

CardioGeneScan

Familial Cardiomyopathy – an Overview

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Overview Summary

Cardiomyopathy, with an estimated prevalence of between 1:500 and 1:5000, is generally characterized by impaired contractile function of the myocardium, putting patients at high risk of arrhythmias, embolic stroke, and sudden cardiac death (SCD; reviewed in^{1,2}). Myocardial dysfunction associated with cardiomyopathy can either be mechanical or electrical and may or may not include structural abnormalities.^{1,2} The four most common forms of cardiomyopathy are hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmo-genic right ventricular dysplasia/cardiomyopathy (ARVD/C), and left ventricular noncompaction (LVNC).¹ Rarer forms of cardiomyopathy include restrictive cardiomyopathy (RCM) and the amyloid-associated cardiomyopathies, including transthyretin amyloidosis (ATTR) and apolipoprotein A1 amyloidosis (AApoA1).¹ While each of these forms of cardiomyopathy has a different etiology and different prognosis, the cardiac clinical presentation is generally similar, including heart failure, stroke, and sudden cardiac death (see Table 1). Prevention of stroke and SCD can be achieved through treatments including administration of anti-arrhythmic and/or anti-coagulation drugs, implantable cardioverter

defibrillator (ICD) therapy, and certain lifestyle changes (see Table 1); however, identification of at-risk individuals who may benefit from these treatments can be difficult since abnormal electrocardiogram or echocardiogram profiles may not always be clear and since stroke or SCD may be the presenting clinical manifestation.² Genetic testing for presence of a germline mutation in the genes known to be associated with cardiomyopathy can confirm a diagnosis, help differentiate between different forms of cardiomyopathy, and also facilitate detection of at-risk individuals in familial forms of cardiomyopathy, which account for between 30% and 100% of all cases.³⁻⁶ Family members carrying familial mutations detected in the index patient for the family are at highly increased risk of cardiomyopathy, while family members not carrying familial mutations are at lesser risk.⁵ Familial cardiomyopathies are most commonly transmitted in an autosomal dominant manner, and less commonly in an autosomal recessive, X-linked, or mitochondrial manner.¹ Genetic causes of cardiomyopathy tested for in the CARDIOMYOPATHY DNA sequencing evaluation account for up to 66% of familial cardiomyopathy cases (see Table 2).

Table 1: Disease Facts¹⁻¹¹

Disease Name	Hypertrophic Cardiomyopathy (HCM)	Dilated Cardiomyopathy (DCM)	Arrhythmogenic Right Ventricular Dysplasia/ Cardiomyopathy (ARVD/C)	Left Ventricular Noncompaction (LVNC)	Restrictive Cardiomyopathy (RCM)	TTR and ApoAI Amyloidosis (ATTR and AApoAI)
MIM Number	192600	115200	107970	604169	115210	176300 (TTR); 107680 (APOA1)
Characteristic morphological changes	Cellular disarray within the myocardium; left ventricular thickening	Enlarged left ventricle	Replacement of normal myocardial tissue with fibrotic adipose tissue; right ventricular thickening	Prominent “spongy” trabeculations and deep recesses in the left ventricle	Increased ventricular rigidity and enlarged atria	Amyloid deposition in heart and other tissues
Arrhythmias	Atrial and ventricular	Atrial and ventricular	Ventricular	Atrial and ventricular	Atrial	Atrial
Dilation	Left ventricular	Left ventricular	Right ventricular		Atrial	Left and right ventricular
Left ventricular failure	Diastolic dysfunction	Systolic dysfunction		Systolic and diastolic dysfunction	Diastolic dysfunction	Diastolic dysfunction
Estimated Prevalence	1:500	1:5000	1:1000	1:2000 (adult form); rare (congenital form)	rare	rare
Penetrance	40-100%	40-80%	20-100%	50-100%	40%	50-90%
Average Age of Onset (years)	30	40	30	40 (adult form); 6 (congenital form)	30 (adult form); 6 (congenital form)	40
Selected Symptoms	Chest pain, palpitations, dyspnea, syncope, edema, thrombo-embolisms/stroke, sudden cardiac death (SCD)					
Additional SCD information	Common cause of SCD in young competitive athletes ¹²		Common cause of SCD in juveniles and athletes ^{13,14}		Mortality rate due to SCD is 32-44% in adults and 66-100% in children within a few years of diagnosis. ⁹	
Selected Therapies	Anti-arrhythmic drugs, anti-coagulation drugs, implantable cardioverter defibrillator or pacemaker, catheter ablation, avoidance of competitive sports or other strenuous physical activities					

