

GENETIC DIAGNOSTIC LABORATORY
UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE
DEPARTMENT OF GENETICS
Tel: (215) 573-9161 • Fax: (215) 573-5940
CLIA ID: 39D0893887

SMAD4

Background: Hereditary hemorrhagic telangiectasia (HHT), also called Osler-Weber-Rendu disease, is a blood vessel disorder characterized by abnormal, direct connections between arteries and veins. Telangiectases, small abnormal blood vessels, which appear as red spots are often found on the lips, tongue, fingers, intestines, or nose. Larger abnormal blood vessels called arteriovenous malformations (AVMs) can occur in the internal organs, most commonly the lung, liver, spine, gastrointestinal tract, and brain. Bleeding telangiectases in the nose or intestines can be either a minor annoyance or a major medical problem, sometimes requiring transfusions.

Juvenile Polyposis Syndrome (JPS) is an autosomal dominant disease in which individuals are predisposed to hamartomatous polyps and gastrointestinal cancer. In patients with JPS, 20% have been shown to have a mutation in *SMAD4*.

Some individuals with the combined HHT and JPS carry a mutation in the *SMAD4* gene. Approximately 2-3% of individuals with a clinical diagnosis of HHT but no juvenile polyposis have reportedly been found to have a mutation in *SMAD4* gene.

Eligibility: Patients who meet the established clinical criteria for HHT (at least 2 of the following): spontaneous and recurrent nosebleeds (epistaxis); multiple mucocutaneous telangiectases at characteristic sites, including lips, oral cavity, fingers, and nose; visceral arteriovenous malformation (AVM) of the lung, brain or spine; a family history of a first-degree relative with a clinical diagnosis of HHT; and **a history of GI bleeding**.

Patients who meet the diagnostic criteria for Juvenile Polyposis Syndrome (JPS) (5 or more hamartomatous gastrointestinal polyps or any number of polyps in addition to a family history of polyposis).

Once a family member has had a mutation identified, relatives are eligible for site specific testing.

Assay: Direct mutation analysis by full sequencing of *SMAD4*.

Sensitivity: Approximately 20% of individuals affected with JPS have mutations in the *SMAD4* gene. (Reference: *The Rate of Germline Mutations and Large Deletions of SMAD4 and BMPR1A in juvenile polyposis. Clin Genet, 75:79-85, 2009*).

Approximately 2-3% of HHT patients who are negative for *ENG* or *ALK1* mutations may have a *SMAD4* mutation. (Reference: *SMAD4 Mutations Found in Unselected HHT Patients. J. Med.Genet. 43:793-7, 2006*).

Full sequencing identifies the mutation >99% of the time. Mutations in non-coding sequences, insertions, deletions or other rearrangements will not be detected by sequencing.

Turnaround: 8-10 weeks for screening, 2-3 weeks for familial mutation

Fees: \$560 for full sequencing, \$340 for known familial mutation \$340 for prenatal diagnosis

CPT codes: Full sequencing-83891, 83894x5, 83898x8, 83904x8, 83909x2, 83912
Familial mutation-83891, 83898x6, 83904x6, 83912
Prenatal diagnosis-83891x2, 83898x4, 83904x5, 83912

SMAD 4 Testing INSTRUCTIONS FOR SAMPLE SUBMISSION

Documentation: Each sample must be accompanied by:

1. A requisition for DNA analysis completed by the physician, nurse or genetic counselor requesting screening. ***Please note: ICD-9 code is required for billing purposes. If ICD-9 code is unknown, please provide patient's clinical symptom(s) or family history that prompted testing.***
2. The patient's pedigree to include three generations, if possible.
3. An informed consent signed by the patient (if under 18 years of age, the parent or guardian should sign) and the professional obtaining the consent. Please have the patient initial at the top of each page and send **all** pages of the consent.
4. A verification of blood tubes form signed by the patient, parent or guardian. The form should be signed at the time of the blood draw.
5. A completed registration form with check, money order, credit card authorization or information for billing the referring institution.

IN THE EVENT THAT ALL PROPERLY COMPLETED FORMS DO NOT ACCOMPANY THE SPECIMEN, YOU WILL BE NOTIFIED, AND TESTING WILL BE HELD UNTIL PAPERWORK IS COMPLETE.

Preparing Sample:

- Obtain 2 EDTA tubes (lavender top) of blood - approx. 4 mL per tube
- Label each tube with the patient's name and date sample was obtained
- We accept banked or recently extracted DNA; please include the concentration.

