Cerebral Palsy Xpanded
A targeted test for genetic causes of cerebral palsy using a trio approach

Clinical Features:
Cerebral palsy (CP) is a clinically heterogeneous group of disorders impacting both movement and posture due to fetal or infantile brain injury (Rosenbaum et al., 2007). CP is diagnosed in approximately 1 in 500 births and is frequently attributed to pre- and perinatal complications (Van Eyk et al., 2018; MacLennan et al., 2018). Typical motor features of CP include spasticity, dyskinesia, ataxia, and hypotonia. Other features include intellectual disability, epilepsy, musculoskeletal issues, and behavioral problems (Novak et al., 2017).

Due to the heterogenous nature of CP, it can be challenging to determine a specific cause. While current evidence suggests CP frequently has a genetic etiology, it is hard to pinpoint the responsible gene based on clinical features alone. It is often necessary to perform testing of multiple genes (concurrently or as reflex tests) to identify an underlying genetic cause in an individual. Moreover, new genes known to cause CP are being discovered regularly, making it challenging for clinical laboratories to keep traditional testing panels updated. Additionally, interpretation of the clinical significance of variants in these newly discovered genes is often difficult in the absence of parental testing to clarify which variants are de novo or inherited.

The Cerebral Palsy Xpanded Panel uses a trio approach that includes concurrent analysis of the affected proband and both parents, which increases the likelihood of identifying a definitive genetic explanation for CP. Depending on the family structure, family history, and the availability of both parents, other family members of the affected individual may be evaluated in conjunction with the proband. Please contact GeneDx for prior approval when both parents are not available to submit samples for the Cerebral Palsy Xpanded Panel. The Cerebral Palsy Xpanded Panel is based on whole exome capture, Next Generation sequencing (NGS), and targeted analysis of a comprehensive list of genes currently associated with CP. The design of the panel allows for a comprehensive, dynamic gene list that is updated regularly to ensure inclusion of genes newly associated with CP.

Inheritance Pattern/Genetics:
CP can be genetic or caused by a number of clinical and environmental risk factors including but not limited to birth asphyxia, prematurity, congenital anomalies, and infections (Van Eyk et al., 2018). A genetic etiology, including chromosomal abnormalities, may be identified in up to 50% of CP cases (van Eyk et al., 2018). The inheritance pattern can be autosomal dominant, autosomal recessive, X-linked, or mitochondrial. Additionally, multiple studies have reported a high frequency of de novo variants in patients with neurodevelopmental disorders, including CP, highlighting the importance of a trio approach including the affected proband and both parents when performing genetic testing (van Eyk et al., 2018). Confirmation of the molecular genetic cause of CP may have implications for medical management, surveillance for associated complications or other organ systems involvement, eligibility for needed services, and treatment.

Test Methods:
Using genomic DNA from the submitted specimen(s), the exonic regions and flanking splice junctions of the genome were captured using a proprietary system developed by GeneDx and sequenced by massively parallel (NextGen) sequencing on an Illumina sequencing system with 100bp or greater paired-end reads. Reads are aligned to human genome build GRCh37/UCSC hg19 and analyzed for sequence variants in targeted genes using a custom-developed analysis tool (Xome Analyzer). Capillary sequencing or another appropriate method is used to confirm all potentially pathogenic variants identified in the proband and relative samples, if submitted. Sequence and copy number alterations are reported according to the Human Genome Variation Society (HGVS) and International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. A list of additional variants not included in the report is available upon request.

Please note that while the Cerebral Palsy Xpanded Panel captures and sequences the whole exome, analysis is targeted to the specific phenotype-driven gene list for this panel. The Cerebral Palsy Xpanded Panel gene list includes more than 1000 genes. The list was developed by searching for genes associated with CP in multiple sources, including OMIM, HGMD, and Human Phenotype Ontology (HPO) terms. Additionally, genes were added to the list using GeneDx data from clinical whole exome sequencing done on patients with CP. The gene list is systematically updated at least quarterly.

Result Reporting:
The Cerebral Palsy Xpanded Panel is performed on the proband and the parental samples (and/or additional relatives) when submitted together for analysis. A single report will be issued on the affected proband in the family. A separate report will not be issued for unaffected parents or other family members who may also have submitted a specimen for the purpose of allowing better interpretation of the results from the affected individual. If additional reports are requested for other affected family members, extra fees will apply.

