Severity of cardiomyopathy associated with adenine nucleotide translocator-1 deficiency correlates with mtDNA haplogroup

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Résumé en anglais	Mutations of both nuclear and mitochondrial DNA (mtDNA)-encoded mitochondrial proteins can cause cardiomyopathy associated with mitochondrial dysfunction. Hence, the cardiac phenotype of nuclear DNA mitochondrial mutations might be modulated by mtDNA variation. We studied a 13-generation Mennonite pedigree with autosomal recessive myopathy and cardiomyopathy due to an SLC25A4 frameshift null mutation (c.523delC, p.Q175RfsX38), which codes for the heart-muscle isoform of the adenine nucleotide translocator-1. Ten homozygous null (adenine nucleotide translocator-1(-/-)) patients monitored over a median of 6 years had a phenotype of progressive myocardial thickening, hyperalaninemia, lactic acidosis, exercise intolerance, and persistent adrenergic activation. Electrocardiography and echocardiography with velocity vector imaging revealed abnormal contractile mechanics, myocardial repolarization abnormalities, and impaired left ventricular relaxation. End-stage heart disease was characterized by massive, symmetric, concentric cardiac hypertrophy; widespread cardiomyocyte degeneration; overabundant and structurally abnormal mitochondria; extensive subendocardial interstitial fibrosis; and marked hypertrophy of arteriolar smooth muscle. Substantial variability in the progression and severity of heart disease segregated with maternal lineage, and sequencing of mtDNA from five maternal lineages revealed two major European haplogroups, U and H. Patients with the haplogroup U mtDNAs had more rapid and severe cardiomyopathy than those with haplogroup H.
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