliferation of mesenchymal cells.

Numerous mice models in which inactivation of genes encoding transcription factors like Nkx2.5 and Tbx2.5 exhibit septal defects associated with other gross abnormalities in the heart. Atrioventricular node defects are observed in humans and mice with dominant mutations in Nkx2.5 and Tbx5; thus further delineates their role in the formation of a functional conduction system.

Heart development processes including gradient-like expression of some genes, as well as the chamber-specific expression of others, are tightly regulated by combinatorial interactions of several transcription factors and their cofactors. Transcription factors are proteins involved in the regulation of gene expression that bind to the promoter elements upstream of genes and either facilitate or inhibit transcription. Through this process they control and regulate gene expression. Transcription factors are composed of two essential functional regions: a DNA-binding domain and an activator domain. The DNA-binding domain consists of amino acids that recognize specific DNA bases near the start of transcription. Transcription factors are typically classified according to the structure of their DNA-binding domain, which are of one of the following types: zinc fingers, helix-turn-helix, leucine zipper, helix-loop-helix, and high mobility groups.

II- CONGENITAL HEART DISEASE

We will present a brief description of the various CHDs including an overview of the genes associated or implicated in the development of these defects (Table 1). Moreover, we will review several syndromes associated with CHD, and describe the genes associated with these syndromes.

The improvement in molecular genetic techniques such as PCR and fluorescent in situ hybridization (FISH) can now rapidly identify specific genes and chromosomes. FISH can also reveal abnormalities within individual chromosomes. Labeled gene probes, often derived from animals, can localize genes on chromosomes. A multitude of genes are involved in programming heart development which renders the immediate clinical application somewhat remote. However, molecular genetics is likely to produce in the near future answers about the mechanics involved in abnormal cardiogenesis.

A. Specific Cardiac Defects

1. Ventricular Septal Defect (VSD)

Mutations in a large number of genes in animal models have been associated with VSDs, usually in association with other cardiac or extra-cardiac abnormalities. Examples of knock-out mice developing VSD are those where Nkx2.5, FOG2, and Hey2 genes are inactivated. Heterozygous mice for the Tbx5 gene also develop VSD. Some human syndromes and sporadic cases of VSD have been associated with Nkx2.5, Tbx5, and GATA4 mutations.

2. Atrial Septal Defect (ASD)

Patients with Holt-Oram Syndrome (HOS) have ASDs in association with limb deformities. This disorder is due to mutations in the T-box transcription

factor gene TBX5. Interestingly, mutations in the Nkx2.5 gene which interacts with Tbx5 have also been linked to familial and sporadic cases of ASDs. Recently, mutations in GATA4 were found in two familial cases of ASDs. These findings point to a major role for GATA4 in septation, with both Tbx5 and Nkx2.5 being GATA4 partners, and define a network of cooperative activity that contributes to ASD.

3. Patent Ductus Arteriosus (PDA)

Recent linkage analysis pointed to the 12q24 locus as potentially implicated in PDA. The 12q24 locus includes different potential cardiac genes like Tbx5 implicated in HOS and Shp2 implicated in Noonan Syndrome.

4. Atrioventricular Canal Defects (AVC)

The syndrome most often associated with atrioventricular canal defects in trisomy 21.

It has been estimated that 22% of people with AVSD who do not have Down Syndrome or heterotaxy have a Mendelian genetic syndrome. Of note the involvement of tyrosine kinase receptors ErbB2 and B3 which binds neuregulin in the formation of the atrioventricular canal in mice.

5. Persistent Truncus Arteriosus (PTA)

Micro-deletion of chromosome 22 has been noted in as many as 1/3 of patients with PTA. 22q11 deletions are commonly associated with the Di-George Syndrome. The PTA phenotype is also found in numerous engineered mouse models like the ones with inactivation of the genes encoding the BMP2, the Pax3 homeobox transcription factor, and the vasoconstrictor hormone Edn1.



