Recent advances in understanding the genetic etiology of congenital heart disease

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The genetic etiologies of multiple cardiovascular disorders have been identified recently. For the most part, familial cardiomyopathic, vascular, or arrhythmogenic disorders have been studied given the opportunity to identify the disease gene by linkage analyses, positional cloning, and analysis of candidate genes. Given that structural congenital heart disease rarely occurs in the context of large families, alternative approaches to understand the possible genetic etiologies have been taken. In particular, molecular evaluations of genetic syndromes in which cardiac defects are a cardinal feature are providing new insights into disease-related genes and developmental pathways. The identification of rare families with multiple affected members also has provided some insight into the genetic contribution to structural congenital heart defects. This review highlights the newest findings on the genetic etiology or implications in each of the subcategories of congenital cardiovascular disorders, and will provide the reader with both a brief overview and update. Particular note will be made of the genotype/phenotype analyses of hypertrophic cardiomyopathy and the long QT syndromes, as well as the identification of new disease-related genes for dilated cardiomyopathy, idiopathic ventricular fibrillation, and structural heart disease.

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Abbreviations

ASD	atrial septal defect
CHD	congenital heart disease
DCM	dilated cardiomyopathy

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Although congenital heart disease (CHD) is the most common major organ malformation, little is known about its etiology. Identifying the genetic etiology of these defects has been difficult for several reasons. Historically, neither the mechanisms of cardiac development nor the proteins involved were known, and the necessary genetic techniques were not developed. During the last decade, the methodology of linkage analysis and positional cloning has allowed for the identification of disease-related genes in those cardiovascular disorders in which affected individuals survive to reproduce and large families with multiple affected members could be identified. These disorders include mostly myocardial, vascular, and arrhythmogenic defects. In contrast, many children with structural heart disease previously have not survived to reproduce, so large families with multiple affected members are very rare. Thus, linkage analyses to identify disease loci for structural CHD frequently have not been performed. However, recent examinations of patients with syndromes of known chromosomal abnormalities have begun to provide insight into the related forms of heart disease. In addition, researchers are identifying genes critical to cardiovascular development from mammalian experiments and models. Some of these genes may prove to be disease-related. This review focuses on the most recent advances made in understanding the genetic etiology of congenital cardiovascular disorders, including diseases of the myocardium, vasculature, rhythm, and cardiac structure. Table 1 summarizes the disorders under investigation, though only those with recent advances are reviewed in detail here.

Cardiomyopathies

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy was one of the first cardiovascular disorders for which a genetic etiology was identified. The availability of large families with multiple affected members permitted linkage analyses to be performed. Linkage analyses as well as mutation analyses of candidate genes have mapped eight disease loci for which seven disease genes have been identified (Table 1). These disease genes are estimated to account for 70% of all hypertrophic cardiomyopathy, of which 30% to 35% of occurrences are explained by mutations in the β cardiac myosin heavy chain, 10% to 20% by mutations in the cardiac troponin T gene, and 10% to 15% by mutations in the cardiac myosin binding protein

Table 1. Genetic loci associated with congenital cardiovascular diseases

Category	Disease	Map location	Gene/protein
Myocardial	Hypertrophic cardiomyopathy	14q1	β Cardiac myosin heavy chain
		15q2	α-Tropomyosin
		1q31	Cardiac troponin T
		11p13–q13	Myosin binding protein-C
		12q23	Cardiac/slow myosin regulatory light chain
		13p21	Ventricular/slow myosin essential light chain
		19p13.2–19q13.2	Cardiac troponin I
	HCM with Wolf-Parkinson-White syndrome	7q3	Unknown
	Primary dilated cardiomyopathy	Xp21	Dystrophin
		Xp28	*G4.5*
		1q32	Unknown
		1p1–1q1	Unknown
		2q31	Unknown
		3p22-25	Unknown
		9q13-22	Unknown
		10q21-23	Unknown
		15q14	Unknown
Vascular	Marfan's syndrome	15q21	Fibrillin-1
	Familial SVAS	7q11	Elastin
	Williams syndrome	7q11	Elastin plus other genes
Arrythmial	Long-QT syndrome	11p15	*KVLQT1*
		7q35-q36	*HERG*
		3p21-p24	*SCN5A*
		21	*KCNE1*
		4q25-q27	Unknown
	Complete heart block	19q13	Unknown
	Arrhythmogenic RV dysplasia	14q23-q24	Unknown
		1q42-q43	Unknown
		14q12-q22	Unknown
	Arrythmogenic RV dysplasia/Naxos disease	3p23	Unknown
		17q21	Unknown
	Familial atrial fibrillation	10q22-q24	Unknown
	Familial ventricular fibrillation	3p21-p24	*SCN5A*
Structural	Holt-Oram syndrome	12q2	*TBX5*
	Familial ASD with heart block	5q35	*NKX2.5* (or *CSX*)
	DGS/VCFS	22q11	Unknown
	Alagille syndrome	20p12	*JAGGED1*
	Familial situs abnormalities	Xq24-2q7	*ZIC3*
	Familial TAPVR	4p13-q12	Unknown
	CAVC with trisomy 21	21q22	Unknown

