

INSR Gene

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1. Introduction

The *INSR* gene provides instructions for making a protein called an insulin receptor, which is found in many types of cells. Insulin receptors are embedded in the outer membrane surrounding the cell, where they attach (bind) to the hormone insulin circulating in the bloodstream. Insulin plays many roles in the body, including regulating blood sugar levels by controlling how much sugar (in the form of glucose) is passed from the bloodstream into cells to be used as energy.

The insulin receptor is initially produced as a single long protein that must be processed by being cut (cleaved) into four parts: two alpha subunits and two beta subunits. These subunits work together as a functioning receptor. The alpha subunits stick out from the surface of the cell, while the beta subunits remain inside the cell. The alpha subunits attach (bind) to insulin, which causes the beta subunits to trigger signaling pathways within the cell that influence many cell functions.

2. Health Conditions Related to Genetic Changes

2.1. Donohue Syndrome

Researchers have identified more than 150 *INSR* gene mutations that cause a spectrum of related disorders known as severe insulin resistance syndromes. These include Donohue syndrome and two other conditions, Rabson-Mendenhall syndrome and type A insulin resistance syndrome (described below). Insulin resistance is a condition in which the body's tissues and organs do not respond properly to insulin. Severe insulin resistance syndromes are characterized by problems with regulating blood sugar levels and impaired development and function of organs and tissues throughout the body. Donohue syndrome is the most severe of the three syndromes; affected children do not survive beyond age 2.

The *INSR* gene mutations associated with Donohue syndrome occur in both copies of the gene in each cell. Some of these mutations interfere with the normal processing of the protein initially produced from the *INSR* gene, which prevents the formation of a functioning insulin receptor. Other mutations impair the receptor's ability to bind to insulin or disrupt the cell signaling pathways that insulin binding normally triggers. All of these mutations greatly reduce or eliminate the function of insulin receptors. Although insulin is present in the bloodstream, without functional receptors it cannot exert its effects on cells and tissues. This severe resistance to the effects of insulin impairs blood sugar regulation and affects many aspects of development.

2.2. Rabson-Mendenhall Syndrome

INSR gene mutations also cause Rabson-Mendenhall syndrome, a severe insulin resistance syndrome whose features are intermediate in severity between Donohue syndrome (described above) and type A insulin resistance syndrome (described below). Affected individuals have features similar to those of Donohue syndrome, but they usually survive into their teens or twenties. Insulin resistance ultimately leads to a condition called diabetes mellitus, in which blood sugar levels can become dangerously high.

The *INSR* gene mutations that cause Rabson-Mendenhall syndrome occur in both copies of the gene in each cell. These mutations reduce the number of insulin receptors that reach the cell membrane or disrupt the function of these receptors, but generally not as severely as the mutations associated with Donohue syndrome. Although insulin is present in the bloodstream, without enough functional receptors it is less able to exert its effects on cells and tissues. This severe resistance to the effects of insulin impairs blood sugar regulation and affects many aspects of development.

2.3. Type A Insulin Resistance Syndrome

INSR gene mutations also underlie the mildest of the severe insulin resistance syndromes, type A insulin resistance syndrome. Females with this condition develop abnormalities of the menstrual cycle, excessive body hair growth (hirsutism), ovarian cysts, a skin condition called acanthosis nigricans, and diabetes mellitus. Affected males tend to have fewer signs and symptoms, although they also develop diabetes mellitus. The features of type A insulin resistance syndrome often do not become apparent until puberty or later, and it is generally not life-threatening.

Most of the *INSR* gene mutations that cause type A insulin resistance syndrome occur in one of the two copies of the gene in each cell. These mutations lead to the production of a faulty insulin receptor that cannot transmit signals properly. The changes are described as "dominant-negative" mutations because the faulty receptor produced from the mutated copy of the gene interferes with the normal receptor produced from the non-mutated copy of the gene. Less commonly, type A insulin resistance syndrome results from mutations in both copies of the *INSR* gene in each cell. These mutations impair the function of the insulin receptor.

Although insulin is present in the bloodstream, the defective receptors make it less able to exert its effects on cells and tissues. This severe resistance to the effects of insulin impairs blood sugar regulation and leads to diabetes mellitus. In females with type A insulin resistance syndrome, excess insulin in the bloodstream interacts with hormonal factors during adolescence to cause menstrual abnormalities, ovarian cysts, and other features of the disorder.

3. Other Names for This Gene

- CD220
- HHF5
- insulin receptor isoform Long preproprotein
- insulin receptor isoform Short preproprotein
- IR

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