UAB MEDICAL GENOMICS LABORATORY

Next-Gen Sequencing of *GNAS* Only (GNAS-NG)

Ordering Information

Acceptable specimen types:

- Fresh blood sample (3-6 ml EDTA; no time limitations associated with receipt)
- Saliva (OGR-575 DNA Genotek; kits are provided upon request)
- DNA (extracted from lymphocyte cells; a minimum volume of 25µL at 3µg; O.D. of 260:280nm ≥1.8; must be extracted in a CLIA or equivalent certified lab)

Turnaround time:

25 working days

Price, CPT codes, and Z code:

$700 (USD – institutional/self-pay);

CPT: 81479

Z code: ZB67W

Candidates for this test:

Patients with abnormal CAL spots (frequently large and with irregular borders); clear polyostotic fibrous dysplasia, which may present as fractures, uneven bone growth, or deformity; and/or precocious puberty or other endocrine problems.

Specimen shipping and handling:

- Please find acceptable specimen type above.
- All submitted specimens must be sent at room temperature. DO NOT ship on ice.

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www.uab.edu/medicine/genetics/medical-genomics-laboratory

- Specimens must be packaged to prevent breakage and absorbent material must be included in the package to absorb liquids in the event that breakage occurs. Also, the package must be shipped in double watertight containers (e.g. a specimen pouch + the shipping company's diagnostic envelope).
- To request a sample collection kit, please visit the website or email medgenomics@uabmc.edu to complete the specimen request form.
- Please contact the MGL (via email at medgenomics@uabmc.edu, or via phone at 205-934-5562) prior to sample shipment and provide us with the date of shipment and tracking number of the package so that we can better ensure receipt of the samples.

Required forms:

- Test Requisition Form
- Form for Customs (for international shipments)

Note: Detailed and accurate completion of this document is necessary for reporting purposes. The Medical Genomics Laboratory issues its clinical reports based on the demographic data provided by the referring institution on the lab requisition form. It is the responsibility of the referring institution to provide accurate information. If an amended report is necessary due to inaccurate or illegible documentation, additional reports will be drafted at charge.

Requests for testing may not be accepted for the following reasons:

- No label (patients full name and date of collection) on the specimens
- No referring physician's or genetic counselor's names and addresses
- No billing information
- DNA samples must be extracted in a CLIA or equivalent certified lab

For more information, test requisition forms, or sample collection and mailing kits, please call: 205-934-5562.

Disorder Background

The UAB Medical Genomics Laboratory now provides testing for *GNAS* given the overlap between segmental/mosaic NF1/Legius syndrome and McCune-Albright syndrome. The disorder is characterized by polyostotic fibrous dysplasia, café-au-lait hyperpigmentation and precocious puberty. The disorder is highly variable, depending on the specific tissues involved and the extent of the involvement. Part of this variability can be accounted for by the fact that pathogenic GNAS variants are not inherited, as completely affected embryos are thought to be incompatible with life, meaning that all variants occur *de novo* and pathogenic variants are not present in every cell in the body (mosaic).

The *GNAS* gene codes for an alpha subunit of the stimulatory guanine nucleotide-binding protein (G protein), which is responsible for transducing extracellular signals received by transmembrane receptors in a cascade to effector proteins. The majority of all GNAS-related pathogenicity is caused by gain-of-function postzygotic somatic GNAS variants in exon 8 or 9, which leads to a constitutively active G protein. *GNAS*-related G protein over-activation results in the overproduction of a number of hormones associated with abnormal bone growth and other symptoms of McCune-Albright syndrome.

Test Description

The DNA-based ***GNAS*-only by NGS** involves NextGen sequencing of exons 8 and 9. The test uses an extensively customized and optimized set of Agilent HaloPlex capture probes, followed by sequencing of overlapping amplicons within the regions of interest using 300bp paired-end Illumina sequencing chemistry. Each coding exon plus ~50bp of flanking intronic sequence are simultaneously sequenced. 5' and 3' untranslated sequences are not included.

The average coverage of the *GNAS*-only by NGS for exons 8 and 9 is >2500x, allowing detection of very low level mosaicism, down to 3% variant allele fraction with 95% confidence.

REFERENCES available on website.

Other related testing options:

- Next-Gen Sequencing and Deletion/Duplication analysis of *NF1* only (NF1-NG)
- Expanded *NF1*-Rasopathy panel by Next-Gen Sequencing (RAS-NG)
- RNA-based *NF1* testing on blood (NF1-R)
- RNA-based *NF1* and DNA-based SPRED1 testing on blood (NFSP-R)
- RNA-based *NF1/SPRED1* testing on affected tissues (NF14N/NF14C)