- For prenatal testing: cultured amniotic fluid or CVS cells, 2 confluent T-25 flasks. Please call the lab prior to sending a prenatal sample. We are often able to offer testing on a direct villi or amnio sample, and we can discuss the requirements with you. 5mL of whole blood from each parent should accompany the prenatal sample.

Shipping Sample: Ship at room temperature via Federal Express or other overnight courier that guarantees AM delivery to arrive Monday-Friday. There is no one in the laboratory evenings and weekends to receive samples. If sample is drawn on a Friday, please refrigerate it until shipment on the following business day.

Shipping Address: Genetic Diagnostic Laboratory
University of Pennsylvania
415 Anatomy-Chemistry Building
3620 Hamilton Walk
Philadelphia, PA 19104

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REQUEST FOR SMAD4 TESTING

PATIENT FIRST NAME _____ PATIENT LAST NAME _____
BIRTH DATE _____ SEX _____ RACE _____ ETHNICITY _____
STREET ADDRESS _____
CITY _____ STATE _____ ZIP _____ HOME PHONE _____

Check any HHT symptoms in this patient: telangiectases, location _____
 nosebleeds, frequency _____ PAVM CAVM GI Bleeding
 juvenile polyps positive family history (please include a three generation pedigree)
 Patient is at-risk for HHT or juvenile polyposis but is currently asymptomatic
Has anyone in the family had DNA testing for HHT? No Yes
If yes, who and where was testing done? _____
What was the result? _____

REFERRING PHYSICIAN _____ PHONE _____ FAX _____

GENETIC COUNSELOR _____ PHONE _____ FAX _____

EMAIL ADDRESS FOR COUNSELOR OR PHYSICIAN _____
INSTITUTION and
DEPARTMENT _____

STREET ADDRESS _____

CITY _____ STATE _____ ZIP _____ COUNTRY _____

ICD-9 CODE (or patient's clinical symptoms) _____

TEST REQUESTED

- Full Sequencing of the coding regions of *SMAD4*
 Screening for known familial sequencing mutation in *SMAD4*
 Prenatal diagnosis of known familial sequencing mutation in *SMAD4*

Please include a copy of genetic result for affected family member for any familial or prenatal test requests
For all prenatal requests, please call the laboratory to discuss requirements; 5mL of whole blood from both parents should accompany any prenatal sample for MCC studies.

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Patient Registration Form

Please provide the following information. We cannot perform your test without ALL of this information. PLEASE PRINT ALL ANSWERS

PATIENT INFORMATION

LAST FIRST MI

PATINET'S MAIDEN NAME IF PREVIOUS TESTING WAS PERFORMED

Date of Birth: _____

Gender: ___ Male ___ Female

Patient Address: _____
STREET/APT NO.

CITY, STATE, ZIP COUNTRY IF OUTSIDE UNITED STATES

HOME TELEPHONE

REFERRING PHYSICIAN

NAME MD DO OTHER

INSTITUTION

STREET ADDRESS

CITY, STATE, ZIP

TELEPHONE

FAX

PAYMENT OPTIONS (must choose one) [a receipt will be mailed to patient for self-pay options]

_____ I have enclosed a check payable to the "Genetic Diagnostic Laboratory" for \$ _____

_____ Please charge my credit card for the amount of \$ _____
___ VISA ___ Master Card ___ Discover ___ American Express

Card Number: _____ Exp date: _____

Name as it appears on card: _____

_____ I have Pennsylvania Medicaid. A copy of my Medicaid card is attached.

_____ INSTITUTIONAL BILLING: The Institution where my testing originated has agreed to pay all charges for the testing. INCLUDE Billing Address, Person Authorizing Payment, Telephone, and Fax below:

BILLING ADDRESS

BILLING ADDRESS

PERSON AUTHORIZING PAYMENT

PHONE

FAX

Verification of Correctly Identified Blood Tubes

I am a participant in genetic DNA testing.

I have been shown the tubes containing my blood for this genetic testing and my name has been correctly placed on each one of these tubes.

I have signed a copy of the consent form regarding this genetic testing to be sent along with my blood samples. I have been given a copy of the consent form to keep.

