NHS Lothian
South East Scotland Genetic Laboratories

SEVERE DEVELOPMENTAL DISORDERS – INFORMATION SHEET

Background

In July 2019, South East Scotland Genetic Service started offering an exome-based diagnostic test to patients presenting with severe developmental disorders. To date, we have analysed over 1,500 families and made a genetic diagnosis in 30% of the affected individuals (36% including variants of uncertain clinical significance deemed actionable following a multidisciplinary team discussion). We have reported pathogenic or likely pathogenic variants in more than 278 genes involved in a developmental disorder.

Test process

Referrals meeting the following criteria are accepted from each of the four clinical genetic centres in Scotland - severe neurodevelopmental disorder and congenital anomalies, or abnormal growth parameters, or dysmorphic features, or unusual behavioural phenotype. Phenotype information is provided by the referring clinician within a secure project in the DECIPHER database (https://www.deciphergenomics.org/).

DNA library construction is performed using genomic DNA from patients and their unaffected parents using a Twist Bioscience panel for whole exome capture. Whole exome sequencing is carried out by an external sequencing facility based at the University of Edinburgh. This has received approval from the Caldicott Guardian and NHS Lothian Information Governance.

Trio-based analysis of the DDG2P gene panel (https://www.ebi.ac.uk/gene2phenotype; PMID 31147538) is performed by a dedicated bioinformatics team within a highly secure computing space provided by the University of Edinburgh. Filtered variants in DDG2P genes with a confidence category of moderate, strong, or definitive are transferred to clinical scientists at South East Scotland Genetic Service, who use the current ratified ACGS Best Practice Guidelines for Variant Classification in Rare Disease (https://www.acgs.uk.com) to classify the variants. When appropriate, the high evidence (green) genes from the PanelApp panel, Fetal anomalies, are also analysed. All significant variants are confirmed by Sanger sequencing in our UKAS-accredited laboratory.

Re-analysis of data

The DDG2P gene panel is regularly updated as new disease-gene associations are established. We update our diagnostic DDG2P gene panel every six months. Every 12-18 months, we re-analyse all exome data using the most up-to-date version of this panel. Patient data also benefit from re-analysis following significant improvements to the analytical pipeline. We ask that referring clinicians inform the laboratory if re-analysis of data is not appropriate for their patient.

Test sensitivity and specificity

Our in-house validation data indicate that this analysis has a sensitivity of at least 96% (95% C.I. 96-97%) for SNV and small insertions/deletions combined, and a specificity of 96%. However, the test is currently unable to detect structural or copy number variants, or sequence variants in non-coding regulatory regions, and may not detect low level mosaicism, variants within repeat regions or regions with coverage <20X.