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Relations of mitochondrial genetic variants to measures of vascular function

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ABSTRACT

Mitochondrial genetic variation with resultant alterations in oxidative phosphorylation may influence vascular function and contribute to cardiovascular disease susceptibility. We assessed relations of peptide-encoding variants in the mitochondrial genome with measures of vascular function in Framingham Heart Study participants. Of 258 variants assessed, 40 were predicted to have functional consequences by bioinformatics programs. A maternal pattern of heritability was estimated to contribute to the variability of aortic stiffness. A putative association with a microvascular function measure was identified that requires replication. The methods we have developed can be applied to assess the relations of mitochondrial genetic variation to other phenotypes.

1. Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in the United States and its burden may further increase as a result of the obesity epidemic (Writing Group, M., 2016). Endothelial function is central to maintaining vascular homeostasis and changes in endothelial function serve as early measures of cardiovascular injury (Flammer et al., 2012; Gokce et al., 2002; Mitchell et al., 2010). Additionally, endothelial dysfunction and increased vascular stiffness are associated with increased risk of cardiovascular disease outcomes (Flammer et al., 2012; Gokce et al., 2002; Mitchell et al., 2010). Studies have demonstrated that mitochondrial abnormalities contribute to endothelial dysfunction and may precede the development of atherosclerotic plaques (Yu et al., 2013; Davidson, 2010; Puddu et al., 2009; Ballinger et al., 2002; Corral-Debrinski et al., 1992).

The mitochondrion has long been appreciated for its role as the energy powerhouse of the cell, but more recent studies have underscored mitochondrial involvement in additional roles including the regulation of cell death and proliferation, heme biosynthesis, activation of reduction-oxidation sensitive signaling pathways, calcium homeostasis, heat generation, and steroid hormone synthesis (Wallace, 2005). Mitochondria contain their own genome of approximately 16.6 kb of DNA in humans, and each mitochondrion contains 5–10 copies. The mitochondrial genome encodes 13 protein subunits of the oxidative phosphorylation chain that are essential for ATP generation (Fig. 1). The mitochondrial genome also encodes its own translation machinery (22 tRNAs and 2 rRNAs) necessary for mitochondrial protein biosynthesis (Wallace, 2005). The mitochondrial genome is unique in that it is maternally inherited, does not undergo recombination events, and displays distinct regional variation that reflects maternal ethnic origins, thereby offering potential insights into the pathogenesis of ethnicity-related variation in susceptibility to cardiometabolic diseases (Wallace, 2005; Mishmar et al., 2003; Ruiz-Pesini et al., 2004; da Fonseca et al., 2008).

Analysis of the mitochondrial genome is underrepresented in genetic studies despite the fact the mitochondrion plays an essential role in bioenergetic pathways that are closely linked to pathologic states. A number of deleterious mutations in the mitochondrial genome result in several rare but severe mitochondrial diseases. Such diseases reflect a broad spectrum of phenotypes that often include cardiovascular pathology (Wallace, 2005; Taylor and Turnbull, 2005; Strauss et al., 2013). The mitochondrial genome shows significant diversity and some of the variants are thought to induce small changes in mitochondrial function that may contribute to an individual's susceptibility to cardiometabolic diseases. In fact, a previous study found several mitochondrial genetic variants that were associated with systolic blood pressure

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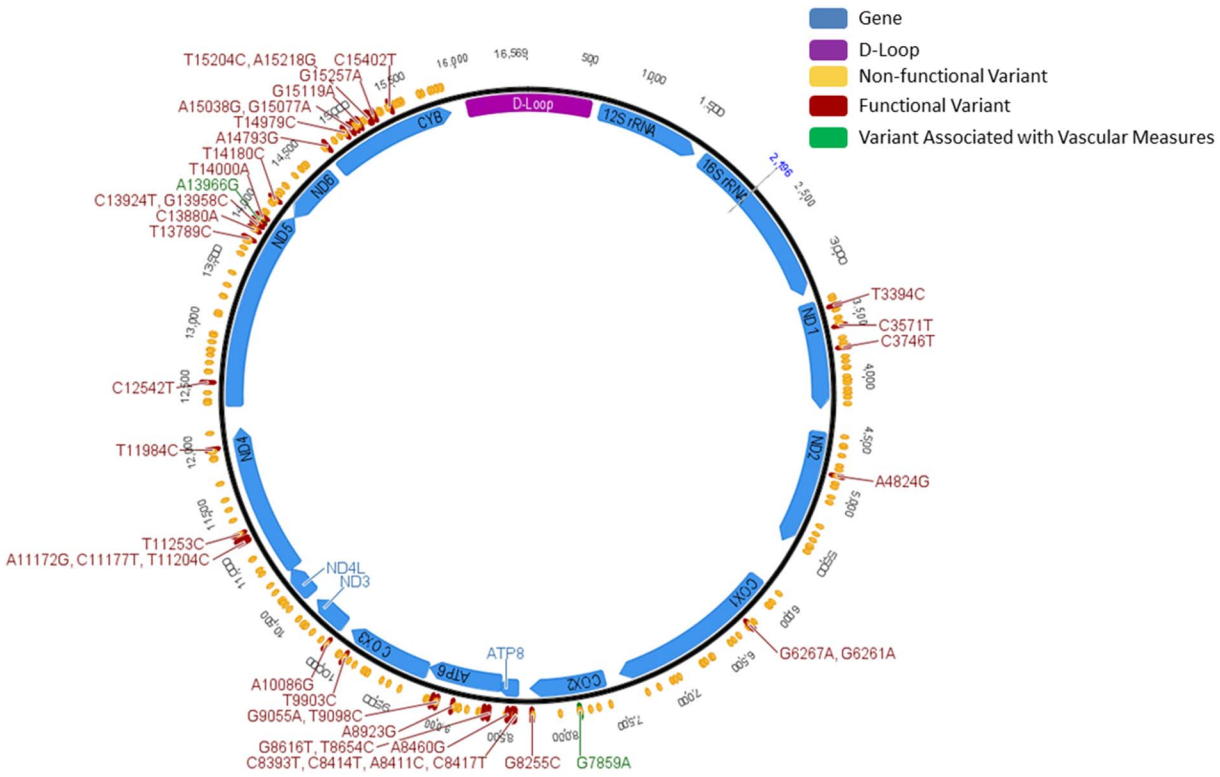

