

Overview

Useful For

Aiding in the diagnosis of hereditary paraganglioma-pheochromocytoma syndrome associated with *SDHB*, *SDHC*, and *SDHD* gene mutations

Genetics Test Information

Testing includes full gene sequencing of the *SDHB*, *SDHC*, *SDHD* genes and multiplex ligation-dependent probe amplification for the detection of large deletions and duplications within the *SDHB*, *SDHC*, *SDHD* genes.

Special Instructions

- [Informed Consent for Genetic Testing](#)
- [SDHB, SDHC, SDHD Gene Testing Patient Information](#)
- [Informed Consent for Genetic Testing \(Spanish\)](#)

Method Name

Polymerase Chain Reaction (PCR) Followed by DNA Sequence Analysis and Gene Dosage Analysis by Multiplex Ligation-Dependent Probe Amplification (MLPA)

NY State Available

Yes

Specimen

Specimen Type

Varies

Shipping Instructions

Specimen preferred to arrive within 96 hours of draw.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Specimen Type: Whole blood

Container/Tube:

Preferred: Lavender top (EDTA) or yellow top (ACD)

Acceptable: Any anticoagulant

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.
2. Send specimen in original tube.

Forms

1. [SDHB, SDHC, SDHD Gene Testing Patient Information \(T659\)](#) in Special Instructions is required.

2. [Informed Consent for Genetic Testing \(T576\)](#) in Special Instructions is required.

3. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-[Informed Consent for Genetic Testing \(T576\)](#)

-[Informed Consent for Genetic Testing-Spanish \(T826\)](#)

4. If not ordering electronically, complete, print, and send an [Oncology Test Request \(T729\)](#) with the specimen.

Specimen Minimum Volume

1 mL

Reject Due To

All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Frozen		
	Refrigerated		

Clinical and Interpretive

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).

Heterozygous pathogenic variants of *SDHB*, *SDHC*, or *SDHD* result in an autosomal dominant tumor syndrome with variable lifetime penetrance. 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. Tumorigenesis is believed to be mediated through the hypoxia-inducible factor (HIF) pathway, which gets activated as a consequence of the loss of function of the enzyme complex. Sympathetic and parasympathetic ganglia are preferentially affected, resulting in development of paragangliomas (PGLs) or pheochromocytomas (PCCs).

PGLs might include parasympathetic ganglia (neck and skull-base) or sympathetic ganglia (paravertebral sympathetic chain from neck to pelvis). PCCs can involve 1 or both adrenal glands. Almost all PCCs 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 usually do not produce catecholamines. SDH-associated PGLs and PCCs are typically not malignant; however, malignancy has been described in a minority of patients (especially in patients with pathogenic *SDHB* variants). In addition, because of the germline presence of the

pathogenic variant, new primary tumors might occur over time in the various target tissues.

SDHB is most strongly associated with PGL (usually functioning), but adrenal PCCs also occur, as do occasional gastrointestinal stromal tumors (GIST) and renal cell carcinomas (RCC). The lifetime penetrance of *SDHB*-related PGL/PCC is relatively low (25%-40%), but approximately half of the clinically affected patients will experience metastatic disease.

SDHD shows a disease spectrum similar to *SDHB*, except head and neck PGLs are more frequent than in *SDHB*, while functioning or malignant PGLs/PCCs and GISTs are less common. RCCs have thus far not been observed. The lifetime penetrance of paternally transmitted pathogenic *SDHD* variants is essentially 100%, while maternal transmission of a dysfunctional *SDHD* copy rarely leads to disease.

SDHC has, thus far, been mainly associated with PGLs of skull base and neck. Abdominal and functioning PGLs or PCCs are uncommon, and GISTs are very rare. RCCs have thus far not been observed. However, there is limited certainty about the *SDHC* genotype-phenotype correlations, as the reported case numbers are low. For the same reason there are no reliable estimates about the lifetime penetrance of *SDHC*-related PGL/PCC.

Collectively, heterozygous germline pathogenic variants of *SDHB*, *SDHC*, or *SDHD* are found in 30% to 50% of apparently sporadic PGL cases, and can be confirmed in approximately 90% of clinically hereditary cases. The corresponding figures are 1% to 25% and 20% to 30% for outwardly sporadic PCC and seemingly inherited PCC, respectively. The prevalence of pathogenic *SDHB* variants is higher than that of *SDHD*, which in turn exceeds the numbers for *SDHC*. *SDHB* and *SDHC* show classical autosomal dominant inheritance, while *SDHD* shows a modified autosomal dominant inheritance with chiefly paternal transmission, suggesting maternal imprinting, the exact molecular correlate of which remains unknown; however, recent evidence suggests tissue-specific distant imprinting that leads to long-range regulation of *SDHD* expression.

A minority of individuals with familial PGL will have pathogenic variants in other genes: *SDHAF2* (also known as *SDH5*), *TMEM127*, and *MAX*.