Participant Name: _____

Participant/Parent Signature: _____

Date: _____

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Informed Consent: Genetic Testing for Mutations in the *SMAD4* Gene

BACKGROUND:

Hereditary hemorrhagic telangiectasia (HHT), also called Osler-Weber-Rendu disease, is a blood vessel disorder characterized by abnormal, direct connections between arteries and veins. Telangiectases are small abnormal blood vessels, which appear as red spots often found on the lips, tongue, fingers, intestines, or nose. Larger abnormal blood vessels, called arteriovenous malformations (AVMs), can occur in the internal organs, most commonly the lung, liver, and brain. Bleeding telangiectases in the nose or intestines can be either a minor annoyance or a major medical problem, sometimes requiring transfusions. Undetected and untreated lung and brain AVMs are significant causes of life-threatening or disabling complications in individuals with HHT.

Familial juvenile polyposis (JP) is an autosomal dominant disease in which individuals are predisposed to hamartomatous polyps and gastrointestinal cancer. Twenty percent of JPS patients have been shown to have a mutation in *SMAD4*. Some individuals with the combined HHT and JP syndrome carry a mutation in the *SMAD4* gene.

PURPOSE:

I, or my child, will be tested for alterations in the *SMAD4* gene. I understand that the testing will take approximately 8-10 weeks to complete. The purpose of this genetic testing is to determine whether I, or my child, have an alteration in the *SMAD4* gene. Both men and women with an alteration in this gene are at a significantly increased risk of developing hamartomatous polyps, gastrointestinal cancer, and/or symptoms of hereditary hemorrhagic telangiectasia (HHT). Individuals identified with *SMAD4* alterations can benefit from medical management specifically designed to minimize the complications of clinical symptoms.

TESTING PROCEDURE:

Genetic testing requires several teaspoons (2 tubes) of blood. Before my blood is drawn, I will watch as my name is written correctly on empty blood tubes, and after my blood is drawn I will sign a form indicating that I have positively identified the tubes containing my blood. The blood sent to the laboratory will be divided into two separate samples. The first sample will be used to complete the genetic testing. The second sample will be tested to confirm the diagnosis if the first sample indicates an alteration. There will be no additional charge for the confirmation testing.

I understand that there are laboratory fees for the genetic testing, and I have discussed the payment options with the ordering physician. I understand that I am responsible for payment for testing regardless of the outcome.

RISKS AND DISCOMFORTS:

I understand that there is usually a minimal amount of risk involved in drawing a blood sample. These include pain at the blood drawing site, bleeding, bruising and infection.

The risks of disclosure of information regarding my genetic susceptibility to telangiectases, AVMs or juvenile polyposis include depression, anxiety, anger, and fear of the future. This result could affect my relationships with family members and loved ones. I understand that if I learn that I have an altered *SMAD4* gene, my ability to obtain health, disability or life insurance could be affected. Certain health, disability and life insurance companies may consider an inherited *SMAD4* alteration to be a "pre-existing condition," and I may be responsible for disclosing this prior to obtaining new health or life insurance.

Initials _____

PROBAND SEQUENCING

I may learn that my, or my child's, results are inconclusive at the present time and that the laboratory was unable to determine whether I have a clinically significant *SMAD4* alteration.

ALTERNATIVE TO GENETIC TESTING:

I understand that my participation in this testing is completely voluntary and will not affect my medical treatment now or in the future. The alternative is not to undergo testing; in which case I will not learn whether I have an altered form of the *SMAD4* gene. This decision is perfectly acceptable.

RESULTS:

When results of the laboratory testing are available, I will be given the option of postponing or declining disclosure of these results.

I understand that there are three possible results to this testing:

1. I may learn that I, or my child, have a clinically significant altered *SMAD4* gene. I understand that this means that there is a high risk to developing clinical symptoms of hereditary hemorrhagic telangiectasia (HHT) and/or juvenile polyposis.
2. I may learn that the testing did not detect an altered *SMAD4* gene. I know that the methods currently in use might be unable to detect all mutations and I, or my child, may still have a DNA mutation that was not detected by the current technology.
3. The laboratory may detect an alteration in the *SMAD4* gene of currently unknown significance, called a "variant of unknown significance (VUS)". Our laboratory will work with your physician to help determine if the VUS can be further classified as to whether it is disease-causing for HHT and/or juvenile polyposis.

BENEFITS OF RECEIVING INFORMATION:

This study may provide information about whether my relatives, including my children, are at high risk of developing telangiectases, AVMs, or juvenile polyposis. If I am found to have a clinically significant alteration, I may choose to advise my relatives of this finding. They can have counseling and decide whether or not they wish to be tested to see if they inherited the same alteration.

