

Guidelines towards a MITOvariome project

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Analysis of the variation at the mitochondrial DNA (mtDNA) level is a field of growing interest in different spheres of biomedical research, including clinical studies, forensic analysis and human population genetics. There are a number of mtDNA mutations that are responsible for well known mitochondrial disorders, most of them manifested as syndromes of the central and/or peripheral nervous system and thus of particular relevance to the field of neurogenetics. Several features of the mtDNA genome make it particularly suitable for a future variome project (MITOvariome): (i) the whole molecule has a relatively small size (16.9 kb) and codes for only 37 genes; (ii) there is a huge amount of information available in the population and forensic genetic literature and in GenBank (e.g. >5,500 near complete genomes) and; (iii) the phylogeny of the worldwide phylogenetic tree and the geographical and ethnic distribution of mtDNA variants (phylogeography) are particularly well known. This enormous amount of genetic information has been partially recorded in databases (e.g. Mitomap), although generally it lacks careful scrutiny for flawed data. Moreover, all the available mtDNA databases have focused on bookkeeping mtDNA variation or phylogenetic trees, without associating phenotypic information to the recorded variants. On the other hand, the presumable association of common mtDNA polymorphisms with several complex diseases (under a model of common variant: common disease) has unfortunately been reported without the necessary consideration of confounding factors such as population stratification (which is particularly pronounced on the mtDNA) or other standards that aim to guarantee the reproducibility of the results such as suitable sample size and power, correction for multiple test, etc. Finally, somatic variation has also been linked to a plethora of tumors and degenerative diseases. However this seeming association has now been suspected to result from lab artefacts, documentation errors or population genetics misconceptions. A future MITOvariome project aiming to record mtDNA pathogenic variation will require the input of practitioners with full experience of mtDNA disorders and bioinformaticians, but in particular will need the experience of population and forensic geneticists that have invested enormous efforts in unraveling the geographic and ethnic patterns of mito-variation in human populations and meticulously outlined the worldwide mtDNA phylogeny.