ASD, atrial septal defect; CAVC, complete atrioventricular canal; DGS/VCFS, DiGeorge syndrome/velocardiofacial syndrome; HCM, hypertrophic cardiomyopathy; RV, right ventricle; SVAS, supravalvular aortic stenosis; TAPVR, total anomalous pulmonary venous return.

C [1,2]. These investigations have demonstrated that hypertrophic cardiomyopathy is a disease of the sarcomere and is markedly, genetically heterogeneous [3,4••]. Recent work has focused on the relationship of genotype to phenotype in patients with hypertrophic cardiomyopathy. Investigators have studied whether a specific disease gene is associated with a more or less severe phenotype as compared with the other disease genes, and whether specific mutations in one gene are associated with a more or less severe phenotype. Studies have demonstrated that specific mutations of the β cardiac myosin heavy chain gene are more frequently associated with sudden cardiac death and severe hypertrophy (such as the Arg403Gln mutation), whereas other mutations of the same gene are associated with a more benign clinical course (such as the Leu908Val mutation) [5–7]. In contrast, other studies have demonstrated that all cardiac troponin T mutations are associated with minimal hypertrophy and low disease penetrance but a high incidence of sudden cardiac death [1,8]. Most recently, two investigations [2,9] reported that mutations in the cardiac myosin protein C gene are associated with delayed expression of the disease and a favorable prognosis as compared with other genotypes.

Dilated cardiomyopathy

The etiology of dilated cardiomyopathy (DCM) is also markedly heterogeneous and includes inborn errors of fatty acid oxidation, disorders of mitochondrial oxidative phosphorylation, and abnormalities of myocardial structural and contractile proteins [10]. Familial forms have been reported most frequently with autosomal dominant inheritance, but also with autosomal recessive inheritance and X-linked transmission. In particular, previous studies have demonstrated that two forms of X-linked familial dilated cardiomyopathy exist. Several mutations in the dystrophin gene (which is also altered in

Duchenne's and Barth's muscular dystrophy) have been found in different families with X-linked DCM in the absence of skeletal muscle weakness [11]. In addition, the novel gene *G4.5*, identified as the disease gene in Barth's syndrome, has been identified as disease-related in other patients with X-linked DCM who lack the other symptoms generally seen in Barth's syndrome [12,13]. Moreover, mutations in *G4.5* have been reported in neonates with isolated noncompaction of the left ventricular myocardium [14]. Thus, a spectrum of myocardial and skeletal abnormalities result from different mutations in the same genes, namely, dystrophin and the novel gene *G4.5*. Once again, the specific mutation in each of the genes most likely explains the associated phenotypic variability and is under further investigation.

Multiple other familial cases of DCM with autosomal dominant transmission have been reported for which a disease locus has been mapped by linkage analysis, but for which the specific disease-related gene has not been identified (Table 1). Siu *et al.* [15] have identified the newest locus on chromosome 2q31. However, Olson *et al.* [16••] recently identified a novel disease-related gene in two small families with DCM by taking a candidate gene approach. The authors hypothesized that actin dysfunction would lead to heart failure and identified two different mutations of actin in unrelated families, thereby identifying the first autosomal, disease-related gene for DCM. Of further interest, Nezu *et al.* [17] identified mutations in the novel transporter gene *OCTN2* in patients with the autosomal recessive disorder primary systemic carnitine deficiency, a disorder characterized in part by DCM.