As the Cerebral Palsy Xpanded Panel includes more than 1000 genes, the report that is issued for the affected individual will not include a comprehensive list of all observed variants. Specifically, the report includes any pathogenic/likely pathogenic variants in genes responsible for the phenotype of the patient, while variants of uncertain significance (VUS) are not routinely reported, only at our discretion. If desired, clinicians can request a separate file containing a list of identified variants that will be provided upon completion of testing.

In rare instances, this test may reveal a pathogenic variant that is not directly related to the test indication. For example, pathogenic variants in genes associated with an increased risk for cancer, cardiac abnormalities, or metabolic defects could be identified. In the event that an incidental finding is identified, this information will be disclosed to the ordering health care provider if it is likely to impact medical care. The absence of reportable incidental findings for any particular gene does not rule out the possibility of pathogenic variants in that gene.

Test Sensitivity:
The clinical sensitivity of the Cerebral Palsy Xpanded Panel depends in part on the patient's clinical phenotype. Previous WES studies have reported identification of a definitive pathogenic variant in 33% of individuals with a clinical diagnosis of CP (Millan et al., 2018; Teigen et al., 2018). When parents are sequenced and analyzed concurrently (trio-based testing), the positive rate increases to 35% whereas the positive rate is significantly lower (23%) for cases where only the proband is tested (singleton testing) (Millan et al., 2018; Teigen et al., 2018). The sensitivity of this test is expected to be comparable to trio-based whole exome sequencing since it uses a trio approach to test a comprehensive list of genes previously associated with CP. The clinical sensitivity is expected to be significantly lower for alternative testing strategies that do not include both biological parents.

The average coverage of all genes on the panel is greater than 99% at 10X (with a depth of 10 or more reads), and approximately 95% of the genes on the panel have an average coverage of greater than 99% at 10X. Some genes with a relatively high clinical sensitivity have an average coverage of less than 90% at 10X, including CEP152 (88.5%), CHRNA7 (80.4%), OCLN (82.5%), and KIF5C (10.1%). The coverage of each gene on the panel for a specific patient may vary, and the actual coverage for each gene is included in the final report.

Limitations:
Some types of genetic disorders, such as those due to nucleotide repeat expansion/contraction, abnormal DNA methylation, and other mechanisms may not be detectable with this test. Additionally, small sections of a few individual genes have inherent sequence properties that yield suboptimal data and variants in those regions may not be reliably detected. For example, the CGG repeat expansions in FMR1 causing fragile X syndrome, the polyalanine repeat expansions in ARX, polyglutamine expansions in genes that cause ataxic disorders, and abnormal methylation of UBE3A causing Angelman syndrome would not be detectable by this CP Xpanded Panel. Mitochondrial genome sequencing is not performed as part of the CP Xpanded Panel.

The scientific knowledge available about the function of all genes in the human genome is incomplete at this time. It is possible that the Cerebral Palsy Xpanded Panel may identify the presence of a variant in the sequence of an affected individual, but that we will not recognize it as the cause of their disease due to insufficient knowledge about the gene and its function. Even if the Cerebral Palsy Xpanded Panel identifies the underlying genetic cause of a disorder in an affected individual, it is possible that such a diagnosis will not permit an accurate prediction of the prognosis or severity of the disease. While there is a possibility that identifying the genetic cause may help direct management and treatment of the disease, it is also possible that this knowledge will not change management or treatment.

References:

1. Rosenbaum et al. (2007) Dev Med Child Neurol Suppl 109 :8-14 (PMID: 17370477)
2. Van Eyk et al. (2018) Handb Clin Neurol 147 :331-342 (PMID: 29325622)
3. MacLennan et al. (2018) Dev Med Child Neurol 60 (2):209-210 (PMID: 29336076)
4. Novak et al. (2017) JAMA Pediatr 171 (9):897-907 (PMID: 28715518)

5. Millan et al. Genetic testing of 1346 patients with cerebral palsy reveals a monogenetic cause of disease in one-third of cases, vast genetic heterogeneity, and a significant recurrence risk [abstract submitted] To be presented at the 2018 ASHG Annual Genetics Meeting, October 16-20, San Diego, CA
6. Teigen et al. Genetic testing of patients with cerebral palsy reveals one-third of cases have a monogenetic cause and a significant recurrence risk [abstract submitted] To be presented at the 2018 NSGC Annual Conference, November 14-17, Atlanta, GA