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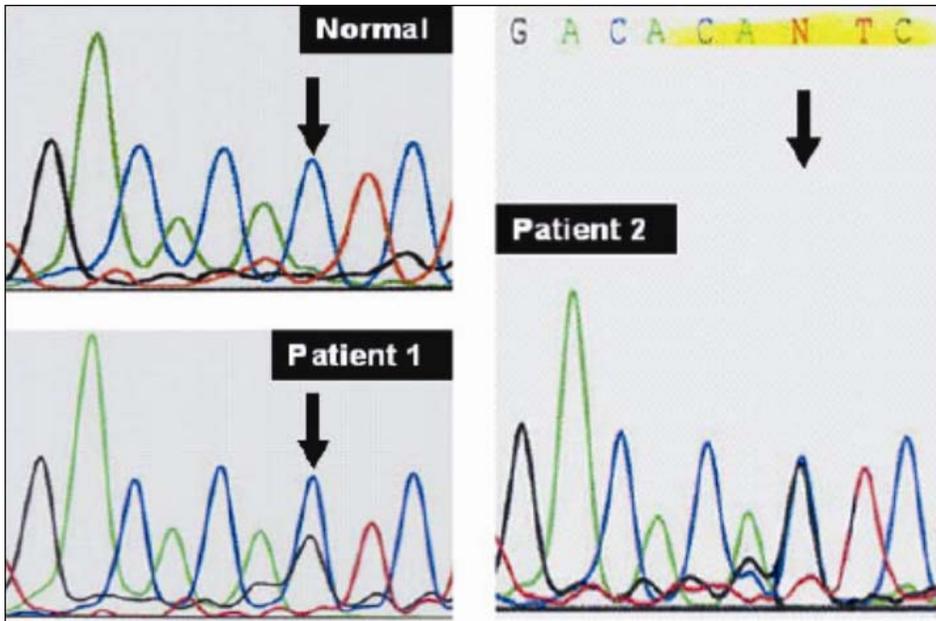


Figure 2. Heterozygous mutation in 2 patients with TOF resulting in a E215D substitution. Three chromatograms showing the results of sequencing with the reverse primer of a normal individual, and the two patients with TOF in which a C is substituted by a G (arrow). The resulting codon GAC will encode an aspartic acid instead of glutamic acid (GAG).

null mice which lack both alleles display a tricuspid atresia (TA) phenotype associated with both atrial and ventricular septal defects.

A recent study at our center designed to look at mutation in GATA-4 included 120 patients with various CHD and their families. We identified two patients out of 26 patients with TOF to harbor a missense mutation in exon 2 resulting in E to D substitution at residue 215 of the first zinc finger of GATA-4 (Figure 2). None of the 94 other patients with different phenotypes, nor in 223 healthy individuals had the mutation. The heterozygous mutation results in an amino acid substitution in the first zinc finger of GATA4 that reduced its transcriptional activation of downstream target genes, without affecting GATA4 ability to bind DNA, nor its interaction with ZFPM2. Further studies are needed in this area.

6. Aortic Stenosis (AS)

No linkage analysis has been performed in humans and no animal model exists so far in which only aortic stenosis is present.

7. Pulmonary Stenosis (PS)

Recently, isolated cases of PS have been associated with mutations in Jagged-1, which was previously linked to patients with the Alagille Syndrome.

8. Coarctation of the Aorta (CoA)

Studies in Zebrafish show that the gridlock mutation is due to mutations in the Hey2 gene causing coarctation of the aorta resembling that found in humans. In humans, some patients with the neurofibromatosis defect characterized by hematopoietic malignancy, presents a CoA. The mutations in this tumor-

suppressor gene (Nf1) cause an increase in the cardiac cushion tissue which will form the valve and in particular the aortic valve.

9. Tetralogy of Fallot (TOF)

No linkage analysis has been done so far, however, isolated cases have been associated with Jagged-1 mutation. Jagged-1 is a ligand to the Notch receptor which has been implicated in different aspects of organogenesis in Drosophila and mammals.

