Clinical Features:
Nicolaides-Baraitser syndrome [NCBRS OMIM #601358] is characterized by severe intellectual disability, early-onset seizures, short stature and sparse hair. Dysmorphic features include thick, anteverted alae nasi, long and broad philtrum, large mouth and thin upper and thick lower vermilion (1). Clinical overlap exists between NCBRS and Coffin-Siris syndrome [CSS OMIM #135900], however CSS differs in the presence of severely hypoplastic or absent fifth finger nails with or without hypoplasia of the terminal phalanges.

Molecular Genetics:
Van Houdt et al, 2012 identified mutations in SMARCA2 in 36/44 individuals with NCBRS (2). In the cases where parental samples were available; all mutations were confirmed to be de novo. SMARCA2 is a member of the SNF2 family of helicase-related proteins that are characterized by the presence of the conserved Snf2 family ATPase domain that is required for transcriptional activity.

Inheritance:
To date, all cases of NCBGRS have been sporadic. Recurrence risk for unaffected parents of an isolated case is low (<1%), but germline mosaicism is possible.

Test methods:
Comprehensive sequence coverage of the coding regions and splice junctions of the SMARCA2 gene is performed. Comprehensive sequence coverage of the coding regions and splice junctions of this gene is performed. Targets of interest are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed 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 novel and/or potentially 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 20 bp.

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.

SMARCA2 sequencing
Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $2200
CPT codes: 81407
Turn-around time: 4 weeks

SMARCA2 deletion/duplication
Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: $1000
CPT codes: 81406
Turn-around time: 4 weeks
Results:
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.

References: