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Mitochondria Single Nucleotide Variation across Six Blood Cell Types

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Abstract

It has been shown that heteroplasmic mitochondrial DNA variants can be tissue specific. However, whether mitochondrial DNA variants are specific by blood cell types has not been investigated. Motivated by this question and using mitochondria sequences extracted from RNAseq data from six distinct blood cell types (neutrophil, monocyte, myeloid dendritic, natural killer, T and B), we thoroughly compared SNPs and heteroplasmies among these cell types. Each cell type from each subject was sequenced at four time points used as biological replicates. We found that mitochondria content is low in neutrophil compared to the other five blood cell types. Subsequent analysis on the other five blood cell types showed that at the SNP level, there was no discrepancy. At the heteroplasmy level, we observed good concordances among all blood cell types. However, the allele frequencies of the heteroplasmy differed between blood cell types for certain heteroplasmic sites. Furthermore, we identified five tri-allelic sites (1610, 2617, 8303, 12146, 13710) that are likely caused by RNA editing. Three out of these five sites are located at the ninth position of tRNA genes, and are likely resulting from post-transcriptional methylation.

Introduction

The human mitochondria genome is a double stranded circular DNA molecule, consisting of 16,569 nucleotides. It contains 13 protein coding genes, 22 transfer RNAs (tRNAs), and two ribosomal RNAs. Mitochondrial DNA (mtDNA) is maternally inherited, thus its genome is haploid. However, many sites in mitochondria DNA are heteroplasmic (Payne et al., 2013), containing two alleles. Mitochondrial DNA variants have been linked to various diseases and important biological processes, including cancer (Bai et al., 2007; Canter et al., 2005; Chen, 2012; Herrmann et al., 2003; Modica-Napolitano and Singh, 2004; Petrosillo et al., 2005), aging (Kann et al., 1998; Smigrodzki and Khan, 2005; Sondheimer et al., 2011), and coronary disease (Griffiths, 2012; Jia et al., 2013).

Previous studies on mtDNA variants typically focused on single source mitochondria from blood or occasionally tissue, and it was commonly assumed that mitochondria heteroplasmy variants were unique among unrelated individuals. However, this assumption was disputed when Samuels et al. reported that multiple unrelated individuals share tissue-specific positive selections of mitochondria variants (Samuels et al., 2013b), an observation that was later confirmed (Li et al., 2015). The authors identified four heteroplasmic somatic mutations in liver and kidney tissues that recurred in multiple subjects. Since liver and kidney tissue arise from the endoderm and mesoderm germ layers, respectively, it is unlikely that that the four identified heteroplasmies share a common developmental origin. While tissues remain the preferred source for detecting somatic mutations, blood is the preferred source in genetic and medical testing due to its easy accessibility. Yet, whether or not mitochondria variants are blood cell type specific