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Test ID: SDHSB
Succinate Dehydrogenase (SDH) Subunit B Gene Analysis

Useful For

Diagnosis of familial *SDHB* gene mutations or deletions in patients with paragangliomas or pheochromocytomas

Tailoring optimal tumor-surveillance strategies for patients, when used in conjunction with phenotyping

Clinical Information

Succinate dehydrogenase (SDH) is a mitochondrial membrane-bound enzyme complex consisting of 4 subunits: SDHA, SDHB, SDHC, and SDHD. SDH is an oxidoreductase that catalyzes the oxidation of succinate to fumarate (tricarboxylic acid cycle function) and the reduction of ubiquinone to ubiquinol (respiratory chain function).

Homozygous loss of function mutations or homozygous deletions of SDH subunit genes are embryonal lethal, with the exception of some biallelic *SDHA* mutations, which cause Leigh syndrome. No disease-associated heterozygote *SDHA* mutations/deletions have been reported. By contrast, heterozygous mutations/deletions of *SDHB*, *SDHC*, or *SDHD* result in a high life-time penetrance autosomal dominant tumor syndrome. Patients have only 1 functioning germline copy of the affected SDH subunit gene. When the second, intact copy is somatically lost or mutated in target tissues, tumors develop. Sympathetic and parasympathetic ganglia are preferentially affected, resulting in development of paragangliomas (PGL) or pheochromocytomas (PC). PGLs might include parasympathetic ganglia (neck and skull-base) or sympathetic ganglia (paravertebral sympathetic chain from neck to pelvis). PCs can involve 1 or both adrenal glands. Almost all PCs overproduce catecholamines, resulting in hypertension with a predilection for hypertensive crises. About 20% of PGL, mostly intra-abdominal, also secrete catecholamines. PGLs in the neck do not usually produce catecholamines. SDH-associated PGLs and PCs are typically benign; however, malignancy has been described in a minority of patients (especially in patients with *SDHB* mutations). In addition, because of the germline presence of the mutation/deletion, new primary tumors might occur over time in the various target tissues. Finally, tumors unrelated to chromaffin tissues, namely renal cell carcinoma (RCC: *SDHB* only) and gastrointestinal stromal tumors (GIST: *SDHB*, *SDHC,* and *SDHD*), affect a minority of patients.

Collectively, heterozygous germline mutations/deletions of *SDHB*, *SDHC*, or *SDHD* are found in 30% to 50% of apparently sporadic PGL cases and can be confirmed in >90% of clinically hereditary cases. The corresponding figures are 1% to 10% and 20% to 30% for outwardly sporadic PC and seemingly inherited PC, respectively. The prevalence of *SDHD* mutations/deletions is higher than that of *SDHB*, which in turn exceeds the figures for *SDHC*. *SDHB* and *SDHC* mutations show classical autosomal dominant inheritance, while *SDHD* mutations show a modified autosomal dominant inheritance with chiefly paternal transmission, suggesting maternal imprinting (the molecular correlate of which remains unknown). *SDHB* is most strongly associated with PGL (usually functioning), but adrenal PCs also occur, as do occasional GISTs and RCCs, with the latter being found exclusively in this subtype. *SDHD*

shows a disease spectrum similar to *SDHB*, except head and neck PGLs are more frequent than in *SDHB*, while functioning or malignant PGLs/PCs and GISTs are less common. *SDHC* has thus far been mainly associated with PGLs of skull base and neck. Abdominal/functioning PGLs or PCs are uncommonly seen in patients with *SDHC* mutations and GISTs are very rare. However, there is limited certainty about the *SDHC* genotype-phenotype correlations, as the reported case numbers are low.

Genetic testing for *SDHB*, *SDHC,* and *SDHD* germline mutations and deletions is highly accurate in identifying affected patients and pre-symptomatic individuals. It is advocated in all patients that present with PGL. Accurate diagnosis assists in designing optimal follow-up strategies, since the rate of new/recurrent tumors is much higher in patients with SDH mutations or deletions than in true sporadic cases.

Screening for mutations in SDH genes is not currently advocated for sporadic adrenal PC, but is gaining in popularity, often alongside tests for mutations of other predisposing genes, *RET* (multiple endocrine neoplasia type 2, MEN2), *VHL* (von Hippel-Lindau syndrome), and *NF1* (neurofibromatosis type 1). Seemingly familial PC cases, who do not have an established diagnosis of a defined familial tumor syndrome, should be screened for SDH gene mutations, along with screening of the other predisposing genes listed above.

In order to minimize the cost of genetic testing, the clinical pattern of lesions in PGL and PC patients might be used to determine the order in which the 3 disease-associated SDH genes are tested. Genetic diagnosis of index cases allows targeted pre-symptomatic testing of relatives.

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations (Genet Med 2008:10[4]:294-300). Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Rare unknown polymorphisms in primer or probe binding sites can rarely result in allelic drop out and false negative genetic tests.

The current test does not examine the promoters, other gene regulatory elements, or most of the intronic portions of the *SDHB, SDHC,* and *SDHD* genes. The impact of this on detection rates is unknown. Based on observations in other genetic disorders, it is generally believed that <5% of disease-causing mutations occur in these regions.

There may be (several) other, as yet unidentified, genes that can cause a phenotypically similar picture as succinate dehydrogenase (SDH) mutations/deletions.

Collectively, the above causes, along with various other preanalytical and analytical problems that are not unique to genetic testing (eg, specimen mix up), probably account for the estimated false-negative rate of <10% (likely <5%) that is observed with genetic SDH testing.

This test does not reliably detect deletions in formalin-fixed paraffin-embedded tissues.

Supportive Data

We sequenced the *SDHB*, *SDHC* and *SDHD* genes in 42 specimens that had previously been tested for succinate dehydrogenase (SDH) mutations at the National Institutes of Health (NIH). We were blinded to the original results until completion of all sequencing. All mutations found previously were confirmed. Overall 27 patients had *SDHB* mutations, 2 patients had *SDHC* mutations, and 8 patients had *SDHD* mutations. Inter- and intra-assay testing showed 100% concordance for all sequenced regions. Fifteen specimens from healthy individuals were also sequenced. All showed wild-type sequence for *SDHB*, *SDHC,* and *SDHD*.

Another 42 specimens from the NIH were tested for deletions of *SDHB*, *SDHC,* and *SDHD*, using multiplex ligation-dependent probe amplification-Luminex Flexmap technology. Seventeen specimens were found to have deleted portions of 1 of the SDH genes. These results were confirmed by the NIH. In addition, 50 specimens from healthy individuals were tested for deletions. We detected no deletions of *SDHB*, *SDHC,* or *SDHD* in any of these individuals.

Clinical Reference

1. Briere JJ, Favier J, Gimenez-Roqueplo AP, Rustin P: Tricarboxylic acid cycle dysfunction as a cause of human diseases and tumor formation. Am J Physiol Cell Physiol 2006 Dec;291(6):C1114-1120
2. Young WF Jr: Paragangliomas: Clinical Overview. Ann N Y Acad Sci 2006 Aug;1073:21-29
3. Bornstein SR, Gimenez-Roqueplo AP: Genetic testing in pheochromocytoma: increasing importance for clinical decision making. Ann NY Acad Sci 2006;1073:94-103
4. Benn DE, Richardson AL, Marsh DJ, Robinson BG: Genetic testing in pheochromocytoma and paraganglioma-associated syndromes. Ann NY Acad Sci 2006;1073:104-111

Special Instructions and Forms

- **Informed Consent for Genetic Testing**
- **SDHB, SDHC, SDHD Gene Testing Patient Information Sheet**