Fig. 1. Annotation of Mitochondrial Genetic Variants. The mitochondrial variants assessed within the FHS cohorts were mapped to the Revised Cambridge Reference Sequence (blue blocks = gene, purple block = D-loop, yellow = non-functional variant, red = functional variant, green = variant associated with vascular measures). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and fasting blood glucose (Liu et al., 2012). However, the contribution of mitochondrial genetic variation to alterations in vascular function has not been explored in a community-based sample. We investigated the associations of mitochondrial variants with measures of vascular function in Framingham Heart Study (FHS) participants. We assessed the association of maternal inheritance and the association of both common and rare mitochondrial variants, grouped by gene, with measures of vascular function. Finally, we identified mitochondrial variants that are predicted to have deleterious effects on the function of the coded protein and explored whether such variants were associated with measures of vascular function. These complementary approaches provide novel methodology for relating mitochondrial variants to vascular phenotypes and can promote our understanding of the role of mitochondrial genetics in human disease.

2. Methods

2.1. Study participants

The Original FHS cohort consists of 5209 individuals recruited in 1948 and participants have been examined every two years (Dawber et al., 1951). The children and spouses of the children of the Original FHS cohort were recruited in to the FHS Offspring cohort in 1971 and consists of 5124 individuals who have been examined every 4–8 years (Feinleib et al., 1975). The Third Generation cohort was recruited in 2002–2005 and consists of 4095 children of the Offspring cohort (Splansky et al., 2007). Vascular phenotypes were assessed in subsets of the Offspring and Third generation cohorts as outlined in Table 1. All participants gave written informed consent for genetic research and assessment of vascular traits, and all protocols were approved by the Institutional Review Board of Boston University Medical Center.

Table 1
Characteristics of the Study Participants.

Variable	Offspring cohort		Generation 3 cohort	
	N	Mean (%)	N	Mean (%)
Women, N (%)		1476 (46)		1898 (47)
Age, years	3197	60 ± 9	4050	40 ± 8
Body mass index, kg/m^2	3197	28.1 ± 5.2	4050	26.9 ± 5.5
Baseline brachial artery diameter, mm	2308	4.3 ± 0.9	3893	4.1 ± 0.8
Baseline brachial velocity, cm/s	2307	8.2 ± 4.8	3894	7.4 ± 4.3
Hyperemic flow velocity, cm/s	2307	50.6 ± 21.4	3894	62 ± 18.4
Flow-mediated dilation, %	2308	2.8 ± 2.8	3852	5.9 ± 3.7
ln baseline pulse amplitude	2331	5.7 ± 0.9	1975	5.6 ± 0.9
Peripheral arterial tonometry ratio	2331	0.7 ± 0.4	1975	0.7 ± 0.4
Carotid-femoral pulse wave velocity, m/s	2553	10.6 ± 3.8	3875	7.0 ± 1.4

The measurements were measured at the seventh examination cycle (1998–2001) for Offspring cohort and at the first examination cycle for the Third Generation (2002–2005). SD, standard deviation. Ln, natural logarithm.

2.2. Vascular phenotypes

2.2.1. Noninvasive measures of endothelial function

Conduit arterial endothelial function was assessed using flow-mediated vasodilation as previously described (Benjamin et al., 2004). Hyperemic flow serves as the stimulus for vasodilation and is an indicator of microvascular function. A Toshiba SSH-140A ultrasound system was used to determine brachial artery diameter at baseline and for one minute following 5 min of forearm cuff occlusion. Flow-mediated dilation data were assessed with commercially available software (Brachial Analyzer version 3.2.3, Medical Imaging Applications). Hyperemic flow was assessed using semi-automated signal averaging (Cardiovascular Engineering).