Hemiplegic Migraine Panel
Sequence Analysis and Exon-Level Deletion/Duplication Testing

Panel Gene List: *ATP1A2, CACNA1A, SCN1A, PRRT2*

Clinical Features:
Hemiplegic migraine (HM) is a rare subtype of migraine that is characterized by the presence of an aura and temporary numbness and/or muscle weakness that is typically unilateral.[1] Symptoms of HM may include visual disturbances such as blind spots, flashing lights, or double vision; sensory loss, including numbness and parasthesias of the face or extremities; and speech difficulties including dysphasia and dysarthria.[1,2,3,4] Approximately 40% of individuals experience prolonged aura attacks that can lead to impaired consciousness, confusion, agitation, fever, psychosis, or in severe cases even coma.[1,4] The hemiplegic attacks may alternate with non-hemiplegic aura in some people. Individuals with HM may also experience cerebellar nystagmus and ataxia that is often episodic but in some cases may be progressive and chronic, and intellectual disability may occur in some individuals.[1,3] Additionally, there is an association between migraine and epilepsy.[5] Individuals with HM have an increased risk for seizures, and overall 8%–24% of individuals with epilepsy also experience migraines.[2]

HM attacks may be triggered by stress, sleep deprivation, light, food, sound, or head trauma.[1,3] The prevalence of HM is estimated to be approximately 0.01% in European populations.[1]

Inheritance Pattern/Genetics:
An estimated 50% of individuals with HM have at least one other close relative with the disorder and are diagnosed with familial hemiplegic migraine (FHM).[3] Individuals with no known family history are labeled with sporadic hemiplegic migraine (SHM), although absence of a family history does not exclude the possibility of a genetic form of HM.[3] FHM is inherited in an autosomal dominant manner. The penetrance has been estimated to be 70–90%.[1] The type, severity, and age-of-onset of symptoms can vary among individuals in the same family.[1]

Pathogenic variants causing HM have been identified in three ion channel genes: *CACNA1A*, *SCN1A*, and *ATP1A2*. Pathogenic variants in these genes can also cause other neurological disorders, including ataxia and epilepsy. Individuals with a pathogenic variant in one of these genes may have isolated HM, HM in conjunction with other neurological features as part of a more complex disorder, or they may exhibit only the other neurological features and not experience HM.[3] Pathogenic variants in these three ion channel genes result in abnormal neuronal excitability that is hypothesized to cause HM due to cortical spreading depression

(CSD), which is the strong depolarization of a large group of nerve cells or neuroglia that spreads to adjacent areas and inhibits neural activity.[2]

Less commonly, pathogenic variants in the *PRRT2* gene have been identified in individuals with FHM.[3,] The *PRRT2* gene plays a role in presynaptic function and causes benign familial infantile seizures (BFIS) and/or paroxysmal kinesigenic dyskinesia (PKD). The risk for HM is increased in individuals with *PRRT2*-related BFIS and PKD, although isolated HM is uncommon.[3,6,7]

Test Methods:
Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel 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 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.

Test Sensitivity:
Overall, approximately 14% of individuals with FHM will have a detectable pathogenic variant in the *ATP1A2, CACNA1A, SCN1A,* or *PRRT2* gene.[4] Pathogenic variants in the *ATP1A2* and *CACNA1A* genes are each identified in about 7% of families, while variants in *SCN1A* or *PRRT2* genes are rare.[4] The remaining individuals with FHM do not have an identifiable genetic cause for their features. Individuals with a pathogenic variant in one of the genes included on this panel typically have onset of attacks at an earlier age, have more frequent

attacks, and are more likely to have associated neurological features such as progressive ataxia or intellectual disability.[3,4,8]

Overall, the likelihood of identifying a pathogenic variant is low in individuals with SHM. However, a de novo variant in *ATP1A2* or *CACNA1A* was identified in 76% of individuals with early-onset (prior to age 16) SHM, many of whom had associated neurologic signs such as ataxia, epilepsy, or intellectual disabilities.[8]

Genetic testing using the methods applied at GeneDx is expected to be highly accurate. Normal findings do not rule out the diagnosis of a genetic disorder since some genetic abnormalities may be undetectable by this test. The methods used cannot reliably detect deletions of 20bp to 500bp in size, or insertions of 10bp to 500 bp in size.

References:

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