Paraganglioma-Pheochromocytoma Panel: Sequencing and CNV Analysis

Test Code: MM203
Turnaround time: 4 weeks
CPT Codes: 81404 x1, 81405 x1, 81406 x1, 81479 x1

Condition Description

The estimated prevalence of pheochromocytomas (PHEOs) is 1:4500 and 1:1700 for paragangliomas (PGLs), with an annual incidence of 3 to 8 cases per 1 million a year in the general population. The age of onset for PGL individuals is between 15 and 45 years of age, with early symptoms typically consisting of local swelling and cranial nerve injury. Although the tumors are benign in nature, only 4-16% shows malignant degeneration, giving rise to swelling causing cranial nerve damage, facial asymmetry, deafness, or hoarseness. PGLs are composed of pheochromocytomas (PCC, PPGs, PH, or PHEOs) and extra-adrenal PGLs, and are characterized by the tumor production and secretion of catecholamines arising from the adrenal medulla (pheochromocytoma) or sympathetic nervous ganglia. Diagnosis for PGLs is determined by a biochemical assay, tumor location, function, inheritance, and gene mutation. If the tumor has metastasized the overall five year survival rate in patients is 40-72%. Size and location of the primary tumor has been correlated with risk for metastasis and the duration of survival.

Reference:

Genes

\textit{PH, MAX, SDHAF2, SDHB, SDHC, SDHD, TMEM127, VHL}

Indications

The test is indicated for:

- Individuals with a clinical or suspected diagnosis of pheochromocytomas and paragangliomas.

Methodology

\textbf{Next Generation Sequencing:} In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

\textbf{Copy Number Analysis:} Comparative analysis of the NGS read depth (coverage) of the targeted regions of genes on this panel was performed to detect copy number variants (CNV). The accuracy of the detected variants is highly dependent on the size of the event, the sequence context and the coverage obtained for the targeted region. Due to these variables and limitations a minimum validated CNV size cannot be determined; however, single exon deletions and duplications are expected to be below the detection limit of this analysis.

Detection

\textbf{Next Generation Sequencing:} Clinical Sensitivity: Unknown. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical/biochemical phenotype.

Analytical sensitivity for sequence variant detection is \textasciitilde 99%.

\textbf{Copy Number Analysis:} The sensitivity and specificity of this method for CNV detection is highly dependent on the size of the event, sequence context and depth of coverage for the region involved. The assay is highly sensitive for CNVs of 500 base pairs or larger and those containing at least 3 exons. Smaller (< 500 base pairs) CNVs and those that involving only 1 or 2 exons may or may not be detected depending on the sequence context, size of exon(s) involved and depth of coverage.

Specimen Requirements

\textit{Submit only 1 of the following specimen types}

\textbf{Type: Whole Blood (EDTA)}

\textbf{Specimen Requirements:}
- EDTA (Purple Top)
- Infants and Young Children (2 years of age to 10 years old): 3-5 ml
- Older Children & Adults: 5-10 ml
- Autopsy: 2-3 ml unclotted cord or cardiac blood

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Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

**Type: DNA, Isolated**

**Specimen Requirements:**
- Microtainer
- 8µg

Isolation using the Perkin Elmer™Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Specimen Collection and Shipping:**
Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

**Type: Saliva**

**Specimen Requirements:**
- Oragene™ Saliva Collection Kit

Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

**Specimen Collection and Shipping:**
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

**Special Instructions**

This test is for germline mutation analysis. DNA isolated from FFPE tumor samples is not suitable for this test.

**Related Tests**

- Hereditary Cancer Syndrome: Sequencing Panel.
- Paragangioma-Pheochromocytoma: Deletion/Duplication Panel.