Metabolic gene defects and risk of arrhythmia

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Abstract

Inherited single-gene disorders offer unique insights into the role of metabolic processes in arrhythmogenesis. Although many metabolic defects result in cardiomyopathy as a physiologic compensation, it is clear that specific perturbations are associated with particular arrhythmias. Metabolic gene defects may cause arrhythmia through many different pathways, including developmental effects on cardiac patterning, pathologic disruption of specific myocardial cell types, and the perturbation of several cellular processes. Understanding the precise pathways linking individual gene defects with discrete clinical arrhythmias will shed light, not only on monogenic disease, but also on common disorders such as ischemia or diabetes.

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Introduction

Myocardial metabolism can adapt to a wide range of substrates, but the precise pattern of substrate utilization is dependent on availability, oxygen delivery, workload, and physiologic regulation. As a consequence of these constraints, and the demands on myocardial functional reserve throughout life, many single-gene metabolic defects cause cardiomyocyte dysfunction, including arrhythmia [1,2].

Specific metabolic gene defects associated with arrhythmia

Lipid metabolism

At rest, free fatty acids constitute the predominant myocardial substrate, so it is not surprising that several inherited disorders of fatty acid oxidation present with early onset cardiomyopathy and arrhythmias. Abnormal carnitine transport into cells or into mitochondria, in addition to defects in several mitochondrial enzymes required for fatty acid oxidation, can result in cardiomyopathies (*Table I*) [3,4]. Overt cardiac involvement is present in more than 50% of those with defects of fatty acid oxidation. Presentation is usually precipitated by fasting, depletion of glycogen stores, and consequent dependence on fatty acid as an energy substrate. In typical acute metabolic crises, characterized by hypoglycemia, lactic acidosis, hepatic dysfunction, blunted ketone formation, and hypotonia, ventricular tachycardia is the most common arrhythmia [3]. However, other arrhythmias may be prominent in a substantial minority of cases, irrespective of overt evidence of cardiomyopathy. Sinus node dysfunction, paroxysmal supraventricular arrhythmias, atrioventricular block, and intraventricular conduction abnormalities all have been reported [3]. It is difficult to make definitive correlations in such rare disorders, but there may be a propensity to specific arrhythmias with different defects. The majority of fatty acid oxidation disorders are recognized in the first 2–3 years of life, but there are well-documented cases that have presented in adulthood [5].

Table I. Metabolic gene defects associated with arrhythmias.

Disorder	OMIM	Gene defect	Mode of inheritance	Arrhythmias	Comments	References
Lipid metabolism						
CPT-II	608836	Carnitine palmitoyltransferase*	AR	VT, AVB		[3,4]
CACT deficiency	212138	SLC25A20, carnitine–acylcarnitine translocase*	AR	VT, SVT, AVB		[3,4]
MCAD	201450	Medium-chain acyl dehydrogenase*	AR	VT	Late onset reported	[3–5]
LCAD	201460	Long-chain acyl dehydrogenase	AR	VT		[3]
VLCAD	201475	Very-long-chain acyl dehydrogenase	AR	VT, AVB		[3]
MADD	231680	Multiple acyl CoA dehydrogenase deficiency	AR	VT, SVT		[3]
Barth	302060	Tafazzin*	XLD	VT, SCD		[6,7]
Glycogen storage						
Pompe	232200	Lysosomal acid glucosidase*	AR	PE, CD	MLVT, EFE, several forms	[1,2,9]
McArdle's	232600	Glycogen phosphorylase*	AR	AVB, CD	DCM	[1,2]
Brancher	232500	Amylo-1,4-1,6-transglucosidase*	AD, AR	AVB, SCD	DCM	[1,2]
Debrancher	232400	Amylo-1,6-glucosidase*	AR	AVB	DCM	[1,2]
PRKAG2	602743	AMP-activated protein kinase γ-2 subunit*	AD	PE, AVB	MLVT	[10–12]
Danon	300257	Lysosome-associated membrane protein 2*	XLD	AVB	MLVT	[10]
Glycosphingolipid storage						
Fabry	301500	β-Galactosidase A*	XLD	AF, VT	MLVT, RF	[2,13]
Mitochondrial						
KSS	530000	Variable deletion	Mitochondrial	AVB, PE	LVH/DCM	[15]

