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[(33)]. ARVC patients were diagnosed utilizing the criteria set forth by the European Society of Cardiology and International Society and Federation of Cardiology[(34)]. In cases

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

Supplemental Table 1. Summary of the Modified Walker Criteria

Investigation	Major Criteria	Minor Criteria
Clinical	Clinical complete respiratory chain encephalomyopathy Or a mitochondrial cytopathy fullfilling all three of the following conditions: 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	Symptoms compatible with a respiratory chain defect
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

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* *PRKAG2*	I284F S109A	+/0
	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.