Two recent reports have also linked mutation in the FOG2 and Nkx2.5 genes to isolated cases of Tetralogy of Fallot. FOG2 (friend of GATA) encodes a multi-zinc fingers protein that interacts specifically with GATA proteins to modulate their transcriptional activity mainly by repressing it. In comparison, the FOG2

10. Hypoplastic Left Heart Syndrome (HLHS)

No linkage analysis has been performed and no association to a single gene mutation has been documented in humans. Recently inactivation of the gene encoding the cardiac lineage restricted nuclear protein-1 (CLP-1) has produced embryonic lethality in mice due to a severe hypoplastic left ventricle that is in part the result of a differentiation deficit of progenitor myocytes.

11. Tricuspid Atresia (TA)

No single gene mutation has been identified so far in humans and no linkage analysis has been performed. In mice, the inactivation of FOG2 (friend of GATA) lead to a phenotype resembling TA associated to both an ASD and VSD.

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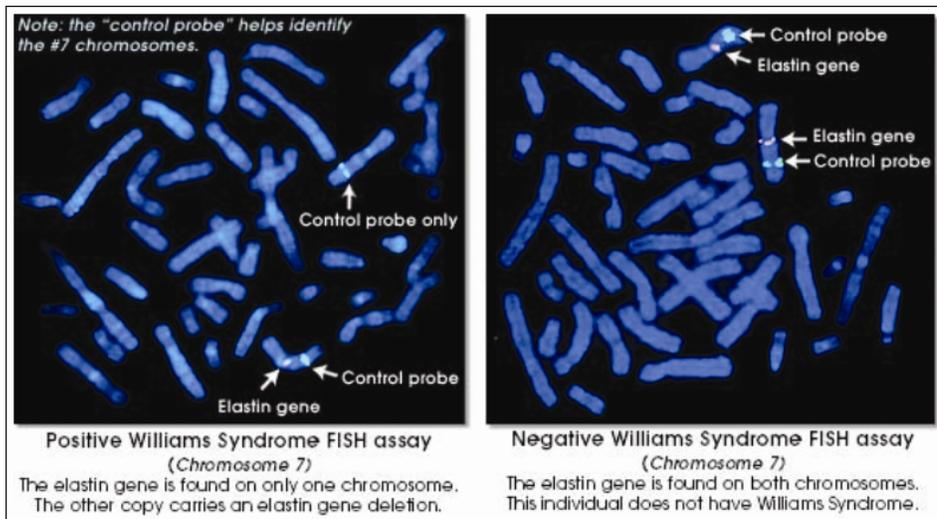


Figure 3. Williams Syndrome FISH assay (Chromosome 7). Courtesy of the University of Utah, Genetic Science Learning Center.

12. Transposition of the Great Arteries (TGA)

No linkage analysis has been performed on familial cases of TGA, and the animal models that recapitulate TGA have additional embryonic defects besides the heart.

The *Pitx2* null mice in particular confirm the role of *Pitx2* as the downstream effector of left-right asymmetry along the body axis starting with the heart and embryos lacking *Pitx2* display in addition to TGA a wide variety of left-right defects.

Inactivation of genes encoding the type II activin receptor, the *Cited2* co-activator, and the transduction cytoplasmic protein *Dishevelled2* associated to Wnt signaling, all lead to TGA in addition to cardiac and extra-cardiac phenotypes.

13. Double Outlet Right Ventricle (DORV)

No genes have been yet linked to DORV in humans. However, a large number of

mouse mutations result in a DORV phenotype. Mutations in the type IIB activin receptor result in complex defects, which include DORV. Over-expression of *Pitx2* in transgenic mice leads also to DORV.

B. Syndromes

1. DiGeorge Syndrome

Recently, genetically modified mice with targeted disruption of only one allele of the gene encoding *Tbx1* have been generated. In addition to being found at the 22q11 locus in humans, *Tbx1* expression pattern matches the organs affected in the DiGeorge Syndrome.

2. Holt-Oram Syndrome

Linkage studies have shown that the syndrome was linked to 12q2. The subsequent identification of mutations in the *Tbx5* gene that is found on 12q2 in HOS patients, and the cloning and pattern of expression of its mouse homolog confirmed that *Tbx5* is the gene implicated

in HOS. The fact that only one *Tbx5* allele less in mice is sufficient to mimic HOS correlates well with the fact that in humans mutations are found on one allele in an autosomal dominant manner of transmission and introduces the notion of haploinsufficiency which results in reduction of the total amount of proteins produced.