Other genes have been described, but need additional study to confirm their clinical relevance and the utility of genetic testing: (i) *SDHA* variants have been described in familial PCC/PGL; however, all *SDHA* variants described thus far have been found in patients with seemingly sporadic PCC/PGL, not in familial cases. Moreover, the available data suggests that *SDHA* variants may have low penetrance and thus clinical utility of genetic testing is difficult to determine. (ii) *EGLN1/PHD2*, *HIF2 alpha*, *IDH1*, and *KIF1 beta* have also been proposed to predispose to PCC or PGL, but have thus far not been confirmed to do so, or, only do so very rarely.

Screening for pathogenic variants in *SDH* genes is not currently advocated for sporadic PCC, but is gaining in popularity, often alongside tests for mutations of other predisposing genes: *SDHAF2*, *TMEM127*, *MAX*, *RET* (multiple endocrine neoplasia type 2: MEN2), *VHL* (von Hippel-Lindau syndrome), *NF1* (neurofibromatosis type 1). However, seemingly familial PCC cases that do not have an established diagnosis of a defined familial tumor syndrome, may benefit from *SDH* gene testing, along with screening of the other predisposing genes previously listed.

In order to minimize the cost of genetic testing, the clinical pattern of lesions in PGL and PCC patients may be used to determine the order in which the various predisposing genes listed above should be tested. The latest Endocrine Society Clinical Practice Guideline for pheochromocytoma and paraganglioma (2014) provides the current favored targeted testing approach. Genetic diagnosis of index cases allows targeted pre-symptomatic testing of relatives.

Reference Values

An interpretive report will be provided.

Interpretation

Evaluation and categorization of variants is performed using the most recent published American College of Medical

Genetics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Cautions

Some individuals who have involvement of the *SDHB*, *SDHC*, or *SDHD* gene may have a pathogenic variant that is not identified by the methods performed (eg, promoter variants, deep intronic variants). The absence of a variant, therefore, does not eliminate the possibility of SDH-related disease. For predictive testing of asymptomatic individuals, it is important to first document the presence of a pathogenic gene variant in an affected family member.

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Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete. In some cases, DNA variants of undetermined significance may be identified. Rarely, sequence variants in primer- or probe-binding sites can result in false-negative test results (DNA sequencing) or either false-positive or false-negative results (multiplex ligation-dependent probe amplification: MLPA; deletion screening), due to selective allelic drop-out. False-negative or false-positive results can occur in MLPA deletion screening assays due to poor DNA quality. If results obtained do not match the clinical findings, additional testing should be considered.

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In addition to disease-related probes, the MLPA technique utilizes probes localized to other chromosomal regions as internal controls. In certain circumstances, these control probes may detect other diseases or conditions for which this test was not specifically intended. Results of the control probes are not normally reported. However, in cases where clinically relevant information is identified, the ordering physician will be informed of the result and provided with recommendations for any appropriate follow-up testing.

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Unless reported or predicted to cause disease, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported. These and common benign variants identified for this patient are available upon request.

Supportive Data

We sequenced the *SDHB*, *SDHC*, and *SDHD* genes in 42 specimens that had previously been tested for succinate dehydrogenase (*SDH*) variants at the National Institutes of Health (NIH). We were blinded to the original results until completion of all sequencing. All variants previously identified were confirmed. Overall, 27 patients had *SDHB* variants, 2 patients had *SDHC* variants, and 8 patients had *SDHD* variants. 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. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-423
2. 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
3. Young WF Jr: Paragangliomas: clinical overview. Ann NY Acad Sci 2006;1073:21-29
4. Bornstein SR, Gimenez-Roqueplo AP: Genetic testing in pheochromocytoma: increasing importance for clinical decision making. Ann NY Acad Sci 2006;1073:94-103
5. Benn DE, Richardson AL, Marsh DJ, Robinson BG: Genetic testing in pheochromocytoma and paraganglioma-associated syndromes. Ann NY Acad Sci 2006;1073:104-111

Performance

Method Description

Bidirectional sequence analysis is used to test for the presence of a mutation in all coding regions and intron/exon boundaries of the *SDHB*, *SDHC*, and *SDHD* genes. Additionally, gene dosage analysis by multiplex ligation-dependent probe amplification (MLPA) is used to test for the presence of large deletions and duplications in the *SDHB*, *SDHC*, and *SDHD* genes. (Unpublished Mayo method)

PDF Report

No

Day(s) and Time(s) Test Performed

Performed weekly, Varies

Analytic Time

14 days

Maximum Laboratory Time

20 days

Specimen Retention Time

Whole Blood: 2 weeks (if available) Extracted DNA: 3 months

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact [Customer Service](#).

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

81403 x 2

81404 x 2

81405 x 2

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
SDHP	SDHB, SDHC, SDHD Gene Panel	82532-3

Result ID	Test Result Name	Result LOINC Value
37460	Result Summary	50397-9
37461	Result	82939-0
37462	Interpretation	69047-9
37463	Additional Information	48767-8
37464	Specimen	31208-2
37465	Source	31208-2
37466	Released By	18771-6