AD, autosomal dominant; AF, atrial fibrillation; AR, autosomal recessive; AVB, atrioventricular block; CD, diffuse conduction disease; DCM, dilated cardiomyopathy; EFE, endocardial fibroelastosis; KSS, Kear–Sayre syndrome; LVH, left ventricular hypertrophy; MLVT, massive left ventricular wall thickening; OMIM, Online Mendelian Inheritance in Man(http://www.ncbi.nlm.nih.gov/omim/); PE, pre-excitation; RF, renal failure; SCD, sudden cardiac death; SVT, supraventricular tachycardia; VT, ventricular tachycardia; XLD, X-linked dominant.

Barth's syndrome is characterized by cardiomyopathy, skeletal myopathy, neutropenia, organic aciduria, and growth retardation. Ventricular arrhythmia and cardiac arrest are typical [6]. The syndrome is caused by mutations in tafazzin [7], a gene of unknown function with a suspected role in mitochondrial phospholipid metabolism [8].

Storage disorders

Many of the classic metabolic storage disorders are associated with cardiac involvement (*Table I*) [2]. Neurologic or respiratory failure is often the cause of early death. Cardiac manifestations, including massive left ventricular wall thickening (a combination of deposition and true hypertrophy) and valvular involvement, although present to some degree in all cases, may emerge as a problem only later in life in those who survive as a result of therapeutic intervention or less penetrant alleles [1,2]. Prominent evidence of atrioventricular conduction disease, often with ventricular pre-excitation, is seen in all these diseases, and atrial arrhythmias are also a frequent problem.

Glycogen storage

Pompe's disease typically results in massive thickening of the ventricular wall in childhood, sometimes with endocardial fibroelastosis [1,2]. There is usually evidence of ventricular pre-excitation, in addition to bizarre fractionation of the entire surface electrogram [9]. Ectopy is commonly seen, but arrhythmias do not dominate the clinical course and death is usually from cardiorespiratory failure. Defects in glycogen phosphorylase (McArdle's disease), brancher or

debrancher enzymes, all are reported to cause atrioventricular conduction system disease and dilated cardiomyopathy with disproportionate wall thickening [2]. In these disorders, heart failure and sudden death are seen occasionally.

Dominant mutations in the γ2 subunit of the AMP-activated protein kinase gene (PRKAG2)* have recently been shown to result in massive myocardial thickening, atrioventricular conduction system disease, and ventricular pre-excitation [10]. Affected families had previously been included under the rubric of hypertrophic cardiomyopathy on the basis of their inheritance patterns, adult onset, and echocardiographic features [11]. Atrial fibrillation and atrial flutter are common, but high-grade atrioventricular block is the dominant clinical arrhythmia [11]. Clinical studies suggest that, in many cases, asymptomatic individuals are maximally pre-excited at rest, and therefore are probably dependent on accessory atrioventricular connections from an early age. Syncope and sudden death are reported in families with PRKAG2 mutations, but the mechanism is not always clear.

Danon disease has previously been classified as a glycogen storage disorder, despite the inconsistent presence of glycogen on biopsy [12]. The identification of mutations in the lysosomal-associated membrane protein, LAMP2, confirmed this as a vacuolar myopathy. The clinical course is malignant, complicated by ventricular arrhythmias and intractable heart failure.