3. Alagille Syndrome

It is caused by mutations in *Jagged-1* (20p12), a ligand for the Notch receptor.

4. Char Syndrome

This is an autosomal dominant trait mapped at 6p12. Linkage analysis in families with this syndrome revealed mutations in the transcription factor AP-2 type B (TFAP2B).

5. Marfan syndrome

Mutations in the fibrillin gene (15q21.1) which encodes an extra-cellular matrix protein result in Marfan's syndrome.

6. Noonan Syndrome

Fifty percent of patients with the Noonan Syndrome have been linked to mutations in the gene encoding the protein-tyrosine phosphatase *Shp2* (or *Ptpn11*) on 12q24. Mice models with inactivation of the *Shp2* gene have been generated and they recapitulate phenotypically the syndrome.

7. Williams Syndrome

It is caused by a very small chromosomal deletion on the long arm of chromosome 7 (Figure 3). The deleted region includes the elastin gene, which encodes a protein that gives blood vessels its elasticity and strength. (Role of FISH assay in the diagnosis of Williams Syndrome; Courtesy of the University of Utah, Genetic Science Learning Center).



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Table 1. Cardiac phenotypes associated with mutations in genes encoding transcription factors		
<i>Cited2</i>	Mouse	ASD, VSD, DORV, PTA
<i>Isl1</i>	Mouse	RV and Atrial hypoplasia
<i>Gata4</i>	Mouse, Human	ASD, VSD, TOF, <i>cardia bifida</i>
<i>Hand1</i>	Mouse	Looping abnormality
<i>Hand2</i>	Mouse	RV hypoplasia, Ao arch hypoplasia
<i>HoxA3</i>	Mouse	CT abnormalities
<i>NFATc</i>	Mouse	Valve defects, VSD
<i>Nkx2-5</i>	Mouse, Human	ASD, VSD, TOF
<i>COUP-TFII</i>	Mouse	Atrial hypoplasia, ASD
<i>Pax3</i>	Mouse	PTA, CT defects
<i>HF-1b</i>	Mouse	Conduction system defect
<i>Pitx2</i>	Mouse	Laterality, AVSD, PTA, TGA, DORV
<i>RAR/RXR</i>	Mouse	VSD, PTA, DORV, CT Defects
<i>Sox4</i>	Mouse	AVSD, TGA, valve defects, PTA
<i>Tbx1</i>	Mouse, Human	DiGeorge Syndrome
<i>Tbx5</i>	Mouse, Human	Holt-Oram Syndrome, atrial hypoplasia
<i>TEF-1</i>	Mouse	Noncompaction, trabecular abnormality
<i>FOG2</i>	Mouse, Human	TA, ASD, VSD, PS, TOF, AVSD
<i>MEF2C</i>	Mouse	RV and LV hypoplasia
<i>Hey2</i>	Mouse, Zebrafish	Ao Coarctation, VSD, TOF
<i>TFAP2B</i>	Human	PDA
<i>Gata5</i>	Zebrafish	<i>Cardia Bifida</i>
<i>Zic3</i>	Mouse, Human	TGA, laterality

III. Conclusion

In spite of the amazing success during the past half-century in diagnosis and treatment of congenital heart disease, very little is known with regard to its causes. However, a genetic cause has been clearly established for many forms of cardiovascular disease, and new understandings in the molecular genetics of congenital heart disease will provide further insight. The availability of complete genome sequences for humans and model organisms should revolutionize our understanding of cardiac development.

References

Nemer G, Bitar FF. Molecular Markers of Congenital Heart Disease. Nova Science Publishers, Inc. Editor-in-Chief: Marlene Horry; Frank Columbus. 2006. ISBN: 1-59454-489-1, pp39-65.

Nemer G, Fadlallah F, Usta J, Nemer M, Dbaibo G, Obeid M, Bitar FF. A novel mutation in the GATA4 gene in patients with Tetralogy of Fallot. Hum Mutat. 2006; 27(3):293-294.

