Deciphering exome sequencing data: Bringing mitochondrial DNA variants to light

Titre	Deciphering exome sequencing data: Bringing mitochondrial DNA variants to light
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Auteur	Garret, Philippine [1], Bris, Céline [2], Procaccio, Vincent [3], Amati-Bonneau, Patrizia [4], Vabres, Pierre [5], Houcinat, Nada [6], Tisserant, Emilie [7], Feillet, François [8], Bruel, Ange-Line [9], Quéré, Virginie [10], Philippe, Christophe [11], Sorlin, Arthur [12], Tran Mau-Them, Frédéric [13], Vitobello, Antonio [14], Costa, Jean-Marc [15], Boughalem, Aïcha [16], Trost, Detlef [17], Faivre, Laurence [18], Thauvin-Robinet, Christel [19], Duffourd, Yannis [20]
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Résumé en anglais	The expanding use of exome sequencing (ES) in diagnosis generates a huge amount of data, including untargeted mitochondrial DNA (mtDNA) sequences. We developed a strategy to deeply study ES data, focusing on the mtDNA genome on a large unspecific cohort to increase diagnostic yield. A targeted bioinformatics pipeline assembled mitochondrial genome from ES data to detect pathogenic mtDNA variants in parallel with the "in-house" nuclear exome pipeline. mtDNA data coming from off-target sequences (indirect sequencing) were extracted from the BAM files in 928 individuals with developmental and/or neurological anomalies. The mtDNA variants were filtered out based on database information, cohort frequencies, haplogroups and protein consequences. Two homoplasmic pathogenic variants (m.9035T>C and m.11778G>A) were identified in 2 out of 928 unrelated individuals (0.2%): the m.9035T>C (MT-ATP6) variant in a female with ataxia and the m.11778G>A (MT-ND4) variant in a male with a complex mosaic disorder and a severe ophthalmological phenotype, uncovering undiagnosed Leber's hereditary optic neuropathy (LHON). Seven secondary findings were also found, predisposing to deafness or LHON, in 7 out of 928 individuals (0.75%). This study demonstrates the usefulness of including a targeted strategy in ES pipeline to detect mtDNA variants, improving results in diagnosis and research, without resampling patients and performing targeted mtDNA strategies.
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