Finally, several reports have begun to demonstrate that primary, isolated DCM is more frequently familial than previously had been recognized. Grunig *et al.* [18] took detailed family histories from index cases and examined all willing living relatives with suspected familial disease. These authors found that up to 35% of patients with DCM may have an inherited disorder that could be divided into five categories, including DCM with muscular dystrophy, DCM without skeletal involvement, DCM with segmental hypokinesia of the left ventricle, DCM with conduction abnormalities, and DCM with sensorineural hearing loss. In a second study, Baig *et al.* [19••] performed examinations and echocardiograms on 408 willing, asymptomatic relatives of 110 consecutive patients with DCM. Nearly one third of the relatives (29%) were found to have echocardiographic abnormalities, including DCM (3%), left ventricular enlargement (20%), and diminished left ventricular fractional shortening (6%). Of further note, 27% of those relatives with only left ventricular enlargement progressed to DCM over a 14-month follow-up period. These studies underline the importance of taking a detailed family history when a patient is newly diagnosed with DCM and raise the question as to whether relatives should be prospectively examined for subtle signs of early DCM in the interest of improved management.

Arrhythmias

Long QT syndrome

The long QT syndrome is transmitted as an autosomal dominant trait (Romano-Ward) or as an autosomal recessive trait in association with congenital deafness (Jervell and Lange-Nielsen). The frequent familial occurrence of these disorders has permitted linkage analyses and the identification of five disease loci thus far; other disease loci are likely to exist (Table 1). To date, four disease genes have been identified including *KvLQT1*, *HERG*, *SCN5A*, and *KCNE1* [20–22]. Molecular studies repeatedly have confirmed that significant overlap exists between the QTc measurement in gene carriers compared with noncarriers, underlining the limitations of diagnosis by clinical criteria alone [23,24••]. However, at this time, routine clinical diagnostic molecular testing is not available given the genetic heterogeneity and limited molecular techniques.

Recent studies have focused on genotype/phenotype analyses to determine whether specific mutations in one gene or the different disease genes are associated with a different clinical course. An early study [25] demonstrated that patients with mutations in either *KvLQT1*, *HERG*, or *SCN5A* had distinct T wave patterns, though considerable overlap also occurred. A recent study [26••] demonstrated that the genotype influenced the clinical course of the disease before the initiation of β blockade therapy. In particular, patients with *KvLQT1* or *HERG* mutations experienced more frequent cardiac events, at an earlier age, than did those patients with mutations in *SCN5A*. However, the likelihood of a lethal outcome following a cardiac event was greater in the group with *SCN5A* mutations. The cumulative mortality by age 40 turned out to be similar among all three groups. Wilde *et al.* [27•] examined what stimuli triggered cardiac events in each genotypically distinct group. They found that whereas exercise-related events occurred more frequently in patients with *KvLQT1* mutations, auditory stimuli triggered cardiac events in patients with *HERG* mutations.

In addition to determining the clinical phenotype associated with each genotype, studies investigating gene-specific therapies have been initiated. Schwartz *et al.* [28] hypothesized that the QTc would shorten in patients with mutations in the sodium channel *SCN5A* when treated with the sodium channel blocker mexilitine or at moments of increased heart rates, as compared with patients with mutations in *HERG*, a potassium channel. The QTc shortened significantly in patients

with *SCN5A* mutations when treated with mexilitine or at times of increased heart rate, as compared with patients with *HERG* mutations. Such trials begin to identify ways in which therapy might be tailored to specific genotypes.

Other arrhythmias

Using linkage analyses or analysis of candidate genes, progress recently has also been made in the identification of disease loci or specific genes in other familial conduction abnormalities (Table 1). Brink *et al.* [29] mapped a disease locus for progressive, complete heart block in three families to 19q13. Several disease loci have been mapped for arrhythmogenic right ventricular dysplasia (Table 1), the most recent locus mapping to 3p23 [30]. To date, no specific disease-related gene has been identified for this disorder. A disease locus for familial atrial fibrillation was recently reported on 10q22-q24 [31]. Using a candidate gene approach, Chen *et al.* [32••] demonstrated that mutations in the sodium channel *SCN5A* were present in three unrelated families with inherited, asymptomatic electrocardiogram changes and idiopathic ventricular fibrillation. Although *SCN5A* is a disease gene for long QT syndrome, the investigators demonstrated that the families with idiopathic ventricular fibrillation were clinically distinct. Each of these studies identify disease loci or genes specific to one family. However, the same genes or mechanisms may prove to be operative in sporadic cases as well. Further, these findings help to elucidate the overall mechanisms of arrhythmias.

Structural congenital heart disease

Atrial septal defects

Classic studies on the genetic etiology of the Holt-Oram syndrome provided the first insight into the genetic etiology of associated atrial septal defects (ASDs). Linkage analyses of families with Holt-Oram syndrome demonstrated that at least one disease locus mapped to chromosomal locus 12q [33,34]. Subsequently, two separate groups, using a positional cloning strategy, demonstrated that *TBX5*, a member of the brachyury gene family, was the disease gene [35,36]. Though sporadic cases of Holt-Oram syndrome have been found to have mutations in *TBX5*, to date, mutations of *TBX5* have not been found in sporadic cases of nonsyndromic patients with ASDs.

