



## Hereditary Paraganglioma: *SDHB*, *SDHC*, *SDHD* gene assessment

**Background:** Paragangliomas are tumors of vascular autonomic tissues in the body, particularly in the head and neck area, frequently involving the carotid body located at the bifurcation of the common carotid artery. Pheochromocytomas are a form of paraganglioma, and abdominal extra-adrenal paragangliomas also occur, some of which are functional (catecholamine-secreting). Paragangliomas are seen with equal frequency in both sexes. Between 10-50% of paragangliomas are hereditary (familial), associated with mutations in one of several genes (below), and show autosomal dominant inheritance (more below). Treatment of small tumors carries a lower risk of morbidity and mortality, so MRI screening is recommended biannually for at-risk individuals over the age of 16. Screening may be eliminated for patients who are shown by genetic testing to lack a known predisposing mutation in familial tumors.

**Hereditary paraganglioma (PGL) genes:** Genetic alterations (mutations) responsible for the hereditary form of PGL have been identified in genes coding for succinate-ubiquinone oxidoreductase subunit D (SDHD) and B (SDHB) and C (SDHC) genes which map to chromosomes 11, 1 and 1, respectively. Mutations are most common in SDHB and SDHD with only a few described for SDHC. PGL is inherited in an autosomal dominant fashion for all genes, although there is incomplete penetrance for SDHD mutations depending on whether the abnormality is inherited through the mother or father. Only patients who inherit an SDHD mutation from the father are at risk to develop paragangliomas, although they may pass the mutation to offspring. It is thought this parent-of-origin effect occurs because the gene carrying the mutation is only activated during spermatogenesis and not during oogenesis, a phenomenon known as genetic imprinting. Parent-of-origin effects are not seen with SDHB or SDHC mutations.

**Benefits/risks of DNA sequence-based testing:** The test is performed by sequencing of all coding regions (and adjacent noncoding areas) of one or more of the SDH genes. Individuals from families where a sequence change has been identified are generally screened only for the region of the particular gene in question. A customized report is generated which takes into account family history (if provided) and the inheritance pattern of this disorder. A clinical information sheet is faxed to the referring clinician/genetic counselor after sample receipt to obtain information that allows us to start testing focusing on the gene with the highest probability of success and to aid in construction of the final report.

DNA sequencing is a precise technique capable of finding small changes in the 'coding' regions of genes and immediate surrounding regions that may cause disease through disordered gene function. DNA sequencing will not detect abnormalities located in regulatory regions outside a gene's coding regions or 'deep within' the sequences that separate individual coding regions of a gene, or that lead to functional compromise through partial loss or duplication of a gene. Such changes have not yet been described for the SDHB, SDHC or SDHD genes to our knowledge. Sequence variants may be found whose function is uncertain. Such results may cause confusion, uncertainty and increased anxiety in patients who should be informed of this possible outcome when informed consent is obtained.

**Turnaround Time:** 2-7 weeks (generally run monthly) depending on laboratory workflow.

**Specimen Requirements:** See Oncology/Genetics Specimen Handling Protocol or Molecular Diagnostics Genetics Requisition Form.

**Informed Consent:** It is the responsibility of the referring health care professional to obtain proper informed consent from the patient for genetic testing. Test results are released only to the primary referring physician and/or genetic counselor. The laboratory report contains information that may be useful for genetic counseling of the patient and/or family members, although adjunct use of an experienced genetic counselor or medical geneticist may be beneficial for this genetic disorder.