

OncoGeneDx: Paraganglioma/Pheochromocytoma Panel

Panel Gene List: *FH, MAX, MEN1, NF1, RET**, *SDHA**, *SDHAF2, SDHB, SDHC, SDHD, TMEM127, VHL*

*Testing includes sequencing and deletion/duplication analysis for all genes except *RET* (seq only) and *SDHA* (seq only).

Clinical Features:

Paragangliomas (PGL) are very rare neuroendocrine tumors that arise from neural crest tissue of the sympathetic and parasympathetic paraganglia. Pheochromocytomas (PCC) refer to paragangliomas that are confined to the adrenal medulla. These tumors are exceptionally rare in the general population and occur in approximately 1/300,000 individuals per year.¹ These tumors are often benign, but may undergo malignant transformation. It has been estimated that 20-30% of those individuals diagnosed with either PGL or PCC will harbor a pathogenic variant in one of the genes included in this panel.² The features of a personal and/or family history that are suggestive of a hereditary predisposition to PGL/PCC include: young ages at diagnosis, multiple primary tumors in a single individual, diagnosis of a tumor or cancer type that is not common in general population (such as a pheochromocytoma), and several relatives affected with cancer or tumors spanning multiple generations. Due to the rare nature of PGL and PCC, any individual diagnosed with one of these tumors at any age, regardless of family history, should be considered for genetic evaluation.

Hereditary paraganglioma/pheochromocytoma has been described in association with several syndromes. These include hereditary paraganglioma/pheochromocytoma syndrome (*SDHA, SDHAF2, SDHB, SDHC, SDHD*), neurofibromatosis type 1 (*NF1*), multiple endocrine neoplasia type 2 (*RET*), and von Hippel-Lindau disease (*VHL*). Pathogenic variants in these eight aforementioned genes account for a significant portion of hereditary PGL/PCC predisposition and have been well described in the literature. In addition, other well described syndromes include a risk of PGL/PCC cancer as a minor feature. These include multiple endocrine neoplasia type 1 (*MEN1*) and hereditary leiomyomatosis and renal cell carcinoma (*FH*). Management guidelines are available for a number of these genes.

Several newer genes, including *MAX* and *TMEM127*, have been identified in families with PGL/PCC and may increase the risk for other cancers or tumors as well. The evidence available to date may be derived from a small number of patients with wide confidence intervals or is based upon an ethnic cohort with one specific variant. Accurate risk assessment may be complicated by the low penetrance of pathogenic variants in these genes and/or ascertainment bias.

Inheritance Pattern:

All genes on this panel are associated with an autosomal dominant cancer risk. Some of the genes on this panel are also associated with extremely rare conditions when inherited in an autosomal recessive fashion. The specifics of this inheritance are outlined in the table below.

Test Methods:

Genomic DNA is extracted from the submitted specimen. For skin punch biopsies, fibroblasts are cultured and used for DNA extraction. This DNA is enriched for the complete coding regions and splice site junctions of the genes on this panel 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. For *RET* and *SDHA*, only sequencing is performed. 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.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the 12 genes included in the OncoGeneDx Paraganglioma/Pheochromocytoma Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with features suggestive of a hereditary predisposition to cancer/tumors as outlined above. DNA sequencing will detect nucleotide substitutions and small insertions and deletions, while NGS-CNV analysis, array CGH, or MLPA will detect exon-level deletions and duplications. These methods are expected to be greater than 99% sensitive in detecting pathogenic variants identifiable by sequencing or CNV technology.

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 250bp in size, or insertions of 10bp to 250 bp in size. Sequencing cannot detect low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect mosaicism and cannot identify balanced chromosome aberrations. Rarely, incidental findings of large chromosomal rearrangements outside the gene of interest may be identified. Regions of certain genes have inherent sequence properties (for example: repeat, homology, or pseudogene regions, high GC content, rare polymorphisms) that yield suboptimal data, potentially impairing accuracy of the results. False negatives may also occur in the

setting of bone marrow transplantation, recent blood transfusion, or suboptimal DNA quality. In individuals with active or chronic hematologic neoplasms or conditions, there is a possibility that testing may detect an acquired somatic variant, resulting in a false positive result. As the ability to detect genetic variants and naming conventions can differ among laboratories, rare false negative results may occur when no positive control is provided for testing of a specific variant identified at another laboratory. The chance of a false positive or false negative result due to laboratory errors incurred during any phase of testing cannot be completely excluded. Interpretations are made with the assumption that any clinical information provided, including family relationships, are accurate. Consultation with a genetics professional is recommended for interpretation of results.