Because ASDs are generally not lethal forms of CHD, multiple familial cases have been reported, some of which are associated with conduction disturbances. Previous reports have demonstrated that the genetic etiology of these familial cases is heterogeneous [37]. Using linkage analysis followed by evaluation of a candidate gene, Schott *et al.* [38••] identified the first disease-related gene for nonsyndromic ASDs. These authors demonstrated that the transcription factor and tinman homologue *NKX2.5* (or *CSX*) was mutated in four unrelated families with ASDs and conduction abnormalities. Of note, a few members in one family had different types of CHD (tetralogy of Fallot), whereas one member of another family had the typical conduction abnormality but no ASD. Thus, it is possible that mutations in *NKX2.5* can cause other forms of CHD or isolated atrioventricular block. This possibility is under further investigation.

Conotruncal defects and the 22q11 deletion syndrome

Several investigations have demonstrated that the majority of patients with DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly facies syndrome share a common genetic etiology, namely, a deletion of chromosomal region 22q11. Now referred to as the 22q11 deletion syndrome or CATCH 22, the clinical phenotype of this syndrome is highly variable and can include CHD, hypocalcemia, immunodeficiency, palatal abnormalities, speech and learning disabilities, renal anomalies, psychiatric problems, and facial dysmorphia [39,40]. Two large series [41,42] have described the clinical phenotype associated with the 22q11 deletion in detail. Conotruncal cardiac defects, including tetralogy of Fallot, truncus arteriosus, and interrupted aortic arch type B, are a cardinal feature of the 22q11 deletion syndrome. Several studies have assessed the frequency with which patients with a conotruncal cardiac defect have the 22q11 deletion. One of the largest recent series reported that nearly 16% of all patients with tetralogy of Fallot, 35% with truncus arteriosus, and 50% with interrupted aortic arch type B had a 22q11 deletion [43]. In contrast, only one of 20 patients with double outlet right ventricle, and none of 46 patients with transposition of the great arteries, had a 22q11 deletion. These findings concur with those reported in previous, smaller series. In addition, this report and others also demonstrated that aortic arch anomalies are more frequently seen in patients with the 22q11 deletion as compared with those without it. In other words, the relative risk of having the deletion varied substantially with the primary cardiac diagnosis and increased in the presence of additional aortic arch anomalies.

Given the high frequency of the deletion in this patient population, this author and others have suggested that all *infants* with tetralogy of Fallot, truncus arteriosus, or interrupted aortic arch type B should undergo screening for the 22q11 deletion until further prospective outcome studies are completed. This recommendation is controversial; some favor screening only those patients with syndromic features. This author questions that approach for several reasons. First, the syndromic features are highly variable and can be overlooked in the infant. Therefore, some infants would not be diagnosed with

the 22q11 deletion syndrome in the newborn period and would miss the opportunity for early clinical intervention for noncardiac features of the disorder. Second, a significant proportion of the parents of such patients have been found to be carriers of the deletion with minimal features and have come to be diagnosed with the deletion only after their children with more severe phenotypes have been diagnosed. Thus, the opportunity to offer appropriate counseling for the family considering additional children potentially would be lost or delayed. Additional prospective analyses likely will provide further insight into this controversy.

The specific gene or genes that are disease-related in the 22q11 deletion syndrome have yet to be conclusively determined. The commonly deleted region spans more than 2 megabases of DNA [40]. Already 25 genes have been identified from the deleted region. Presumably, haploinsufficiency, or half the dosage, of one or more of these genes causes the phenotype. Though some variation in the deletion size has been found, the size of the deletion does not correlate with phenotype. In fact, unique patients with unusual deletions have similar phenotypes to those with the common deletions, complicating the ability of investigators to determine a specific molecular explanation for the disorder [44–46].

Although several genes mapping into the deleted region are interesting candidates for the disease, Yamagishi *et al.* [47•] provide evidence to implicate the gene *UFDL1*. Their experiments indicate that *UFDL1* participates in the same developmental pathway as *dHAND*, a transcription factor that participates in aortic arch and right ventricular development [48]. Moreover, in the mouse embryo, *UFDL1* was expressed in the conotruncus, branchial arches, limb buds, palatal precursors, and frontonasal regions, all anatomic regions affected in the 22q11 deletion syndrome. Finally, Yamagishi *et al.* [47•] identified a unique patient with the clinical features of the syndrome but who had a much smaller, atypical deletion than any previously reported subject. The deletion encompasses the first three exons of *UFDL1*. Although these data support the hypothesis that *UFDL1* is the disease-related gene, the story is more complicated, for the unique deletion in that patient also includes part of a neighboring gene, *CDC-45*. In addition, it remains to be determined whether *UFDL1* alone causes all features of the disease or whether other genes in the deleted region are also required for manifestation of the disease phenotype. Finally, any explanation for the disease must account for the unique patients whose deletions do not include *UFDL1*.

