Comparative Analysis of Tools for Predicting the Functional Impact of mtDNA Variants

Madeline P. Griffin
Rhodes College
Memphis, Tennessee
grimp-20@rhodes.edu

Catherine E. Welsh
Rhodes College
Memphis, Tennessee
welshc@rhodes.edu

ABSTRACT

Recent advances in DNA sequencing technologies has transformed the study of DNA sequence variation. Over the last decade, the development of a number of functional impact predictors and annotation tools have been implemented to aid in this DNA variant analysis. While many annotation tools and pipelines have been built to annotate nuclear genome variants, only a few software predictors address the thousands of variants found in human mitochondrial DNA. Many prediction tools built for nuclear DNA have been retrofitted to annotate mitochondrial DNA, but because of the vast differences between the two, nuclear annotators fail to produce accurate predictions for mitochondrial mutations. Conventional annotation tools and predictors such as SIFT [3] and PolyPhen2 [1] are a few of the tools that produce less than accurate pathogenicity scores for mitochondrial variants. More recently, tools such as APOGEE [2] have addressed the need for specialized tools to annotate mtDNA exonic variants with high-confidence. In addition, most of the annotation tools only annotate exonic mutations, but variants in mitochondrial tRNA and rRNA are important and are a common cause of mitochondrial disease. A few papers have addressed the need to accurately predict the pathogenicity of tRNA variants, such as MitoTIP [4], while no known tools exist for annotating rRNA variant pathogenicity for mtDNA variants.

We have constructed a comparative analysis of both standard and non-standard annotation tools and their ability to accurately predict the pathogenicity of mitochondrial mutations. We carefully curated a complete list of all potential non-synonymous exonic, tRNA and rRNA mitochondrial mutations and ran selected tools for each dataset. We have analyzed the accuracy and precision of each tool compared to the consensus among the tools combined with pathogenicity predictions from MITOMAP disease associations. Over the course of our testing, we confirmed that many of the prediction tools typically used for nuclear DNA were subpar when tested on mitochondrial DNA. Newer annotation tools built specifically for mtDNA such as APOGEE had higher overall assessment scores. Based on our analysis, we are creating an online annotation tool specifically for mtDNA variants that integrates pathogencity scores from our top-rated prediction tools.

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computational biology; mitochondria; mtDNA variants; variant functional impact

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REFERENCES

[1] IA Adzhubei, S Schmidt, L Peshkin, VE Ramensky, A Gerasimova, P Bork, AS Kondrashov, and SR Sunyaev. 2010. A method and server for predicting damaging missense mutations. *Nature Methods* (April 2010). http://dx.doi.org/10.1038/nmeth0410-248

[2] S Castellana, C Fusilli, G Mazzoccoli, T Biagini, D Capocefalo, M Carella, AL Vescovi, and T Mazza. 2017. High-confidence assessment of functional impact of human mitochondrial non-synonymous genome variations by APOGEE. *PLoS Computational Biology* (June 2017). http://dx.doi.org/10.1371/journal.pcbi.1005628

[3] P Kumar, S Henikoff, and PC Ng. 2009. Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. *Nature Protocols* 4 (June 2009). http://dx.doi.org/10.1038/nprot.2009.86

[4] S Sonney, J Leipzig, MT Lott, S Zhang, V Procaccio, DC Wallace, and N Sondheimer. 2017. Predicting the pathogenicity of novel variants in mitochondrial tRNA with MitoTIP. *PLoS Computational Biology* (Dec. 2017). http://dx.doi.org/10.1371/jounral.pcbi.1005867