

Inherited Insulin Resistance Syndromes (INSR) Genetic Testing

Extreme insulin resistance is characterized by the inability of insulin receptors to bind to insulin, leading to ketoacidosis. Donohue syndrome (leprechaunism), Rabson-Mendenhall syndrome, and Type A insulin resistance are all caused by *INSR* gene variants. Severity of symptoms and survival rates vary greatly between syndromes.

Disease Overview

Incidence

Unknown, but estimated to be rare

Clinical Presentation

Syndromes and Associated Symptoms Caused by <i>INSR</i> Variants		
Donahue Syndrome (Most Severe)	Rabson-Mendenhall Syndrome (Intermediate Phenotype)	Type A Insulin Resistance Syndrome (Least Severe)
Intrauterine growth restriction	Growth retardation	Hirsutism
Failure to thrive	Hyperinsulinemia	Reduced subcutaneous fat
Loss of glucose homeostasis	Acanthosis nigricans	Diabetes mellitus
Hyperinsulinemia	Diabetes mellitus	Diabetes mellitus
Enlarged heart and kidneys	Dysmorphic features (premature or dysplastic teeth, gingival hyperplasia, pineal hyperplasia)	Acanthosis nigricans
Dysmorphic features (prominent eyes, thick lips, upturned nostrils, low-set and posteriorly rotated ears)	Survival ranges from early childhood to adolescence	Hyperinsulinemia
Thick skin with lack of subcutaneous fat		Amenorrhea and polycystic ovaries in females
Distended abdomen		Survival often beyond middle age
Enlarged genitalia		
Polycystic ovaries in females		
Death often occurs before 1 yr of age		

Tests to Consider

[Inherited Insulin Resistance Syndromes \(INSR\) Sequencing 2006274](#)

Method: Polymerase Chain Reaction/Sequencing

- Confirm diagnosis of inherited insulin resistance syndromes in individuals with clinical and/or biochemical evidence
- Not intended for evaluation of individuals with nonsyndromic forms of insulin resistance, such as isolated diabetes mellitus with no other physical features

See [Related Tests](#)

Pathophysiology

Insulin resistance occurs through the following process:

- Insulin receptors are unable to bind to insulin
- Insulin action on target organs decreases
- Pancreas compensates for decreased insulin action by increasing insulin release
- Pancreatic beta cells eventually unable to compensate
- Glucose production by the liver and lipolysis of adipose tissue increases
- Ketoacidosis results

Diagnosis

Inherited insulin resistance syndrome is often diagnosed based on:

- Clinical features
- Glucose and insulin levels
- Fibroblast studies for insulin binding
- Genetic testing

Genetics

Gene

INSR

Inheritance

- Donohue syndrome: autosomal recessive
- Rabson-Mendenhall syndrome: autosomal recessive
- Type A insulin resistance syndrome: autosomal recessive or autosomal dominant
 - Recessive forms are more severe
 - Dominant forms may require contribution of other genetic or environmental factors to produce phenotype

Penetrance

Unknown, but expected to be reduced for individuals with a dominant variant

Test Interpretation

Sensitivity/Specificity

Clinical sensitivity: predicted to be >90% in individuals with a clinical diagnosis

Analytical sensitivity/specificity: 99%

Results

Result	Variation Detection	Interpretation
Positive	One pathogenic <i>INSR</i> gene variant detected	Predicts carrier status for an inherited insulin resistance syndrome Depending on other genetic and environmental factors, may indicate an increased likelihood for developing type A insulin resistance
	Two pathogenic <i>INSR</i> gene variants detected	Predicts a diagnosis of an inherited insulin resistance syndrome
Negative	No pathogenic variants detected	Reduced likelihood of being a carrier of or affected with an inherited insulin resistance syndrome
Inconclusive	<i>INSR</i> gene variants of unknown clinical significance may be detected by this test	n/a

n/a, not applicable

Limitations

- Diagnostic errors can occur due to rare sequence variations
- Regulatory region and deep intronic variants and large deletions/duplications are not detected
- Genes other than *INSR* will not be evaluated
- Medical management of patient should rely on clinical and/or biochemical findings

Related Information

[Diabetes Mellitus](#)

Related Tests

[Insulin, Fasting 0070063](#)

Method: Quantitative Chemiluminescent Immunoassay

[Glucose, Plasma or Serum 0020024](#)

Method: Quantitative Enzymatic

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