Alagille syndrome

Alagille syndrome is an autosomal dominant disorder characterized by bile duct paucity in conjunction with cardiac disease (particularly right-sided defects), skeletal and ocular abnormalities, and a characteristic face. *JAGGED1*, a gene coding for a cell surface protein known to function as a ligand for the Notch transmembrane receptor, recently has been shown to be the Alagille syndrome disease gene [49,50]. Although the diagnosis of Alagille syndrome has previously required bile duct paucity, recent studies have demonstrated that the phenotype associated with Alagille syndrome is highly variable and may include cardiac disease and only subtle syndromic features in the absence of clinically overt liver disease. Krantz *et al.* [51] studied two cardiac patients for *JAGGED1* mutations because they had typical right-sided cardiac defects of Alagille syndrome even though their symptoms did not fulfill the clinical criteria for the syndrome. The investigators identified *JAGGED1* mutations in these patients nonetheless. Thus, *JAGGED1* appears to be an interesting candidate gene for right-sided cardiac defects. Further investigations are underway to better define the cardiac disease associated with Alagille syndrome and to determine whether *JAGGED1* is a disease-related gene in patients with isolated right-sided cardiac defects.

Heterotaxy syndrome

Familial cases of heterotaxy syndrome (also called situs ambiguous or asplenia/polysplenia syndromes) have been reported displaying either autosomal dominant, autosomal recessive, multifactorial, or X-linked inheritance. Although mammalian experiments have identified a number of genes involved in establishing asymmetry in the developing embryo, only one human disease-related gene has been identified to date. Gebbia *et al.* [52] identified mutations in a novel zinc-finger transcription factor, *ZIC3*, in familial and sporadic cases of situs ambiguous. Studies investigating the role of other candidate genes in this class of disorders are ongoing.

Conclusions

Significant progress has been made in the effort to identify the genetic etiology of congenital heart disease. More discoveries have been made in familial disorders, but evaluation of rare families with CHD and of genetic syndromes offers great promise as well. At this time, routine clinical diagnostic testing for mutations in a patient suspected of having one of these disorders is not available (except at times through a research laboratory), given the marked genetic heterogeneity and complexity of detecting a mutation in any one familial or sporadic case. Thus, the diagnosis of each disorder still relies on the clinical evaluation. In the future, molecular testing is likely to become available. In the meantime, these studies provide insight into the mechanism of disease and begin to investigate therapies based upon the specific disease gene. Many questions remain to be

answered even once a disease gene is identified, and include the role of genetic screening and the course and treatment of the clinically silent patient who tests positive for a mutation. Finally, animal studies continue to identify new genes participating in cardiovascular developmental pathways and will undoubtedly help identify candidate genes for different cardiac defects in the future.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • Of special interest
- •• Of outstanding interest

1 Watkins H, McKenna WJ, Thierfelder L, Suk HJ, Anan R, O'Donoghue A, et al.: Mutations in the genes for cardiac troponin T and α-tropomyosin in hypertrophic cardiomyopathy. N Engl J Med 1995, 332:1058–1064.

2 Niimura H, Bachinski LL, Sangwatanaroj S, Watkins H, Chudley AE, McKenna W, et al.: Mutations in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy. N Engl J Med 1998, 338:1248–1257.

3 Seidman CE, Seidman JG: Molecular genetic studies of familial hypertrophic cardiomyopathy. Basic Res Cardiol 1998, 93(suppl 3):13–16.

4 •• Maron BJ, Moller JH, Seidman CE, Vincent GM, Dietz HC, Moss AJ, et al.: Impact of laboratory molecular diagnosis on contemporary diagnostic criteria for genetically transmitted cardiovascular disease: hypertrophic cardiomyopathy, long-QT syndrome, and Marfan syndrome. Circulation 1998, 98:1460–1471.

In this article, the authors review the clinical and molecular genetics of hypertrophic cardiomyopathy and also discuss the practical and ethical issues of molecular diagnosis for clinical purposes.

