Transcription factors bind negatively selected sites within human mtDNA genes.

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Abstract:

Transcription of mitochondrial DNA (mtDNA)-encoded genes is thought to be regulated by a handful of dedicated transcription factors (TFs), suggesting that mtDNA genes are separately regulated from the nucleus. However, several TFs, with known nuclear activities, were found to bind mtDNA and regulate mitochondrial transcription. Additionally, mtDNA transcriptional regulatory elements, which were proved important in vitro, were harbored by a deletion that normally segregated among healthy individuals. Hence, mtDNA transcriptional regulation is more complex than once thought. Here, by analyzing ENCODE chromatin immunoprecipitation sequencing (ChIP-seq) data, we identified strong binding sites of three bona fide nuclear TFs (c-Jun, Jun-D, and CEBPb) within human mtDNA protein-coding genes. We validated the binding of two TFs by ChIP-quantitative polymerase chain reaction (c-Jun and Jun-D) and showed their mitochondrial localization by electron microscopy and subcellular fractionation. As a step toward investigating the functionality of these TF-binding sites (TFBS), we assessed signatures of selection. By analyzing 9,868 human mtDNA sequences encompassing all major global populations, we recorded genetic variants in tips and nodes of mtDNA phylogeny within the TFBS. We next calculated the effects of variants on binding motif prediction scores. Finally, the mtDNA variation pattern in predicted TFBS, occurring within ChIP-seq negative-binding sites, was compared with ChIP-seq positive-TFBS (CPR). Motifs within CPRs of c-Jun, Jun-D, and CEBPb harbored either only tip variants or their nodal variants retained high motif prediction scores. This reflects negative selection within mtDNA CPRs, thus supporting their functionality. Hence, human mtDNA-coding sequences may have dual roles, namely coding for genes yet possibly also possessing regulatory potential.

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