If I do have an altered *SMAD4* gene, I will be able to initiate a comprehensive surveillance plan for the early detection of telangiectases, AVMs or polyps of the colon. It is the opinion of acknowledged experts in the field that enhanced surveillance will be of benefit. Prenatal and pre-implantation diagnosis will also be available options once a mutation is identified.

LIMITATIONS OF DNA TESTING FOR SMAD4:

I understand that there are limitations as to what these test results can tell me. This testing is intended to provide me with an estimate about my lifetime chance of developing telangiectases, AVMs or juvenile polyposis.

If an alteration is detected in me, there is a 50% chance the alteration has been passed on to each of my children or will be passed on to any future children.

USE OF SPECIMENS:

I understand that any blood or tissue specimens obtained for the purposes of this genetic testing become the exclusive property of the Genetic Diagnostic Laboratory. After the specific tests requested have been completed and reported, the Laboratory may dispose of, retain, or preserve these specimens and may use these specimens for research. I understand that my identity will be protected and that research results will not be provided to me or to any other party. If there are new developments in the field, my physician/genetic counselor may be contacted by the Genetic Diagnostic Laboratory staff to offer me the opportunity to have additional clinical testing. If use of this genetic material results in a scientific publication, it will not contain any identifying information.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about this testing and my results at any time. At the Genetic Diagnostic Laboratory, Susan Walther, MS, CGC (215-573-9161) and Arupa Ganguly, PhD, FACMG (215-898-3122) will be available to answer questions as they arise. I will be given a copy of this consent form to keep.

I have explained to _____ the purpose of this genetic testing, the procedures required and the possible risks and benefits to the best of my ability.

Printed Name of Professional Obtaining Consent

Signature of Professional Obtaining Consent

Date

CONSENT OF PATIENT:

I have read and received a copy of this consent form. I agree to have genetic testing and accept the risks. I understand the information provided in this document, and I have had the opportunity to ask questions I might have about the testing, the procedure, the associate risks and the alternatives.

Printed Name of Patient

Patient's DOB

Signature of Patient

Date

CONSENT OF PARENT OR GUARDIAN:

I have read and received a copy of this consent form. I agree to have genetic testing performed for my child and accept the risks. I understand the information provided in this document, and I have had the opportunity to ask questions I might have about the testing, the procedure, the associate risks and the alternatives.

Printed Name of Parent/Guardian

Relationship to Child

Signature of Parent/Guardian

Child's Name

Child's DOB

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Informed Consent: Genetic Testing for *SMAD4* Known Familial Mutation

BACKGROUND:

Hereditary hemorrhagic telangiectasia (HHT), also called Osler-Weber-Rendu disease, is a blood vessel disorder characterized by abnormal, direct connections between arteries and veins. Telangiectases are small abnormal blood vessels, which appear as red spots often found on the lips, tongue, fingers, intestines or nose. Larger abnormal blood vessels called arteriovenous malformations (AVMs) can occur in the internal organs, most commonly the lung, liver and brain. Bleeding telangiectases in the nose or intestines can be either a minor annoyance or a major medical problem, sometimes requiring transfusions. Undetected and untreated lung and brain AVMs are a significant cause of life-threatening or disabling complications in individuals with HHT.

Juvenile Polyposis Syndrome (JPS) is an autosomal dominant disease in which individuals are predisposed to hamartomatous polyps and gastrointestinal cancer. Twenty percent of JPS patients have been shown to have a mutation in *SMAD4*.

Some individuals with combined HHT and JPS carry a mutation in the *SMAD4* gene.

PURPOSE:

I, or my child, will be tested for the alteration in the *SMAD4* gene which has been identified in one of my family members. I understand that the testing will take approximately 2-3 weeks to complete. The purpose of this genetic testing is to determine whether I, or my child, have an altered *SMAD4* gene. I have had the opportunity to discuss the benefits and drawbacks of *SMAD4* testing for myself or my child. No information pertaining to my genetic test results will be provided to anyone without my express written consent. No information will be provided to me by phone or mail from the University of Pennsylvania, regardless of the outcome.