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Corresponding Author:



Fadi Bitar, MD
 Professor of Pediatrics
 Director, Pediatric Cardiology Program
 Coordinator: External Programs:
 Medicine
 AUBMC
 Riad El Solh, P.O. Box: 11-0236
 A#22
 11072020, Beirut, Lebanon
 Fax: 011-961-1-342517
 Email: fadi.bitar@aub.edu.lb

Corresponding Author:



Georges Nemer, PhD
 Assistant Professor of Biochemistry
 Director of the CHD Genetics Program
 AUBMC
 Email: gn08@aub.edu.lb

Mariam Arabi, MD
 First Year Fellow in Pediatric Cardiology
 American University of Beirut-Medical
 Center (AUBMC)

Marianne Majdalani, MD
 Assistant Professor of Pediatrics
 Director, Pediatric Intensive Care Unit
 AUBMC



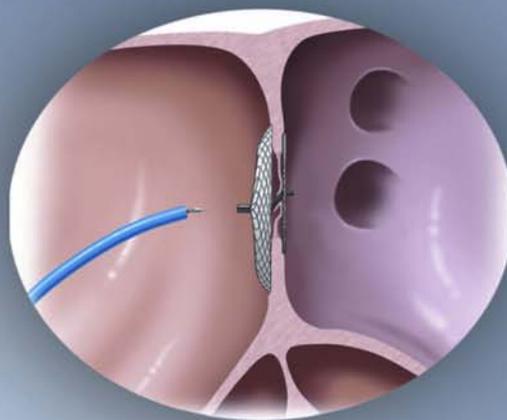
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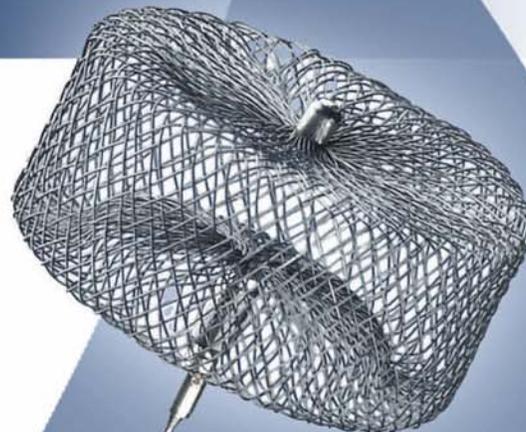
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HEMORRHAGIC PERICARDIAL EFFUSION IN TWO SIBLINGS

By Arkadi Yakirevitch, MD and Nathan Roguin, MD

Introduction

Although in one third of the cases pericarditis is idiopathic, in these instances pericardial effusion is rarely life-threatening. The two cases we report are in siblings from an Arabic family without any history of congenital pathology and are of interest because of the hemorrhagic nature and large amount of pericardial fluid. To the best of our knowledge, idiopathic hemorrhagic pericarditis in siblings has not been described in the English literature.

Case reports

Case 1

A one and a half year old girl, born to healthy parents after a normal pregnancy, vaccinated against poliomyelitis, hepatitis B, measles, mumps and rubella, was referred with a four day history of cough and shortness of breath. On admission, pallor, severe dyspnea and consciousness deterioration were revealed. Laboratory data showed normal electrolytes and blood count with the exception of mild lymphocytosis and thrombocytosis of 626,000/L and a mild increase of the erythrocyte sedimentation rate (28 mm per hour). Electrocardiogram showed ST and T wave changes and chest roentgenogram demonstrated an enlarged heart silhouette. Echocardiography revealed significant amounts of pericardial fluid with pressure on the right atrium and right ventricle.

Urgent open pericardial drainage was performed through a subxiphoid approach. Six-hundred-twenty ml of sanguineous fluid were withdrawn and a pericardial biopsy was also taken.

Fluid analysis revealed glucose 97 mg/dl, total protein 5.9 g/dl, lactate dehydrogenase 662 U/L. Cytologically, the fluid contained mesothelial cells and granulocytes with no anaplastic cells. Virus isolation from pericardial fluid for echovirus, coxsackie A and B, and herpes simplex was negative. Blood and pericardial fluid cultures were sterile.

