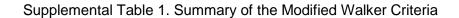
# **Supplemental Methods**

## **Echocardiographic evaluation**

End diastolic left ventricular septal thickness (LVDST), left ventricular posterior wall thickness (LVPWT), left ventricular end-diastolic dimension (LVEDD), and left ventricular end-systolic dimension (LVESD) were obtained through standard parasternal views. Left ventricular maximal wall thickness (LVMWT) was determined by the larger of either LVDST or LVPWT [(31, 32)]. HCM was defined by concentric left ventricular hypertrophy or asymmetric ventricular hypertrophy, with LVMWT z-score > 2. DCM was defined as left ventricular dilation as evidenced by a LVEDD z-score > 2 with or without impaired ventricular function as evidenced by a decreased fractional shortening (z-score < -2). RCM was defined by diastolic dysfunction in the setting of preserved systolic function as indicated by (1) atrial enlargement and catheterization data indicating elevated end-diastolic pressure, (2) absence of significant left ventricular hypertrophy or dilation, and (3) lack of evidence of pericardial disease or infiltrative disease [(10)]. LVNC was diagnosed by (1) LV hypertrophy with deep endomyocardial trabeculations in one or more wall segments, (2) a two-layered endocardium with a non-compacted:compacted ratio of > 2, and (3) deep recesses filled with blood from the ventricular cavity as seen by color Doppler imaging<sup>[(33)]</sup>. ARVC patients were diagnosed utilizing the criteria set forth by the European Society of Cardiology and International Society and Federation of Cardiology<sup>[(34)]</sup>. In cases

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of overlapping phenotypes, patients were assigned according to their primary echocardiographic features at presentation and their clinical designation at the time of diagnosis.



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Investigation	Major Criteria	Minor Criteria
Clinical	Clinical complete respiratory chain encephalomyopathy Or a mitochondrial cytopathy fullfilling all three of the following conditions:	Symptoms compatible with a respiratory chain defect
	1. Unexplained combination of multisystemic symptoms essentially pathognomic for a RC disorder 2. A progressive clinical course with episodes of exacerbation Or a family history that is strongly indicative of a mtDNA mutation 3. Other possible metabolic or nonmetabolic disorders have been excluded by appropriate testing	
Histology	>2% ragged red fibers in skeletal muscle	1%-2% ragged red fibers if aged 30-50 yrs Any ragged red fibers if <30 years >2% subsarcolemmal mitochondrial accumulations if <16 years Widespread electron microscopic abnormalities in any tissue
Enzymology	>2% COX-negative fibers if <50 >5% COX-negative fibers if >50 <20% activity of any respiratory chain complex in a tissue <30% activity of any respiratory chain complex in a cell line <30% activity of the same respiratory chain complex activity in 2 or more tissues	Antibody-based demonstration of a defect in respiratory chain complex expression 20%-30% activity of any respiratory chain complex in a tissue 30%-40% activity of any respiratory chain complex in a cell line 30%-40% activity of the same respiratory chain complex activity in 2 or more tissues
Functional	Fibroblast ATP synthesis rates >3 SD below mean	Fibroblast ATP synthesis rates 2-3 SD below mean Fibroblasts unable to grow on media with glucose replaced by galactose
Molecular	Identification of a nuclear or mtDNA mutation of undisputed pathogencity	One or more metabolic indicators of impaired respiratory chain function

A *definite* diagnosis is the identification of two major criteria OR one major plus two minor criteria. A *probable* diagnosis is one major plus one minor criterion OR at least three minor criteria.

Supplemental Table 2. Variants of Uncertain Significance

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Variants are indicated using protein designations except for an intronic variant which is shown relative to the coding DNA sequence (c.). CM = cardiomyopathy;

Etiology	Phenotype	Age of Onset	Gene	Variant	Positive family hx CM/SCD
Familial	HCM	<1	ACTC	I284F	+/0
			PRKAG2	S109A	
	RCM	11	MYL2	R120Q	+/+
	RCM	7	MYH7	c.3853+7C>T	+/+
Metabolic	LVNC	<1	TAZ	D219D	0/0
Idiopathic	ARVC	17	DSG2	E713L	0/0

SCD = sudden cardiac death.