Table 2: Molecular Genetics

Gene	Proportion (%) of Disease Attributable to Gene (reference) -transmission is autosomal dominant unless otherwise stated-						Comments
	HCM	DCM	ARVD/C	LVNC	RCM	ATTR and AApoAI	
ABCC9		<1% ¹⁵					Certain mutations in <i>ABCC9</i> have been associated with cardiac conduction defects in patients with DCM. ¹⁶
ACTC1	<1% ^{17, 18}	<1% ⁴		>3% ¹⁹	<1% ²⁰		
ACTN2	<1% ¹⁸	<1% ²¹					
ALMS1		15-24% for Alström syndrome with DCM present (AR) ²²					Mutations in <i>ALMS1</i> are associated with Alström syndrome (characterized by cone-rod dystrophy, obesity, progressive sensorineural hearing impairment, insulin resistance syndrome, and developmental delay), with DCM present in 60% of patients. ²²
APOA1						100% (40% of all mutations are associated strictly with cardiac phenotypes ²³⁻²⁵)	Of all the disease-causing <i>ApoA1</i> mutations, those affecting the C-terminus of the protein tend to confer cardiac phenotypes. ²⁶
CAV3	<1% ²⁷						
CSRP3	<1% ^{17, 18}	<1% ^{21, 28, 29}					
CTF1		unknown					
DES		2% ^{30, 31}			<1% (AD; AR) ^{32, 33}		Mutations in <i>DES</i> have been reported in families with RCM and atrioventricular block. ^{32, 33}
DNAJC19		<1% for DCMA (AR) ³⁴					Mutations in <i>DNAJC19</i> have been associated with DCM with ataxia (DCMA) in the Canadian Hutterite population. Cardiac clinical features of DCMA are often severe, presenting at a lower than average age of onset, and may sometimes include long QT syndrome. ³⁴
DSC2			1-5% ^{35, 36}				
DSG2			10% ³⁷⁻³⁹				
DSP			6-16% ^{40, 41} 100% for Carvajal syndrome (AR) ⁴²				

Table 2: Molecular Genetics (Continued 2)

Gene	Proportion (%) of Disease Attributable to Gene (reference) -transmission is autosomal dominant unless otherwise stated-						Comments
	HCM	DCM	ARVD/C	LVNC	RCM	ATTR and AApoAI	
<i>DTNA</i>				<1% ^{43,44}			<i>DTNA</i> mutations have been reported in a 4-generation Japanese family with non-isolated LVNC with congenital heart defects. ⁴³
<i>EMD</i>		>99% for Emery-Dreifuss muscular dystrophy (EDMD) (<i>XR</i>) ⁴⁵					
<i>EYA4</i>		<1% for syndromic DCM with deafness (<i>AR</i>) ⁴⁶					
<i>FKTN</i>		<1% ⁴⁷					
<i>GLA</i>	<1% (<i>XD</i>) ⁴⁸⁻⁵⁰ ~100% for males with Fabry disease (<i>XR</i>) ⁵¹						<i>GLA</i> mutations are associated with Fabry disease, a multi-system metabolic disorder caused by a reduction in the enzyme alpha-galactosidase; in Fabry disease, males tend to manifest very severe HCM. ⁵¹
<i>HOPX</i>		unknown					Mice which over-express <i>HOPX</i> develop cardiac hypertrophy. ⁵²
<i>JUP</i>			<1% ⁵³ 100 for Naxos disease (<i>AR</i>) ⁵⁴				Naxos disease is syndromic ARVD/C with hair and skin abnormalities. ⁵⁴
<i>LAMP2</i>	100% for Danon disease (<i>XD</i>) ⁵⁵	100% for Danon disease (<i>XD</i>) ⁵⁶					HCM tends to be the characteristic cardiomyopathy in males with Danon disease, an X-linked glycogen storage disorder characterized by cardiomyopathy, skeletal myopathy, and mental retardation. DCM tends to be the characteristic cardiomyopathy in female carriers of <i>LAMP2</i> mutations leading to Danon disease in males. ^{55,56}
<i>LDB3</i>	1-5% ¹⁸	1-6% ⁵⁷⁻⁵⁹					Reported mutations in <i>LDB3</i> are associated DCM with higher than average age of onset ⁵⁷ ; Certain mutations in <i>LDB3</i> have been associated with left ventricular non-compaction (LVNC) in DCM patients. ⁵⁸

Table 2: Molecular Genetics (Continued 3)

Gene	Proportion (%) of Disease Attributable to Gene (reference) -transmission is autosomal dominant unless otherwise stated-						Comments
	HCM	DCM	ARVD/C	LVNC	RCM	ATTR and AApoAI	
LMNA		5-10% ⁶⁰⁻⁶²					Certain mutations in <i>LMNA</i> have been associated with skeletal muscle and cardiac conduction defects in DCM patients. ¹⁶
MT-ND1		<1% (mito) ^{63, 64}					
MT-ND5		<1% (mito) ^{64, 65}					
M-TND6		<1% (mito) ⁶⁵					
MT-TG	<1% (mito) ⁶⁶						
MT-TH		<1% (mito) ⁶⁵					
MT-TI	<1% (mito) ^{66, 67}						
MT-TK	90% for MERRF (mito) ⁶⁸ <1% for isolated HCM (mito) ^{66, 67}	90% for MERRF (mito) ⁶⁸ <1% for isolated DCM (mito) ⁶⁷					MERRF (myoclonic epilepsy with ragged red fibers) is a rare multisystem disorder which may include the DCM phenotype. ⁶⁸
MT-TL1		90% for MELAS (mito) ⁶⁹ <1% for isolated DCM (mito) ⁶⁶					MELAS (mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes) is a rare multisystem disorder which may include the DCM phenotype. ⁶⁹
MT-TQ		<1% (mito) ^{63, 70}					
MT-TS1		<1% for MELAS (mito) ⁶⁹					
MT-TS2		<1% (mito) ⁶⁵					
MYBPC3	25-40% ^{7, 17, 18}	2-10% ^{62, 71}					
MYH6	<1% ¹⁸						

