Congenital Disorders of Glycosylation Panel

Panel Gene List: *ALG1, ALG11, ALG12, ALG13, ALG14, ALG2, ALG3, ALG6, ALG8, ALG9, ATP6AP1, ATP6V0A2, B3GALNT2, B3GALT6, B3GALTL, B3GAT3, B4GALNT1, B4GALT1, B4GALT7, B4GAT1, CCDC115, CHST14, CHST3, CHST6, CHSY1, COG1, COG2, COG4, COG5, COG6, COG7, COG8, DDOST, DHDDS, DOLK, DPAGT1, DPM1, DPM2, DPM3, DSE, EOGT, EXT1, EXT2, FKRP, FKTN, FUT8, G6PC3, GALNT3, GFPT1, GMPPA, GMPPB, GNE, ISPD, LARGE, LFNG, MAN1B1, MGAT2, MOGS, MPDU1, MPI, NGLY1, PAPSS2, PGAP1, PGAP2, PGAP3, PGM1, PGM3, PIGA, PIGL, PIGM, PIGN, PIGO, PIGT, PIGV, PIGW, PIGY, PMM2, POFUT1, POGLUT1, POMGNT1, POMGNT2, POMK, POMT1, POMT2, RFT1, RPN2, SEC23A, SEC23B, SLC26A2, SLC35A1, SLC35A2, SLC35A3, SLC35C1, SLC35D1, SLC39A8, SRD5A3, SSR4, ST3GAL3, ST3GAL5, STT3A, STT3B, TMEM165, TMEM199, TMEM5, TRAPPC11, TRIP11, TUSC3, XYLT1*

Clinical Features:

Congenital disorders of glycosylation (CDG) are a clinically and genetically heterogeneous group of disorders caused by defects in the synthesis of glycoprotein and glycolipid glycans and the attachment of glycans to proteins and lipids, a process that is required for about half of all human proteins and which affects protein structure, function and half-life.[1,2] CDG are divided into different biochemical groups: errors in protein *N*-linked glycosylation, protein *O*-linked glycosylation, glycolipid and glycosylphosphatidylinositol anchor glycosylation and those that affect multiple glycosylation pathways.[3] CDG may affect a single organ/system, or multiple organs/systems may be affected with symptoms ranging from mild to extremely life-threatening. Symptoms may include intellectual disability, seizures, muscular dystrophy, skeletal dysplasia, dysmorphic features, heart disease, growth retardation, and hematological and endocrine abnormalities. Diagnosing CDG is challenging since the traditional first line screening used by the majority of metabolic laboratories is based on the analysis of transferrin *N*-glycosylation by isoelectric focusing, which may not be able to detect other biochemical CDG groups and may appear normal in individuals with some CDG types.[4] Due to the biochemical complexity, the large number of CDG and the lack of accurate and/or non-invasive biochemical tests, many clinicians opt for targeted sequencing of CDG gene panels or whole exome sequencing as the primary diagnostic test for patients suspected to have a CDG.

The GeneDx Congenital Disorders of Glycosylation panel includes genes causing errors in *N*-linked glycosylation, *O*-linked glycosylation, glycolipid and glycosylphosphatidylinositol anchor glycosylation and multiple glycosylation pathways. Confirmation of a clinical diagnosis can provide important information for families and help direct treatment and medical management.

Genetics:
The majority of the disorders tested for in this panel are inherited in an autosomal recessive manner; however, disorders associated with autosomal dominant or X-linked inheritance are also included.

Test Methods:
Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: *B3GALT6*, *B4GAT1* and *FKRP* genes, no copy number testing, *POMGNT1* gene only whole gene deletions or duplications may be detected.

Clinical Sensitivity:
In 162 patients referred for testing to an outside laboratory with a suspected diagnosis of CDG, single gene analysis or next-generation sequencing panel testing that included up to 24 CDG genes resulted in a molecular diagnosis in 24 patients (~15%).[5] Forty-five of the 162 patients were reported to have previous biochemical testing suggestive of a CDG, and of this group a molecular diagnosis was made in 12 (~27%).[5] In 6 patients suspected of having a CDG in whom biochemical testing suggested a type I CDG and in whom preliminary testing of single CDG gene(s) did not reveal a diagnosis, whole exome sequencing identified the pathogenic/likely pathogenic variant(s) in 4 (67%).[6] In a third study of 87 unrelated patients

who had strong biochemical evidence of a CDG, single gene testing and/or next-generation sequencing of all disease-associated genes described in the Online Mendelian Inheritance in Man database until 2013, led to a molecular diagnosis in all 87 patients.[7] Seventy-two percent (63/87) had mutations in the *PMM2* gene associated with PMM2-CDG (CDG-Ia) while the remaining patients had variants identified in 17 other CDG genes all of which are included on the GeneDx CDG panel.[7] There are now over 100 genes that have been reported to be involved in the synthesis of glycans or in the glycosylation of proteins and lipids.[7]

References:

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6. Timal et al. (2012) Human Molecular Genetics 21 (19):4151-61 (PMID: 22492991)
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