Clinical Features:
Bilateral frontoparietal polymicrogyria (BFPP) [OMIM #606854] is characterized by moderate-severe mental retardation, seizures, dysconjugate gaze, and characteristic radiological findings. Piao X, et al [2005] suggest the following diagnostic criteria: (1) moderate-severe mental retardation; (2) delay of motor development; (3) seizures; (4) cerebellar signs, primarily ataxia; (5) dysconjugate gaze; (6) bilateral polymicrogyria (more accurately "cobblestone malformation") with anterior to posterior gradient; (7) bilateral patchy white matter signal changes; and (8) brainstem and cerebellar hypoplasia (1). The "polymicrogyria" is actually atypical and more closely resembles the brain malformation seen in muscle-eye-brain disease, known as a "cobblestone malformation". Developmental delay and gaze issues present in early childhood, whereas seizures may not begin until after 5 years of age. Patients with GPR56-associated BFPP do not have findings outside of the central nervous system.

Molecular and Biochemical Genetics:
Mutations of the GPR56 [OMIM #604110] gene, or G-protein coupled receptor 56, have been identified in patients with BFPP (2). GPR56 has 13 coding exons. It appears to be necessary for human cerebral cortical development and patterning. All reported patients, to date, have homozygous mutations. Piao X, et al [2005] studied patients with BFPP along with some patients with other polymicrogyria syndromes. All 29 patients with BFPP were found to be homozygous for GPR56 mutations. However, no patients without the BFPP cortical distribution or without both white matter and posterior fossa changes were found to mutations in GPR56 (1).

Inheritance:
GPR56-related BFPP is inherited in an autosomal recessive pattern. Parents of an affected child are most likely obligate carriers. Recurrence risk for carrier parents is 25%.

Additional Resources:
The Lissencephaly Network  www.lissencephaly.org
Phone: 260-432-4310  Email: li ssnet@lissencephaly.org

The Brain Malformation Research Project at The University of Chicago
William B. Dobyns, Principal Investigator
Contact Mary King at 773-702-8247

Test methods:
Comprehensive sequence coverage of the coding regions and splice junctions of the GPR56 gene is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. The constructed genomic DNA library is sequenced using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20bp.

Deletion/duplication analysis is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.
Please, send a completed GPR56 Clinical Checklist and patient consent form with each sample.

This information will be used to aid in interpretation of the test result. The clinical data form, along with the test result, will be shared with Dr. Dobyns and stored anonymously in a GPR56 database. Patients with BFPP, with or without GPR56 gene mutations, can enroll in Dr. Dobyns’ research study.

GPR56 sequencing may be ordered alone, or as part of our Polymicrogyria panel which includes sequencing of a total of 7 genes. Please see our information sheet on our Polymicrogyria Next Generation Sequencing Panel for more details.

**GPR56 sequencing analysis**
- Sample specifications: 3 to 10cc of blood in a purple top (EDTA) tube
- Cost: $1000
- CPT codes: 81406
- Turn-around time: 4 weeks

**GPR56 deletion/duplication analysis**
- Sample specifications: 3 to 10cc of blood in a purple top (EDTA) tube
- Cost: $1000
- CPT codes: 81405
- Turn-around time: 4 weeks

**Results:**
You will be informed of the results of your case as soon as it has been completed. Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

*For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.*

**References:**