Table 2: Molecular Genetics (Continued 4)

Gene	Proportion (%) of Disease Attributable to Gene (reference) -transmission is autosomal dominant unless otherwise stated-						Comments
	HCM	DCM	ARVD/C	LVNC	RCM	ATTR and AApoAI	
MYH7	25-40% ^{7, 17, 18}	5-10% ^{59, 72, 73}		>5% ¹⁹	<1% ^{74, 75}		
MYL2	<2% ^{17, 18}						
MYL3	<1% ^{7, 17, 18}						
MYLK2	<1% ⁷⁶						
PKP2			10-43% ^{77, 78}				ARVD/C patients with <i>PKP2</i> mutations tend to have a significantly earlier (by ~8 years) age of onset. ⁷⁸
PLN		5% ⁷⁹					A <i>PLN</i> mutation was reported in one family with lower than average age of onset DCM. ⁷⁹
PRKAG2	<1% ⁸⁰						<i>PRKAG2</i> mutations are associated with metabolic HCM which can include Wolff-Parkinson-White syndrome (ventricular pre-excitation and atrial fibrillation) and conduction system defects. ⁸¹
RYR2			<1% ⁸²				<i>RYR2</i> mutations were reported in four Italian families with a history of effort-induced ventricular arrhythmias. ⁸²
SCN5A		2.5% ^{59, 83}					Several families with <i>SCN5A</i> mutations were reported to have earlier than average age of onset DCM with cardiac conduction defects. ^{16, 83, 84}
SGCD		<1% ⁸⁵					Mutations in <i>SGCD</i> have been associated with skeletal muscle disease in DCM patients. ¹⁶
TAZ		80% for Barth syndrome (<i>XR</i>) ⁸⁶ <1% for non-syndromic DCM (<i>XR</i>) ⁸⁶		1% (<i>XR</i>) ^{43, 87}			Mutations in <i>TAZ</i> are typically associated with Barth Syndrome, a rare but serious metabolic and neuromuscular congenital disease characterized by cardiomyopathy (DCM or HCM), skeletal myopathy, short stature, and neutropenia. Barth syndrome only affects males and is often fatal in childhood due to heart failure. ⁸⁶ <i>TAZ</i> mutations have been associated with left ventricular non-compaction in patients with DCM. ¹⁶ LVNC-associated <i>TAZ</i> mutations have been reported in a family with X-linked infantile LVNC. ⁸⁷
TCAP		<1% ^{28, 88}					
TGFB3			<1% ⁸⁹				
TMEM43			<1% ^{90, 91}				Mutations in <i>TMEM43</i> are associated with severe ARVD/C with high penetrance; age of onset earlier for men than women (by 12 years); high incidence of SCD ^{90, 91}

Table 2: Molecular Genetics (Continued 5)							
Gene	Proportion (%) of Disease Attributable to Gene (reference) -transmission is autosomal dominant unless otherwise stated-						Comments
	HCM	DCM	ARVD/C	LVNC	RCM	ATTR and AApoAI	
<i>TNNC1</i>	<1% ¹⁸	<1% ⁹²					
<i>TNNI3</i>	<5% (AR) ^{7, 17, 18}	<1% (AR) ⁹³			>50% ⁹⁴⁻⁹⁶		Mutations in <i>TNNI3</i> were found in seven of ten RCM families: in one large family, the same mutation was associated with RCM or HCM. ⁹⁴
<i>TNNT2</i>	<7% ^{7, 17, 18}	1-10% ^{59, 62, 72, 73, 92}		unknown	<1% ⁹⁷		
<i>TPM1</i>	<5% ^{7, 17, 18}	<1% ⁹⁸					
<i>TTR</i>						100% (13% of all mutations are associated strictly with cardiac phenotypes ¹⁰)	The most common disease variant is Val30Met (a.k.a. Val50Met); penetrance and clinical heterogeneity vary widely in different populations with this variant. The most common <i>TTR</i> variant associated with isolated cardiac amyloidosis is Val122Ile (a.k.a. Val142Ile), which is found in 3.9% of the African American population. ¹⁰
<i>VCL</i>		3% ⁹⁹					

Key: AR (Autosomal Recessive); XD (X-linked Dominant) XR (X-linked Recessive); mito (mitochondrial)

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