Pericardial biopsy showed fibrin deposits, fibroblasts, and isolated granulocytes with no evidence of tuberculosis or malignancy.

Tuberculin skin test was negative.

The girl was treated with aspirin and cefazolin.

On the fourth postoperative day the pericardial drain was removed. The patient convalesced satisfactorily and was discharged on the ninth hospitalization day and required no further medications.

Eleven years later at thirteen years of age she remains in good health; hemostasis screening tests and blood count, including platelets, are normal; electrocardiogram is within normal ranges. Echocardiogram demonstrates normal cardiac contractility and absent pericardial effusion. Serologic tests carried out were negative for immunoglobulin M antibodies and positive for immunoglobulin G antibodies to cytomegalovirus and toxoplasma.

Case 2

A fifteen-year-old, usually healthy boy, vaccinated against poliomyelitis, measles and rubella, elder brother of the first patient, was admitted with epigastric pain, vomiting, subfebrile fever, mild dyspnea and fatigue. Electrocardiogram showed sinus tachycardia with inverted T waves in all the leads. Chest X-ray demonstrated marked cardiac enlargement without any lung findings. Blood count revealed only mild thrombocytosis of 569,000/L; electrolytes, cardiac and liver enzymes levels and thyroid function tests were normal though the erythrocyte sedimentation rate was elevated (74 mm per hour).

With echocardiographic evidence of massive pericardial effusion subxiphoid puncture had been performed under X-ray control and with the help of introducer to minimize pericardial trauma. 750 ml of hemorrhagic fluid was removed followed by rapid clinical improvement.

Despite aspirin and ceftriaxone treatment by the fourth hospitalization day the patient's condition worsened, and a follow-up echocardiogram demonstrated considerable pericardial effusion. Repeated puncture yielded 1200 ml of hemorrhagic fluid. Its analysis showed pH 7.44, glucose 99 mg/dl, total protein 6.2 g/dl. Cytologically it was normal and negative for Ziehl-Neelsen staining.

Serologic studies for antibodies to Epstein-Barr, coxsackie A and B, echo, herpes simplex virus, parvovirus and mycoplasma were negative. Studies for



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immunoglobulin M antibodies to cytomegalovirus and toxoplasma were negative, and positive for immunoglobulin G antibodies to cytomegalovirus and toxoplasma. Pericardial fluid and blood cultures were sterile.

Tuberculin skin test was negative.

By the tenth day the patient was asymptomatic. Repeated echocardiograms demonstrated a small amount of pericardial fluid and the boy was discharged on aspirin treatment which was discontinued two weeks after discharge.

After 6 year follow-up, the patient is in good health, has normal hemostasis tests and complete blood count. Electrocardiogram shows minimal residual ST and T wave changes in leads III, aVF and V3. Echocardiogram demonstrates normal cardiac contractility with no signs of residual pericardial effusion.

Discussion

Hemorrhagic pericardial effusions are infrequent, especially in children, and are usually caused by tuberculosis, tumors, rheumatic fever, uremia and cardiac injury. During the past decade the incidence has been reduced even more due to reduction of bacterial causes so that currently the most common cause is iatrogenic disease, namely, secondary to invasive cardiac procedures [1].

We presented two cases of massive hemorrhagic pericardial effusion that had been observed in two siblings in separate occasions. In both cases there was no history of trauma, no evidence of tuberculosis, coxsackie A or B, echo, herpes simplex virus or bacterial infection. Cases of hemorrhagic pericarditis due to mycoplasma pneumoniae [2], cytomegalovirus [3] and toxoplasma [4] infections have been reported. These three causations were ruled out in the case of the elder sibling. In the younger

sister's case, which was actually studied retrospectively, we are not able to exclude these etiologic agents. Nonetheless, they were unlikely taking into account the clinical picture. It is worth mentioning, that in our region the prevalence of antibodies against Toxoplasma gondii among the Arab population reaches 20.5% in the first decade of life with a gradual increase up to 74% at age 40 [5].

