

Periodic Paralysis Panel

DISORDER ALSO KNOWN AS

PP, Potassium-aggravated myotonia, Hyper/Hypokalemic periodic paralysis.

PANEL GENE LIST

*TP1A2**, *CACNA1S*, *CLCN1*, *KCNJ2**, *KCNJ5**, *RYR1*, *SCN4A*, *SLC12A3*, *SCNN1A**

*Sequence analysis

CLINICAL FEATURES

Periodic paralyses (PP) are a heterogeneous group of muscle disorders characterized by intermittent attacks of muscle weakness or paralysis, which are often associated with altered serum potassium levels, and may be brought on by cessation of strenuous exercise, carbohydrate-rich or high-salt foods, alcohol, cold, stress, prolonged immobility, or anesthesia. Muscle strength between initial attacks may be normal, but persistent muscle weakness typically develops later in life and can be debilitating.^{1,2,3} PP is primarily classified as either hyper- or hypo-kalemic periodic paralysis (HyperPP/HypoPP) based on serum potassium levels during paralytic attacks. Normokalemic periodic paralysis (NormPP) has also been reported as a type of PP; weakness during attacks is reminiscent of both hyperPP and hypoPP, although potassium levels are not altered.^{1,2,3} HyperPP usually presents with episodes of flaccid limb weakness (decreased muscle tone) and hyperkalemia (serum potassium concentration >5 mmol/L); rarely, involvement of the eye, throat or trunk muscles may be observed.² Approximately 45% of individuals with hyperPP also have paramyotonia. Age of onset for hyperPP is typically in the first decade of life. HypoPP presents with proximal, more so than distal, flaccid muscle weakness and hypokalemia (serum potassium concentration <3.5 mmol/L). Attacks less frequently may include muscle pain or cramping. Myopathy can occur independent of paralytic symptoms and may be the sole manifestation of hypoPP.³ Age of onset of hypoPP is typically in the second decade, ranging from two to 30 years. Another form of PP, Andersen-Tawil syndrome (ATS), manifests with a triad of clinical features including episodic flaccid muscle weakness, ventricular arrhythmia, and prolonged QT. Serum potassium concentration may be elevated, normal, or reduced during an attack. Characteristic facies (low-set ears, widely spaced eyes and small mandible), dental anomalies, small hands/feet, fifth-digit clinodactyly and 2-3 toe syndactyly may also be observed.⁶ Cardiac symptoms or muscle weakness may spontaneously occur in the first or second decade of life.

Estimated prevalence of periodic paralysis is approximately 0.17:100,000 for hyperPP, 1:100,000 for hypoPP, and 1:1,000,000 for Andersen-Tawil syndrome.⁴⁻⁶

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

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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. For the *ATP1A2*, *KCNJ2*, *KCNJ5*, and *SCNN1A* genes, sequencing, but not deletion/duplication analysis, was performed.

TEST SENSITIVITY

Overall, molecular genetic testing identifies a causative variant in 60-70% of affected individuals meeting clinical criteria.^{5,7,8} Pathogenic variants in *CACNA1S* and *SCN4A* account for ~40-60% or 7-14% of hypoPP respectively, the majority of which can be detected by sequencing analysis.³ Pathogenic variants in *SCN4A* account for ~80% of hyperPP patients.² Approximately 70% of all individuals with Andersen-Tawil syndrome are found to have pathogenic sequencing variants in *KCNJ2*.^{5,6} Approximately 30% of patients do not have a detectable genetic etiology for their features.

PERIODIC PARALYSIS PANEL

Sequencing and Exon-level Deletion/Duplication analysis of 9 genes

Gene	Disease Associations	Inheritance	Diagnostic Yield in Selected Population(s)
<i>ATP1A2</i>	Migraine; HypoPP	AD	Rare contribution to hypoPP ⁹
<i>CACNA1S</i>	HypoPP; MH; Thyrotoxic PP; Congenital myopathy	AD	~40%-60% of hypoPP ^{4,5}
<i>CLCN1</i>	Myotonia congenital; HypoPP	AD/AR	95% of myotonia congenita; Rare contribution to hypoPP ^{10,11}
<i>KCNJ2</i>	ATS; Short QT syndrome; Long QT syndrome; Atrial fibrillation	AD	70% of ATS ^{5,6}
<i>KCNJ5</i>	Familial hyperaldosteronism; Long QT syndrome; ATS	AD	Rare contribution to ATS ^{5,6}
<i>RYR1</i>	Central core disease; King-Denborough syndrome; Minicore myopathy with external ophthalmoplegia; Congenita neuromuscular disease; MH; atypical PP	AD/AR	Rare contribution to atypical PP ^{1,12}
<i>SCN4A</i>	Hyper/hypoPP, Myasthenic syndrome; Paramyotonia congenita; Atypical myotonia congenita	AD/AR	7%-14% of hypoPP ³ 80% of hyperPP ^{2,5}
<i>SLC12A3</i>	Gitelman syndrome	AR	Rare contribution to hypoPP ¹³
<i>SCNN1A</i>	Bronchiectasis with or without elevated sweat chloride; Pseudohypoaldosteronism type 1	AD/AR	Rare contribution to hyperPP ^{1,14}

Abbreviations:

HyperPP – Hyperkalemic periodic paralysis

MH – Malignant hyperthermia

HypoPP – Hypokalemic periodic paralysis

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