Gene	Protein	Inheritance	Disease Associations
<i>FH</i> ³⁻⁷	FUMARATE HYDRATASE, MITOCHONDRIAL	AD	Hereditary leiomyomatosis and renal cell cancer (HLRCC): Renal cancer (type II papillary), leiomyomas, pheochromocytoma, paraganglioma
		AR	Fumarate hydratase deficiency
<i>MAX</i> ⁸⁻¹²	PROTEIN MAX	AD	Paraganglioma, pheochromocytoma
<i>MEN1</i> ¹³⁻¹⁷	MENIN	AD	Multiple endocrine neoplasia type 1 (MEN1): Parathyroid tumors, pancreatic neuroendocrine tumors, pituitary tumors, pheochromocytoma
<i>NF1</i> ¹⁸⁻²⁰	NEUROFIBROMIN	AD	Neurofibromatosis type 1 (NF1) syndrome: Breast cancer, GIST, optic nerve gliomas, pheochromocytoma, MPNST, neurofibromas, brain tumors
<i>RET</i> ^{15,21-23}	PROTO-ONCOGENE TYROSINE-PROTEIN KINASE RECEPTOR RET	AD	Multiple endocrine neoplasia type 2 (MEN2): Medullary thyroid cancer, pheochromocytoma, hyperparathyroidism
<i>SDHA</i> ^{1,8,24-26}	SUCCINATE DEHYDROGENASE [UBIQUINONE] FLAVOPROTEIN SUBUNIT, MITOCHONDRIAL	AD	Hereditary paraganglioma/ pheochromocytoma (PGL/PCC) syndrome: Paraganglioma, pheochromocytoma, GIST
		AR	Leigh syndrome
<i>SDHAF2</i> ^{1,8,27}	SUCCINATE DEHYDROGENASE	AD	Hereditary paraganglioma/ pheochromocytoma (PGL/PCC)

Gene	Protein	Inheritance	Disease Associations
	ASSEMBLY FACTOR 2, MITOCHONDRIAL		syndrome: Paranganglioma
<i>SDHB</i> ^{1,8,28,29}	SUCCINATE DEHYDROGENASE [UBIQUINONE] IRON-SULFUR SUBUNIT, MITOCHONDRIAL	AD	Hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome: Paranganglioma, pheochromocytoma, renal cancer, GIST
		AR	Isolated complex II deficiency
<i>SDHC</i> ^{1,8,30-32}	SUCCINATE DEHYDROGENASE CYTOCHROME B560 SUBUNIT, MITOCHONDRIAL	AD	Hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome: Paranganglioma, pheochromocytoma, renal cancer, GIST
<i>SDHD</i> ^{1,8,28,33,34}	SUCCINATE DEHYDROGENASE [UBIQUINONE] CYTOCHROME B SMALL SUBUNIT, MITOCHONDRIAL	AD	Hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome: Paranganglioma, pheochromocytoma, renal cancer, GIST, thyroid cancer
		AR	Isolated complex II deficiency
<i>TMEM127</i> ^{8,35,36}	TRANSMEMBRANE PROTEIN 127	AD	Hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome: Pheochromocytoma
<i>VHL</i> ³⁷⁻⁴⁰	VON HIPPEL-LINDAU DISEASE TUMOR SUPPRESSOR	AD	von Hippel-Lindau (VHL) disease: Renal cancer (clear cell), pancreatic neuroendocrine tumors, hemangioblastoma, pheochromocytoma, endolymphatic sac tumors

Because of evolving and expanding phenotypes, this list of cancer/tumor types is not exhaustive. Gene-specific risk for some of the cancers and other features listed are not well-defined.

Abbreviations:

AD – Autosomal Dominant

AR – Autosomal Recessive

CGH – Comparative genomic hybridization

GIST – Gastrointestinal stromal tumor

MLPA – Multiplex ligation-dependent probe amplification

MPNST - Malignant peripheral nerve sheath tumor

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