Bioinformatics Tools and Databases to Assess the Pathogenicity of Mitochondrial DNA Variants in the Field of Next Generation Sequencing

Titre	Bioinformatics Tools and Databases to Assess the Pathogenicity of Mitochondrial DNA Variants in the Field of Next Generation Sequencing
Type de publication	Article de revue
Auteur	Bris, Céline [1], Goudenège, David [2], Desquiret-Dumas, Valérie [3], Charif, Majida [4], Colin, Estelle [5], Bonneau, Dominique [6], Amati-Bonneau, Patrizia [7], Lenaers, Guy [8], Reynier, Pascal [9], Procaccio, Vincent [10]
Editeur	Frontiers Media
Type	Article scientifique dans une revue à comité de lecture
Année	2018
Langue	Anglais
Date	11 Décembre 2018
Pagination	632
Volume	9
Titre de la revue	Frontiers in genetics
ISSN	1664-8021
Résumé en anglais	The development of next generation sequencing (NGS) has greatly enhanced the diagnosis of mitochondrial disorders, with a systematic analysis of the whole mitochondrial DNA (mtDNA) sequence and better detection sensitivity. However, the exponential growth of sequencing data renders complex the interpretation of the identified variants, thereby posing new challenges for the molecular diagnosis of mitochondrial diseases. Indeed, mtDNA sequencing by NGS requires specific bioinformatics tools and the adaptation of those developed for nuclear DNA, for the detection and quantification of mtDNA variants from sequence alignment to the calling steps, in order to manage the specific features of the mitochondrial genome including heteroplasmy, i.e., coexistence of mutant and wildtype mtDNA copies. The prioritization of mtDNA variants remains difficult, relying on a limited number of specific resources: population and clinical databases, and tools providing a prediction of the variant pathogenicity. An evaluation of the most prominent bioinformatics tools showed that their ability to predict the pathogenicity was highly variable indicating that special efforts should be directed at developing new bioinformatics tools dedicated to the mitochondrial genome. In addition, massive parallel sequencing raised several issues related to the interpretation of very low mtDNA mutational loads, discovery of variants of unknown significance, and mutations unrelated to patient phenotype or the co-occurrence of mtDNA variants. This review provides an overview of the current strategies and bioinformatics tools for accurate annotation, prioritization and reporting of mtDNA variations from NGS data, in order to carry out accurate genetic counseling in individuals with primary mitochondrial diseases.
URL de la notice	http://okina.univ-angers.fr/publications/ua18624 [11]

DOI	10.3389/fgene.2018.00632 [12]
Lien vers le document	https://www.frontiersin.org/articles/10.3389/fgene.2018.00632/full [13]
Titre abrégé	Front Genet
Identifiant (ID) PubMed	30619459 [14]

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