Neuronal Ceroid-Lipofuscinoses (NCL)

Introduction

The neuronal ceroid lipofuscinoses (NCL; CLN; Batten disease) are a clinically and genetically heterogeneous group of neurodegenerative disorders characterized by the intracellular accumulation of autofluorescent lipopigment storage material in different patterns ultrastructurally. There are a total of at least 14 genetically distinct diseases associated with a similar phenotype but with variable age of onset. The genes include CLN1/PPT1, CLN2/TPP1, CLN3, CLN4/DNAJC5, CLN5, CLN6, MFSD8/CLN7, CLN8, CLN10/CTSD, CLN11/GRN, CLN12/ATP13A2, CLN13/CTSF, CLN14/KCTD7, and CLCN6. Several genes, including CLN4, CLN6, CLN11/GRN, CLN13/CTSF, and CLCN6, are associated with an adult-onset NCL, which includes Kufs type A (CLN6) and Kufs type B (CLN13/CTSF). Pathogenic variants in CLN10/CTSD cause cathepsin D deficiency, which has a neonatal onset.

Referrals

- Referrals can be accepted from any patient where a diagnosis of NCL is suspected. Clinical, biochemical and histopathological review of the affected patient is recommended to indicate the subtype of NCL (see profile sheets for NCL1, NCL2, NCL3, and variant NCL), so that a specific gene can be targeted. However, testing of all of the 14 known genes can be carried out without this information. If the necessary patient samples are unavailable genetic testing can be undertaken in the parents of an affected child.
- Carrier testing can be offered to the adult relatives of NCL patients once a pathogenic variant has been identified.

Prenatal testing

Prenatal testing is available, if required, for families where specific pathogenic variants have been identified - please contact the laboratory to discuss.

Service offered

- Analysis of the CLN1/PPT1, CLN2/TPP1, CLN3, CLN4/DNAJC5, CLN5, CLN6, MFSD8/CLN7, CLN8, CLN10/CTSD, CLN11/GRN, CLN12/ATP13A2, CLN13/CTSF, CLN14/KCTD7, and CLCN6 genes by next generation sequencing (Agilent SureSelect and Illumina NextSeq). A minimum coverage of 30 reads is required to call a variant. In-house validation attributes a minimum sensitivity of 97.5% (with 95% confidence) for regions covered >30x. This assay is not currently validated to detect large deletions / duplications. All clinically relevant variants are confirmed by Sanger sequence analysis. Known benign polymorphisms and sequence variants which are unlikely to be pathogenic are not reported.
- Detection of known pathogenic variants in relatives of patients with confirmed pathogenic variants by Sanger sequencing.

Target reporting time

8 weeks for NGS screening. 4 weeks for routine testing of specific pathogenic variants. Please contact the laboratory for urgent cases.