NHS Lothian
South East Scotland Genetic Laboratories

COGNITIVE GENE PANEL - TECHNICAL INFORMATION

Design: The cognitive gene panel was designed as part of a custom probe set from Twist Bioscience (TE-98175847) to cover 27 genes associated with neurodegeneration. This panel design provides coverage of 100% of the target coding regions and flanking intronic sequences (+/- 15bp) for the 27 genes listed below. Testing for a C9orf72 expansion is carried out alongside testing for this gene panel, using the Asuragen AmplideX PCR/CE C9orf72 kit. Further details on C9orf72 testing are available from the laboratory on request.

Method: Library preparation and target enrichment was performed using the custom designed TE-98175847 probe set (Twist Bioscience) and Nextera Flex for Enrichment (Illumina). Sequencing was performed using a 150bp paired-end sequencing kit on a MiSeq (Illumina). All stages of the workflow were performed according to the manufacturer's instructions.

Coverage criteria: For each sample reported, >95% of the target coding and flanking intronic regions of the 27 genes was covered to a minimum depth of 20 reads (20x). Any regions of the SOD1 gene for motor neurone disease/amyotrophic lateral sclerosis referrals and any regions of the PSEN1 gene for Alzheimer disease referrals not covered to 20x depth were flagged for follow-up Sanger sequencing. Specific details of coverage and depth for individual tests are available from the laboratory on request.

Variant identification and interpretation: Sequence data were mapped and variants identified using GenomeAnalysisToolKit (GATK) and NextGENe (Softgenetics) with hg19 (GRCh37) human genome as the reference. Variants identified were subsequently classified according to recent ACGS Best Practice Guidelines for Variant Classification using all available evidence. Any clinically significant variants were confirmed by Sanger sequencing.

Variant reporting: Variants were reported according to HGVS guidelines using the accession numbers listed below. Variants categorised as non-pathogenic or likely non-pathogenic were filtered out at the variant interpretation stage and were not included in the clinical report. Details of these variants are available from the laboratory on request.

Test sensitivity: According to the literature, this test will detect a pathogenic variant in C9orf72, SOD1, FUS or TARDBP in approximately 60% of cases with familial amyotrophic lateral sclerosis (1,2); in APP, PSEN1 and PSEN2 in up to 70% of cases with early onset familial Alzheimer disease (3); and in MAPT and GRN in approximately 35% of cases with familial frontotemporal dementia (4). A C9orf72 expansion accounts for approximately 7% of sporadic and 25% of familial frontotemporal dementia cases (2). The detection rate will be significantly lower in sporadic cases and in the other genes tested.

Genes included and associated sequence accession numbers:

ALS2 (NM_020919.3); ANG (NM_001145.4); ANXA11 (NM_145869.1); APP (NM_000484.3); CHCHD10 (NM_213720.3); CHMP2B (NM_014043.3); CSF1R (NM_005211.3); DCTN1 (NM_004082.4); FIG4 (NM_014845.5); FUS (NM_004960.3); GRN (NM_002087.2); ITM2B (NM_021999.4); MAPT (NM_001123066.3); NEK1 (NM_001199397.1); OPTN (NM_001008211.1); PFN1 (NM_005022.3); PRNP (NM_000311.3); PSEN1 (NM_000021.3); PSEN2 (NM_000447.2); SETX (NM_015046.5); SOD1 (NM_000454.4); SQSTM1 (NM_003900.4); TARDBP (NM_007375.3); TBK1 (NM_013254.3); UBQLN2 (NM_013444.3); VAPB (NM_004738.4); VCP (NM_007126.3).

References:

(1) Su et al. 2014 Muscle Nerve 49:786-803
(2) Beck 2013 AJHG 92:345-53
(3) Ertekin-Taner 2007 Neurol Clin 25:611-67
(4) Pickering-Brown et al. 2008 Brain 131:721-31