Glycosphingolipid storage*

Andersen–Fabry disease is an X-linked storage disorder characterized by angiokeratoma, acroparesthesias, abdominal pain, and renal and cardiac disease [2]. Female heterozygotes often exhibit much less penetrant forms of the disease, and cardiac-specific, late-onset variants exist [13]. In these *formes frustes*, the incidence of cardiovascular symptoms in males and females is similar. Ventricular thickening is common, especially in males, and correlates with the risk of non sustained ventricular tachycardia [14]. Atrial fibrillation is the most frequent arrhythmia. Atrioventricular conduction system disease and pre-excitation are less common than in many other storage disorders.

Other storage disorders

Cardiac involvement is the rule rather than an exception with a host of other rare storage disorders, including mucopolysaccharidoses, mucolipidoses, gangliosidoses, and neuronal ceroid lipofuscinosis [2]. The majority of these conditions are recessive and lethal in childhood. Reports of arrhythmias are rare, but are dominated by atrioventricular block.

Mitochondrial disorders

Specific mitochondrial DNA defects have quite variable effects as a result of differences in the extent of tissue heteroplasmy for mutant mitochondria. However, cardiac involvement is a central feature of several of the classic mitochondrial syndromes [1]. Cardiac expression of these defects is usually in the form of cardiomyopathy. Atrioventricular conduction disease is a common feature of Kearns–Sayre syndrome and accessory atrioventricular connections are also reported [15]. In several autosomal disorders in which left ventricular hypertrophy, cardiomyopathy, or conduction system disease are prominent, the mutated genes have recently been implicated in mitochondrial function. These include myotonic dystrophy and Friedreich's ataxia [16].

Metabolic mechanisms of arrhythmogenesis

The reproducible clinical effects of most inherited metabolic diseases suggest a precise relationship between perturbations of metabolism and specific arrhythmias. Discrete metabolic defects may act via developmental patterning events, on distinct myocardial cell types or through particular signaling pathways to cause specific arrhythmias.

Inherited metabolic defects act at several time points throughout development, adolescence, and adulthood. The patterning of cardiac form and function are closely intertwined, and subtle physiologic perturbations may lead to both abnormal myocyte specification and macroscopic anatomic abnormalities [17]. The strong association between atrioventricular conduction abnormalities and ventricular pre-excitation seen across several metabolic gene defects suggests that patterning of the atrioventricular ring is particularly susceptible [2,10,18].

Several cell types exist within the myocardial syncytium. Perhaps the most obvious cell-specific pathology seen with several metabolic gene defects is atrioventricular block (*Table I*). This may reflect not only the role of calcium transport and conductance in the action potentials of these cells, but also many other attributes. Distinctive intercellular junctions, membrane turnover, or unique sarcomeric protein isoforms may predispose the conduction system in metabolic disorders. Differential sensitivity to metabolic defects also extends to other cell types, such as ventricular myocytes, which appear particularly affected by defects in fatty acid oxidation [3]. ''Passive'' storage itself may be quite localized, and many other intracellular processes are highly regionalized throughout the heart [19]. Differential effects across apico–basal or endocardial–epicardial gradients result in myocardial heterogeneity, a major substrate for re-entrant arrhythmias.

Metabolic defects are understood to induce arrhythmia through an increasing number of cellular mechanisms [20]. The function of many ion channels is closely coupled with cellular metabolic function through cyclic nucleotides gating and other mechanisms. Calcium cycling in each intracellular compartment is distinctly affected by particular metabolic pathway perturbations. Syncytial coupling is mediated by gap junctions, which are regulated by intracellular substrate concentration, local calcium and pH [21]. Subtle defects in the posttranslational modification of ion channels and other transmembrane proteins may interfere with the ability of these molecules to reach the sarcolemma [22]. Normal metabolism is required for the activation of some ion channels, acting as a long-term regulator of membrane conductances [23]. Understanding the precise pathways linking individual gene defects with discrete clinical arrhythmias will shed light, not only on monogenic disease, but also on the common disorders such as ischemia or diabetes. ■

* See glossary for definition of these terms.

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