5 Watkins H, Rosenzweig A, Hwang DS, Levi T, McKenna W, Seidman CE, Seidman JG: Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy. N Engl J Med 1992, 326:1108–1114.

6 Epstein ND, Cohn GM, Cyran F, Fananapazir L: Differences in clinical expression of hypertrophic cardiomyopathy associated with two distinct mutations in the β-myosin heavy chain gene. Circulation 1992, 86:345–352.

7 Marian AJ, Roberts R: Recent advances in the molecular genetics of hypertrophic cardiomyopathy. Circulation 1995, 92:1336–1347.

8 Moolman JC, Corfield VA, Posen B, Ngumbela K, Seidman C, Brink PA, Watkins H: Sudden death due to troponin T mutations. J Am Coll Cardiol 1997, 29:549–555.

9 Charron P, Dubourg O, Desnos M, Bennaceur M, Carrier L, Camproux A-C, et al.: Clinical features and prognostic implications of familial hypertrophic cardiomyopathy related to the cardiac myosin-binding protein C gene. Circulation 1998, 97:2230–2236.

10 Kelly DP, Strauss AW: Mechanisms of disease. N Engl J Med 1994, 330:913–919.

11 Beggs AH: Dystrophinopathy, the expanding phenotype: dystrophin abnormalities in X-linked dilated cardiomyopathy. Circulation 1997, 95:2344–2347.

12 Bione S, D'Adamo P, Maestrini E, Gedeon AK, Bolhuis PA, Toniolo D: A novel X-linked gene, *G4.5*, is responsible for Barth syndrome. Nature Genet 1996, 12:385–389.

13 D'Adamo PD, Fassone L, Gedeon A, Janssen EAM, Bione S, Bolhuis PA, et al.: The X-linked gene G4.5 is responsible for different infantile dilated cardiomyopathies. Am J Hum Genet 1997, 61:862–867.

14 Bleyl SB, Mumford BR, Thompson V, Carey JC, Pysher TJ, Chin TK, Ward K: Neonatal, lethal noncompaction of the left ventricular myocardium is allelic with Barth syndrome. Am J Hum Genet 1997, 61:868–872.

15 Siu BL, Niimura H, Osborne JA, Fatkin D, MacRae C, Solomon S, et al.: Familial dilated cardiomyopathy locus maps to chromosome 2q31. Circulation 1999, 99:1022–1026.

16 •• Olson TM, Michels VV, Thibodeau SN, Tai Y-S, Keating MT: Actin mutations in dilated cardiomyopathy, a heritable form of heart failure. Science 1998, 280:750–752.

These investigators hypothesized that actin dysfunction would result in heart failure and that mutations in actin might cause dilated cardiomyopathy. They identified missense mutations of actin in two unrelated families with dilated cardiomyopathy. This report is the first to identify an autosomal disease-related gene (compared with an X-linked gene).

17 Nezu J-I, Tamai I, Oku A, Ohashi R, Yabuuchi H, Hashimoto N, et al.: Primary systemic carnitine deficiency is caused by mutations in a gene encoding sodium ion-dependent carnitine transporter. Nat Genet 1999, 21:91–94.

18 Grunig E, Tasman JA, Kucherer H, Franz W, Kubler W, Katus HA: Frequency and phenotypes of familial dilated cardiomyopathy. J Am Coll Cardiol 1998, 31:186–194.

19 •• Baig MK, Goldman JH, Caforio ALP, Coonar AS, Keeling PJ, McKenna WJ: Familial dilated cardiomyopathy: cardiac abnormalities are common in asymptomatic relatives and may represent early disease. J Am Coll Cardiol 1998, 31:195–201.

The investigators prospectively examined asymptomatic relatives of index cases with dilated cardiomyopathy for echocardiographic changes. Nearly one third of relatives were found to have echocardiographic changes; some went on to develop dilated cardiomyopathy. This study emphasizes that dilated cardiomyopathy is more frequently familial than previously considered. The results lead to unanswered questions about the appropriate screening of family members when an index case is first diagnosed.

20 Roden DM, Lazzara R, Rosen M, Schwartz PJ, Towbin J, Vincent GM: Multiple mechanisms in the long-QT syndrome: current knowledge, gaps and future directions. Circulation 1996, 94:1996–2012.

21 Wang Q, Chen Q, Li H, Towbin J: Molecular genetics of long QT syndrome from genes to patients. Curr Opin Cardiol 1997, 12:310–320.

22 Priori SG, Barhanin J, Hauer RNW, Haverkamp W, Jongsma HJ, Kleber AG, et al.: Genetic and molecular basis of cardiac arrhythmias: impact on clinical management: parts I and II. Circulation 1999, 99:518–528.

