THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

# SHORT syndrome testing: Mutation analysis of *PIK3R1*

## Clinical Features:

SHORT syndrome [MIM# 269880] is an acronym: S = short stature; H = hyperextensibility of joints and/or hernia (inguinal); O=ocular depression; R = Rieger anomaly; T = teething delay. Additional features include characteristic facial features, partial lipodystrophy, insulin resistance, hearing deficits and nephrocalcinosis (1). Affected individuals have a thin body habitus and developmental milestones and cognition is typically normal. Onset of insulin resistance and/or diabetes mellitus typically occurs in adolescence (2)

## Molecular Genetics:

Mutations of the *PIK3R1* [OMIM #171833] gene have been identified in patients with SHORT syndrome. *PIK3R1* has 16 coding exons and is located at 5q13.1. The phosphatidylinositol 3 kinase pathway regulates fundamental cellular processes and its normal activity is critical for adipose differentiation and insulin signaling (3). By whole-exome sequencing, mutations in the *PIK3R1* gene were identified in 2 unrelated patients with SHORT syndrome by Thauvin-Robinet et al. (2013) and in 1 patient with SHORT syndrome by Dyment et al. (2013). Screening *PIK3R1* for mutations in 7 more affected individuals revealed a recurrent missense mutation in all patients (1, 2).

## Inheritance:

Mutations in *PIK3R1* are autosomal dominant and the majority of mutations to date have been *de novo*. However, due to the variability in expression, parents of affected individuals may be carriers. Recurrence risk for affected individuals and carrier parents is 50%.

## Test Methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *PIK3R1* gene is performed. Targets of interests 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 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 20 bp. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

*PIK3R1* sequencing and deletion/duplication analysis

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| Sample specifications: | 3 to 10cc 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.

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

## References:

1. Dyment DA, Smith AC, Alcantara D et al. Mutations in PIK3R1 cause SHORT syndrome. Am J Hum Genet 2013: 93: 158-166.
2. Thauvin-Robinet C, Auclair M, Duplomb L et al. PIK3R1 mutations cause syndromic insulin resistance with lipoatrophy. Am J Hum Genet 2013: 93: 141-149.
3. Chudasama KK, Winnay J, Johansson S et al. SHORT syndrome with partial lipodystrophy due to impaired phosphatidylinositol 3 kinase signaling. Am J Hum Genet 2013: 93: 150-157.