Inherited Insulin Resistance Syndromes (*INSR*) Genetic Testing

Indications for Ordering

- 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

Test Description

Polymerase chain reaction, followed by bidirectional sequencing of the entire coding region and intron/exon boundaries of the *INSR* gene

Tests to Consider

Primary test

Inherited Insulin Resistance Syndromes (*INSR*) Sequencing 2006274

Related tests

Initial biochemical tests for suspicion of inherited insulin resistance syndrome

- Insulin, Fasting 0070063
- Fasting Glucose, Plasma or Serum 0020024

Disease Overview

Incidence – unknown, but estimated to be rare

Clinical presentation

Variants in the *INSR* gene cause three main syndromes

- Donohue syndrome (most severe)
  - Intrauterine growth restriction
  - Failure to thrive
  - Loss of glucose homeostasis
  - Hyperinsulinemia
  - Enlarged heart and kidneys
  - Dysmorphic features
    - Prominent eyes
    - Thick lips
    - Upturned nostrils
    - Low-set, posteriorly rotated ears
  - Thick skin with lack of subcutaneous fat
  - Distended abdomen
  - Enlarged genitalia
  - Polycystic ovaries in females
  - Death often occurs prior to age 1
- Rabson-Mendenhall syndrome (intermediate phenotype)
  - Growth retardation
  - Hyperinsulinemia
  - Acanthosis nigricans
  - Diabetes mellitus
  - Dysmorphic features
    - Premature or dysplastic teeth
    - Gingival hyperplasia
    - Pineal hyperplasia
  - Survival ranges from early childhood to adolescence
- Type A insulin resistance syndrome (least severe)
  - Hirsutism
  - Reduced subcutaneous fat
  - Diabetes mellitus
  - Acanthosis nigricans
  - Hyperinsulinemia
  - Amenorrhea and polycystic ovaries in females
  - Survival often beyond middle age

Pathophysiology

Insulin resistance occurs when insulin receptors are unable to bind insulin

- Results in decreased insulin action on target organs
  - Decreased insulin is compensated for by the pancreas with increased insulin release
    - Pancreatic beta cells become unable to compensate
      - Leads to increased glucose production by the liver and lipolysis of adipose tissue, resulting in ketoacidosis

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

- Positive
  - One copy of pathogenic *INSR* gene variant detected
    - Predicts carrier status for an inherited insulin resistance syndrome
    - In some cases, one copy of a variant may indicate an increased likelihood for developing type A insulin resistance
      - Depends on other genetic and environmental factors
  - Two pathogenic *INSR* gene variants detected
    - Predicts a diagnosis of an inherited insulin resistance syndrome
- Negative
  - No pathogenic variants detected
    - Likelihood is reduced that the individual is a carrier of or is affected with an inherited insulin resistance syndrome
- Inconclusive
  - *INSR* gene variants of unknown clinical significance may be detected by this test

Limitations

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