TESTING PROCEDURE:

Genetic testing requires several teaspoons (2 tubes) of blood. Before my blood is drawn, I will watch as my name is written correctly on empty blood tubes, and after my blood is drawn I will sign a form indicating that I have positively identified the tubes containing my blood. The blood sent to the laboratory will be divided into two separate samples. The first sample will be used to complete the genetic testing. The second sample will be tested to confirm the diagnosis if the first sample indicates an alteration. There will be no additional charge for the confirmation testing.

I understand that there are laboratory fees for the genetic testing, and I have discussed the payment options with the ordering physician. I understand that I am responsible for payment for testing regardless of the outcome.

RISKS AND DISCOMFORTS:

I understand that there is usually a minimal amount of risk involved in drawing a blood sample. These include pain at the blood drawing site, bleeding, bruising and infection.

The risks of disclosure of information regarding my genetic susceptibility to telangiectases, AVMs or juvenile polyposis include depression, anxiety, anger, and fear of the future. This result could affect my relationships with family members and loved ones. I understand that if I learn that I have an altered *SMAD4* gene, my ability to obtain health, disability or life insurance could be affected. Certain health, disability and life insurance companies may consider an inherited *SMAD4* alteration to be a

Initials _____

FAMILIAL MUTATION

"pre-existing condition," and I may be responsible for disclosing this prior to obtaining new health or life insurance.

Some individuals may experience feelings of guilt or other forms of anxiety if they are found not to have an altered gene, while other family members did inherit an altered gene.

ALTERNATIVE TO GENETIC TESTING:

I understand that my participation in this testing is completely voluntary and will not affect my medical treatment now or in the future. The alternative is not to undergo testing; in which case I will not learn whether I have an altered form of the *SMAD4* gene. This decision is perfectly acceptable.

RESULTS:

I understand that there are two possible results to this testing:

1. I may learn that I, or my child, have a clinically significant altered *SMAD4* gene. I understand that this means that I, or my child, have a very high probability to develop juvenile polyps, telangiectases and AVMs
2. I may learn that the testing did not detect the altered *SMAD4* gene.

BENEFITS OF RECEIVING INFORMATION:

This study may provide information about whether my relatives, including my children, are at high risk of developing JPS or HHT. If I am found to have a clinically significant alteration, I may choose to advise my relatives of this finding. They can have counseling and decide whether or not they wish to be tested to see if they inherited the same alteration. This study will provide me with the information currently available regarding my genetic predisposition and may enable me to make better choices about planning my career, my family and children, and my health care needs. If I, or my child, do have an altered gene, I will be able to initiate a comprehensive surveillance plan for the early detection of juvenile polyps, telangiectases and AVMs. It is the opinion of acknowledged experts in the field that enhanced surveillance will be of benefit.

If a gene alteration is not detected I may experience some sense of relief as a result.

USE OF SPECIMENS:

I understand that any blood or tissue specimens obtained for the purposes of this genetic testing become the exclusive property of the Genetic Diagnostic Laboratory. After the specific tests requested have been completed and reported, the Laboratory may dispose of, retain, or preserve these specimens and may use these specimens for research. I understand that my or my child's identity will be protected and that research results will not be provided to me or to any other party. If there are new developments in the field, my physician/genetic counselor may be contacted by the Genetic Diagnostic Laboratory staff to offer me the opportunity to have additional clinical testing.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about this testing and my results at any time. At the Genetic Diagnostic Laboratory, Susan Walther, MS, CGC (215-573-9161) and Arupa Ganguly, PhD, FACMG (215-898-3122) will be available to answer questions as they arise. I will be given a copy of this consent form to keep.

FAMILIAL MUTATION

I have explained to _____ the purpose of this genetic testing, the procedures required and the possible risks and benefits to the best of my ability.

Printed Name of Professional Obtaining Consent

Signature of Professional Obtaining Consent

Date

CONSENT OF PATIENT:

I have read and received a copy of this consent form. I agree to have genetic testing and accept the risks. I understand the information provided in this document, and I have had the opportunity to ask questions I might have about the testing, the procedure, the associate risks and the alternatives.

Printed Name of Patient

Patient's DOB

Signature of Patient

Date

CONSENT OF PARENT OR GUARDIAN:

I have read and received a copy of this consent form. I agree to have genetic testing performed for my child and accept the risks. I understand the information provided in this document, and I have had the opportunity to ask questions I might have about the testing, the procedure, the associate risks and the alternatives.

Printed Name of Parent/Guardian

Relationship to Child

Signature of Parent/Guardian

Child's Name

Child's DOB