Overview

Mitochondrial Disease Working Group: Genetics

The National Institute of Neurological Disorders and Stroke (NINDS) Mitochondrial Disease (Mito) Genetics Common Data Elements (CDEs) Working Group (WG) drafted CDE recommendations based on data elements that are commonly used and validated in the field of genetic research. The WG came up with two forms that will be used to guide and give reference regarding what data elements should and must be collected.

When describing genetic testing for subjects with suspected mitochondrial conditions, there are several factors to consider and several key components of testing to record. It is important to record whether or not the laboratory performing the test is operating in a research environment or is a clinically certified (e.g. CLIA) clinical genetics laboratory. Although either source may produce the same result, certain procedures may be more stringent in laboratories that must pass state, federal or national inspection, thereby resulting in less chance of error. Additionally, research results are not intended to become part of the patient's medical record and ideally should not be reported to the patient until confirmed in a clinical molecular diagnostic (e.g. CLIA) laboratory setting.

The date that the report was issued and the test methodology used should be described in as much detail as possible (including accuracy, coverage, etc.), together with the tissue source from which DNA was extracted and all methods used for preparation of the sample. It is not uncommon that the sample preparation conditions can have downstream effects on testing outcomes. Any notes regarding deviation from standard protocol should be described, if known.

The results of the test should report which regions of which transcripts of which genes were covered and, in the case of the mitochondrial genome, the anticipated lower limit of heteroplasmy which can be detected.

Noting which regions were screened will help when comparing results of multiple subjects to ensure that tests are equal in coverage.

Once a putatively pathogenic genetic variant has been identified, the specific DNA change should be noted including a reference sequence. Reasons for assigning pathogenicity should be described in detail, using established guidelines such as the ACMG recommendations for the interpretation of sequence variants[1] and, if available, previous publications reporting

pathogenicity of the variant should be cited[2]. Often this is performed through literature or database searches (e.g. MITOMAP Database and ClinVar). If the variant is novel, and prediction programs such as PolyPhen and SIFT are used, the specific versions and tools should be cited because, occasionally, multiple programs may issue conflicting predictions.

[1] Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-24. doi: 10.1038/gim.2015.30. Epub 2015 Mar 5.

[2] MacArthur DG, Manolio TA, Dimmock DP, Rehm HL, Shendure J, Abecasis GR, Adams DR, Altman RB, Antonarakis SE, Ashley EA, Barrett JC, Biesecker LG, Conrad DF, Cooper GM, Cox NJ, Daly MJ, Gerstein MB, Goldstein DB, Hirschhorn JN, Leal SM, Pennacchio LA, Stamatoyannopoulos JA, Sunyaev SR, Valle D, Voight BF, Winckler W, Gunter C. Guidelines for investigating causality of sequence variants in human disease. Nature. 2014 Apr 24;508(7497):469-76. doi: 10.1038/nature13127.