THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

INSR Analysis for Type A Insulin Resistant Diabetes with Acanthosis Nigricans

Clinical Features

Heterozygous mutations in *INSR* [OMIM#147670] have been described in patients with type A insulin resistance [OMIM#610549], which is a type of extreme insulin resistance characterized by hyperinsulinemia and acanthosis nigricans, in addition to signs of hyperandrogenism in normal weight females without lipodystrophy (1). Homozygous or compound heterozygous mutations in *INSR* have been associated with Donohue syndrome [OMIM#246200] and Rabson-Medenhall syndrome [OMIM#262190], which are severe insulin resistance disorders characterized by intrauterine and postnatal growth retardation, facial dysmorphism, lack of subcutaneous fat, hyperinsulinemia, acanthosis nigricans and reduced life expectancy (1).

Molecular Genetics

INSR encodes for the insulin receptor, and mutations in this gene lead to resistance to the physiological effects of insulin, and consequent compensatory increased insulin secretion (1, 2). It is thought that phenotypic severity is determined by the degree of insulin binding capacity that remains (1). Heterozygous mutations are hypothesized to have a dominant negative effect and interfere with the function of the normal allele (2). Patients with the most severe *INSR*-related disorder, Donohue syndrome, have severely reduced insulin binding, whereas those with the less severe Rabson-Mendenhall syndrome retain some insulin binding capacity (1).

Inheritance

INSR-related disorders may be either autosomal dominant or autosomal recessive (2). Mutations associated with type A insulin resistance are typically dominant, and children of an affected individual have a 50% risk of being affected. Donahue and Rabson-Mendenhall syndromes follow an autosomal recessive inheritance pattern. Therefore, parents of an affected child are most likely obligate carriers. Recurrence risk for carrier parents is 25%.

Test methods

Comprehensive sequence coverage of the coding regions and splice junctions of the *INSR* 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 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 20bp. Deletion/duplication analysis of the *INSR* gene by oligonucleotide array-CGH identifies copy number changes involving one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. 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.

INSR sequencing

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

INSR deletion/duplication analysis

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Cost:	$1000
CPT codes:	81405
Turn-around time:	4 weeks

Note: The sensitivity of our assay may be reduced when DNA is extracted by an outside laboratory.

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. Takahashi I, Yamada Y, Kadowaki H et al. Phenotypical variety of insulin resistance in a family with a novel mutation of the insulin receptor gene. Endocr J 2010: 57: 509-516.
2. Suliman SG, Stanik J, McCulloch LJ et al. Severe insulin resistance and intrauterine growth deficiency associated with haploinsufficiency for INSR and CHN2: new insights into synergistic pathways involved in growth and metabolism. Diabetes 2009: 58: 2954-2961.

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