

Fibrodysplasia Ossificans Progressiva (FOP)

Background: FOP is a disorder of heterotopic (extraskelatal) ossification in which muscles and connective tissue, such as tendons and ligaments, are replaced by bone over time. This bone formation generally begins in early childhood and typically initiates in the neck and shoulders. Malformation of the great toe is another characteristic clinical feature. The incidence of FOP is ~ 1 in 2 million. Most cases are spontaneous mutations with no prior family history, but autosomal dominant inheritance has been observed.

Assay: DNA is isolated from a blood sample and PCR is performed for coding exon 4 of the Activin Receptor Type 1A gene (ACVR1) and sequenced with positive and negative controls.

Eligibility: Individuals suspected on a clinical basis to be affected.

Utility: Diagnostic confirmation.

Sensitivity: Heterozygous mutations in the ACVR1 gene at c.617G>A (Arg206His) have been identified in patients with classic features of FOP in 100% of cases. It is possible that patients with heterotopic ossification and atypical features of FOP (FOP variants) may not carry the ACVR1 c.617G>A mutation.

Turnaround: 3 weeks

Fee: \$380

CPT codes: 83891, 83898x7, 83904x5, 83909x2, 83912

Additional Information: International Fibrodysplasia Ossificans Progressiva Association

Dr. Frederick Kaplan at the University of Pennsylvania is an expert in the diagnosis and management of FOP. He is available for consultation by calling 215-349-8726.

Mutation Analysis for FOP 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 including 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

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

REQUEST FOR FIBRODYSPLASIA OSSIFICANS PROGRESSIVE (FOP) TESTING

PATIENT FIRST NAME _____ PATIENT LAST NAME _____

BIRTH DATE _____ SEX _____ RACE _____ ETHNICITY _____

STREET ADDRESS _____

CITY _____ STATE _____ ZIP _____ HOME PHONE _____

Does the patient have extra-skeletal bone formation? No Yes

If yes, list locations and age of appearance: _____

Does the patient have any additional skeletal abnormalities? _____

Does the patient have malformed great toes? Hallux Valgus Malformed 1st metatarsal
 Monophalangism None

Does the patient have tibial osteochondromas? No Yes

Additional clinical observations: _____

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

_____ Point mutation analysis of c.617G>A in ACVR1

_____ Prenatal Diagnosis of c.617G>A in ACVR1 (please call the lab prior to sending a fetal sample)

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: _____

Initials _____

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**Informed Consent for Genetic Testing for a Specific Mutation in
Fibrodysplasia Ossificans Progressiva (FOP) (ACVR1 c.617G>A)**

BACKGROUND:

Fibrodysplasia ossificans progressiva (FOP) is a disorder of heterotopic (extra-skeletal) ossification in which muscles and connective tissue such as tendons and ligaments are replaced by bone over time. This bone formation generally begins in early childhood and typically initiates in the neck and shoulders. Malformation of the great toe is another characteristic clinical feature.

The incidence of FOP is ~1 in 2 million. Most cases are spontaneous (new) mutations with no previous family history, although autosomal dominant inheritance is also observed. Heterozygous mutations in the ACVR1 gene at c.617G>A (Arg206His) have been identified in patients with classic features of FOP (progressive heterotopic ossification and malformed great toes) in 100% of cases. It is possible that patients with heterotopic ossification and atypical features of FOP (FOP variants) may not carry the ACVR1 c.617G>A mutation.

PURPOSE:

I, or my child, will be tested for the alteration in the ACVR1 gene that has been identified as a fibrodysplasia ossificans progressiva (FOP) disease associated mutation. I understand that the testing will take approximately 2-4 weeks to complete. The purpose of this genetic testing is to determine whether I, or my child, have an altered FOP gene that is involved in the development of FOP. I have had the opportunity to discuss the benefits and drawbacks of gene testing for myself or my child. No information pertaining to the genetic test results will be provided to any of my relatives or any other parties without my written consent.

TESTING PROCEDURE:

Genetic testing requires several teaspoons (2 tubes) of blood. Before the blood is drawn, I will watch as my name, or my child's name is written correctly on empty blood tubes and after the blood is drawn I will sign a form indicating that I have positively identified the tubes containing the blood. The results of the testing will be provided to the care provider who ordered the tests. No test results will be provided to me by phone or mail from the University of Pennsylvania Genetic Diagnostic Laboratory, 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 diagnosis of FOP 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 ACVR1 gene, my health and life insurance rates, my ability to obtain health, disability or life insurance and my employability could be affected. Certain health, disability and life insurance companies may consider an inherited ACVR1 alteration to be a "pre-existing condition," and I may be responsible for disclosing this prior to obtaining new health or life insurance.

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 ACVR1 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 alteration in ACVR1 gene. I understand that this means that I, or my child, have a very high probability to develop FOP disease.
- 2) I may learn that the testing did not detect the altered ACVR1 gene.

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 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 PARENT OR GUARDIAN:

I have read and received a copy of this consent form. I agree to have genetic testing for FOP 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

Signature of Parent/Guardian

Date

Relationship to Child

Name of Child: _____ Child’s DOB: _____

CONSENT OF PATIENT

I have read and received a copy of this consent form. I agree to have genetic testing for FOP performed for myself 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