23 Vincent GM, Timothy KW, Leppert M, Keating M: The spectrum of symptoms and QT intervals in carriers of the gene for the long-QT syndrome. N Engl J Med 1992, 327:846–852.

24 •• Priori SG, Napolitano C, Schwartz PJ: Low penetrance in the long-QT syndrome. Circulation 1999, 99:529–533.

In this study, the authors found that 33% of asymptomatic relatives (with normal electrocardiograms) of "sporadic" cases with the long QT syndrome carried the mutation. Thus, the penetrance of the disease is lower than previously considered. The investigators also highlight the inadequacy of clinical diagnosis alone in the absence of molecular confirmation. However, they do not fully address the present unavailability and inadequacy of molecular diagnostic tests or the dilemma of treatment for the older, asymptomatic mutation carrier.

25 Moss AJ, Zareba W, Benhorin J, Locati EH, Hall WJ, Robinson JL, et al.: ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. Circulation 1995, 92:2929–2934.

26 •• Zareba W, Moss AJ, Schwartz PJ, Vincent GM, Robinson JL, Priori SG, et al.: Influence of the genotype on the clinical course of the long-QT syndrome. N Engl J Med 1998, 339:960–965.

The authors of this study compare the frequency of cardiac events within a large cohort of patients with long QT syndrome based on the length of their QTc and specific genotype. The patients whose electrocardiogram revealed a longer QTc were at greater risk for cardiac events, whereas patients with mutations in *KvLQT1* or *HERG* were at greater risk for earlier cardiac events, but all three genotypes (*KvLQT1*, *HERG*, and *SCN5A*) had the same cumulative mortality. The strength of this article lies in the large numbers of patients examined, but it should be remembered that this cohort comes from only 38 families who share a more common genetic background than an equivalent number of unrelated people. The genetic background could also influence outcome.

27 • Wilde AAM, Jongbloed RJE, Doevendans PA, Duren DR, Hauer RNW, van Langen IM, et al.: Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS^2) patients from KVLQT1-related patients (LQTS^1). J Am Coll Cardiol 1999, 33:327–332.

Although this study includes only 11 families, it confirms previous work that suggested that the stimuli leading to a cardiac event varied with genotype. Presumably, larger studies investigating this specific question also will be forthcoming.

28 Schwartz PJ, Priori SG, Locati EH, Napolitano C, Cantu F, Towbin JA, et al.: Long QT syndrome patients with mutations of the *SCN5A* and *HERG* genes have differential responses to Na^+ channel blockade and to increases in heart rate. Circulation 1995, 92:3381–3386.

29 Brink PA, Ferreira A, Moolman JC, Weymar HW, van der Merwe P-L, Corfield VA: Gene for progressive familial heart block type 1 maps to chromosome 19q13. Circulation 1995, 91:1633–1640.

30 Ahmad F, Li D, Karibe A, Gonzalez O, Tapscott T, Hill R, et al.: Localization of a gene responsible for arrhythmogenic right ventricular dysplasia to chromosome 3p23. Circulation 1998, 98:2791–2795.

31 Brugada R, Tapscott T, Czernuszewicz GZ, Marian AJ, Iglesias A, Mont L, et al.: Identification of a genetic locus for familial atrial fibrillation. N Engl J Med 1997, 336:905–911.

32 •• Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, et al.: Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature 1998, 392:293–296.

These investigators identify the first disease-related gene in a unique patient population with asymptomatic electrocardiogram changes and ventricular fibrillation. They demonstrate that although the disease gene is the same as that in some patients with long QT syndrome, the families with ventricular fibrillation have a unique syndrome. This report contributes to the evidence that familial arrhythmias are caused by mutations in ion channels.

33 Bonnet D, Pelet A, Legeai-Mallet L, Sidi D, Mathieu M, Parent P, et al.: A gene for Holt-Oram syndrome maps to the distal long arm of chromosome 12. Nature Genet 1994, 6:405–408.

34 Terrett JA, Newbury-Ecob R, Cross GS, Fenton I, Raeburn JA, Young ID, Brook JD: Holt-Oram syndrome is a genetically heterogeneous disease with one locus mapping to human chromosome 12q. Nature Genet 1994, 6:401–404.

35 Li QY, Newbury-Ecob RA, Terrett JA, Wilson DI, Curtis ARJ, Yi CH, et al.: Holt-Oram syndrome is caused by mutations in *TBX5*, a member of the *Brachyury* (*T*) gene family. Nature Genet 1997, 15:21–29.