On the other hand, the familial nature of these cases can be hardly ignored. In this connection familial Mediterranean fever^{6,7} and porphyria⁸ could be suspected but hemorrhagic pericardial effusion is not typical for them; the history of familial Mediterranean fever is absent in this family and both cases didn't have a clinical picture of porphyria.

Therefore, we consider these two familial cases of hemorrhagic pericarditis to be idiopathic, though an infectious origin of the first one cannot be entirely ruled out.

References

1. Atar S, Chiu J, Forrester JS, Siegel RJ. Bloody pericardial effusion in patients with cardiac tamponade: is the cause cancerous, tuberculous, or iatrogenic in the 1990's? *Chest* 1999; 16: 1564-9.
2. Hofner G, Hofbeck M, Koch A, Schmiedl N, Singer H. Intrapericardial hemorrhage as a manifestation of Mycoplasma pneumoniae infection. *Z. Kardiol.* 1997; 86: 423-6.
3. Kassab A, Demoulin JC, Vanlancker MA, Hastir F, Kulbertus FEE. Cytomegalovirus hemopericarditis. Report of 1 case with histologic confirmation. *Acta Cardiol.* 1987; 42: 69-72.
4. Sano J, Saitoh H, Kobayashi Y, Ikeda M, Kodani E, Takayama M et al. Toxoplasma pericarditis without immunosuppressant disorder detected by polymerase chain reaction of pericardial

fluid: a case report. *J. Cardiol.* 2000; 35: 47-54.

5. Raz R, Nishri Z, Mates A, Sartani G, Hadad N, Reichman N, et al. Seroprevalence of antibodies against Toxoplasma gondii among two rural populations in northern Israel. *Isr. J. Med. Sci.* 1993; 29: 636-9.

6. Kees S, Langevitz P, Zemer D, Padeh S, Pras M, Livneh A. Attacks of pericarditis as a manifestation of familial Mediterranean fever(FMF). *QJM* 1997; 90: 643-7.

7. Zimmand S, Tauber T, Hegesch T, Aladjem M. Familial Mediterranean fever presenting with massive cardiac tamponade. *Clin. Exp. Rheumatol.* 1994; 12: 67-9.

8. Adachi S, Amano J, Ito H, Yajima T, Shirai T, Miyahara Y, et al. Porphyria cutanea tarda with constrictive pericarditis in a family. *Jpn. Heart J.* 1997; 38: 749-53.

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Corresponding Author:

*Arkadi Yakirevitch, MD
Department of Cardiology
Western Galilee Hospital
Nahariya Technion Faculty of
Medicine
Haifa, Israel*

*Emek Dotan Str. 14/5
Ramat Gan 52621
Israel
Tel: 972-3-6355324
Fax: 972-3-5305387
E- mail: arkadiyak@gmail.com*

*Nathan Roguin, MD
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MEDICAL NEWS, PRODUCTS AND INFORMATION

Remote Device Allows Cardiologist to Monitor Patients at their Homes

An easy-to-use in home monitoring device for patients is changing the way doctors monitor the health of patients with implanted defibrillators. Rush University Medical Center is participating in a pilot study of the LATITUDE® Patient Management system to determine if the wireless home monitoring system can decrease hospitalizations for heart failure.

A mini-antenna built into the implanted defibrillator sends data to a wireless system placed in the patient's home. The data is automatically transmitted to a secure Internet server where the physician can access this medical information anytime, from anywhere.

Unlike other remote devices which only transmit data if certain parameters are out of range, the LATITUDE system uploads health information that can help physicians monitor the day-to-day changes in patients. In addition to the data stored before, during and after an arrhythmia, the system employs a wireless weight scale and blood pressure monitor to record vital statistics crucial for the management of cardiac failure patients. An abrupt change in weight could indicate worsening heart failure.

"This sophisticated system allows physicians to manage the patient much more closely. The same information that would normally require a visit to the office every few months can now be downloaded to the physician at anytime without the patient ever leaving home," said Dr. Kousik Krishnan, a cardiac electrophysiologist at Rush.

According to Krishnan, the LATITUDE system provides added peace of mind for the patient. The physician can remotely check if the defibrillator is working correctly and assess battery life. If the patient feels the defibrillator activate, he or she can transmit the rhythm information immediately. The physician can quickly analyze the data and determine

if the shock was appropriate or if the patient needs to go to the hospital.

"Now with patient information available weekly, or even daily if needed, we can better monitor our patients," said Dr. Krishnan. "We can pick up abnormalities sooner and act on those before they become serious."

Rush is one of only 18 centers in the country participating in the LATITUDE Inductive Pilot Program which offers remote monitoring for all Boston Scientific/Guidant devices.

35 % of 49 Young People Who Died Suddenly Had Genetic Heart Defects

In 49 young people who died suddenly and inexplicably at an average age of 14, conventional autopsies found no cause of death. But when Mayo Clinic researchers conducted a sophisticated form of postmortem genetic testing -- known as a molecular autopsy -- they found that more than one-third died due to potentially heritable genetic defects that impair the heart's rhythm center.

The defects were caused by mutations, which can be thought of as spelling errors in the genetic code. The defects produced one of two abnormal heart rhythm conditions: Long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT). Both syndromes can declare their presence silently and catastrophically with a sudden death episode as the first symptom. Because they leave no structural or physical clues, the defects can't be detected with conventional autopsy methods -- so families have been left with the additional grief of wondering what caused the premature death.

Mayo Clinic's molecular autopsy is a detailed examination at a molecular level of heart function. Molecular autopsies can help lessen grief burden of families because data show that they exposed the lethal mutations as the cause of death in 35 percent of cases in

which conventional autopsies could not ascertain cause of death. "The fact that conventional autopsy fails to provide an answer is, in fact, a key clue that the killer may be LQTS or CPVT," says Michael J. Ackerman, MD, PhD, the study's chief author who heads the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory.

"To prevent further tragic, premature deaths, the standard of care for the evaluation of sudden unexplained death must now change. Surviving members in a family in which there's been this tragedy should receive medical attention that is equal to a 'full-court press,'" Dr. Ackerman says. "It must involve a careful and sleuth-like search for these inherited glitches in the heart's electrical system."

The Mayo Clinic report appeared in the Jan. 16, 2007, issue of the *Journal of the American College of Cardiology*.

Significance of the Mayo Clinic Research

These results identify a tragic situation that could, with increased medical surveillance, potentially be prevented in many cases. To do so requires physicians and families to work astutely together to take a careful multigenerational heart history. Dr. Ackerman says that to identify at-risk relatives, all immediate family members of the person who died inexplicably must undergo comprehensive cardiac evaluation that includes, at a minimum, an electrocardiogram and an exercise stress test as initial screens for LQTS and CPVT. If evidence of heart problems is found, family members need to act immediately by getting screened for the lethal mutations, and treated, if necessary, he says.

"Families who have lost a loved one to sudden unexplained death should now know that they can do more if the coroner or medical examiner is unable to provide an explanation for their loved one's sudden and unexplained death,"

Dr. Ackerman says. "Postmortem genetic testing could be performed on the victim of sudden death in search of the cause. Now, one-third of the time, we can find the cause."

Although all deaths in the study were officially categorized as unexplained, the medical histories showed that nearly half of those with the lethal mutations had experienced a warning sign prior to death. The warning signs of possible mutation-linked heart abnormality include:

- sudden fainting or a sudden seizure.
- evidence of unexplained death in the family history, such as a motor vehicle accident for which no plausible cause can be found.
- a distant relative with an unexplained death.

With proper recognition of key warning signs, some sudden unexplained deaths may be preventable, Dr. Ackerman says.

The Mayo Clinic report appeared topic in the Jan. 16, 2007, issue of the Journal of the American College of Cardiology.

Collaboration and Support

Also involved in the study was David Tester, senior research technologist of the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory. Funding came from the Mayo Clinic Foundation for Biomedical Research, the Dr. Scholl Foundation, the Hannah Wernke Memorial Foundation, the CJ Foundation for SIDS, the American Heart Association, and the National Institutes of Health (NIH).

For more information, visit: www.mayo.edu.

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