36 Basson CT, Bachinsky DR, Lin RC, Levi T, Elkins JA, Soults J, et al.: Mutations in human cause limb and cardiac malformation in Holt-Oram syndrome. Nature Genet 1997, 15:30–35.

37 Benson DW, Sharkey A, Fatkin D, Lang P, Basson CT, McDonough B, et al.: Reduced penetrance, variable expressivity, and genetic heterogeneity of familial atrial septal defects. Circulation 1998, 97:2043–2048.

38 •• Schott JJ, Benson DW, Basson CT, Pease W, Silberbach GM, Moak JP, et al.: Congenital heart disease caused by mutations in the transcription factor *NkX2-5*. Science 1998, 281:108–111.

In this study, the authors use the classic techniques of linkage analysis and candidate gene screening to identify the first disease-related gene for nonsyndromic congenital heart disease, *ie*, atrial septal defects with conduction abnormalities.

39 Thomas JA, Graham JM: Chromosome 22q11 deletion syndrome: an update and review for the primary pediatrician. Clin Pediatr 1997, 36:253–266.

40 Emanuel BS, Budarf ML, Scambler PJ: The genetic basis of conotruncal cardiac defects: the chromosome 22q11.2 deletion. In Heart Development, edn 26. Edited by Harvey RP, Rosenthal N. San Diego: Academic Press; 1999:463–478.

41 Ryan AK, Goodship JA, Wilson DI, Philip N, Levy A, Seidel H, et al.: Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. J Med Genet 1997, 34:798–804.

42 McDonald-McGinn DM, LaRossa D, Goldmuntz E, Sullivan K, Eicher P, Gerdes M, et al.: The 22q11.2 deletion: screening, diagnostic workup, and outcome of results: report on 181 patients. Genet Testing 1997, 1:99–108.

43 Goldmuntz E, Clark BJ, Mitchell LE, Jawad AF, Cuneo BF, Reed L, et al.: Frequency of 22q11 deletions in patients with conotruncal defects. J Am Coll Cardiol 1998, 32:492–498.

44 O'Donnell H, McKeown C, Gould C, Morrow B, Scambler P: Detection of an atypical 22q11 deletion that has no overlap with the DiGeorge syndrome critical region. Am J Hum Genet 1997, 60:1544–1548.

45 Kurahashi H, Tsuda E, Kohama R, Nakayama T, Masuno M, Imaizumi K, et al.: Another critical region for deletion of 22q11: a study of 100 patients. Am J Med Genet 1997, 72:180–185.

46 Rauch A, Pfeiffer RA, Leipold G, Singer H, Tigges M, Hofbeck M: A novel 22q11.2 microdeletion in DiGeorge syndrome. Am J Hum Genet 1999, 64:659–667.

47 • Yamagishi H, Garg V, Matsuoka R, Thomas T, Srivastava D: A molecular pathway revealing a genetic basis for human cardiac and craniofacial defects. Science 1999, 283:1158–1161.

In this study, the authors report on a unique patient with an atypical deletion of 22q11 that provides some evidence that the gene *UFDL1* may be disease-related in the 22q11 deletion syndrome. Evidence supporting this hypothesis includes expression studies of *UFDL1* in the mouse embryo and experiments implicating *UFDL1* in the same developmental pathway as d-Hand. Most investigators in this field do not consider this hypothesis to be definitive and believe further investigations are required.

48 Srivastava D: HAND proteins: molecular mediators of cardiac development and congenital heart disease. Trends Cardiovasc Med 1999, 9:11–18.

49 Li L, Krantz ID, Deng Y, Genin A, Banta AB, Collins CC, et al.: Alagille syndrome is caused by mutations in human *Jagged1*, which encodes a ligand for Notch1. Nat Genet 1997, 16:243–251.

50 Oda T, Elkahloun AG, Pike BL, Okajima K, Krantz ID, Genin A, et al.: Mutations in the human *Jagged1* gene are responsible for Alagille syndrome. Nat Genet 1997, 16:235–242.

51 Krantz I, Smith R, Colliton RP, Tinkel H, Zackai EH, Piccoli DA, et al.: *Jagged1* mutations in patients ascertained with isolated congenital heart defects. Am J Med Genet 1999, 84:56–60.

52 Gebbia M, Ferrero GB, Pilia G, Bassi MT, Aylsworth AS, Penman-Splitt M, et al.: X-linked *situs* abnormalities result from mutations in *ZIC3*. Nature Genet 1997, 17:305–308.