



## **INSR-Related Severe Insulin Resistance Syndrome**

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### **Summary**

#### **Clinical characteristics**

*INSR*-related severe insulin resistance syndrome (*INSR*-SIRS) comprises a phenotypic spectrum that is a continuum from the severe phenotype of Donohue syndrome to the milder phenotype of Rabson-Mendenhall syndrome (RMS).

Donohue syndrome is characterized by severe insulin resistance (hyperinsulinemia with associated fasting hypoglycemia and postprandial hyperglycemia), severe prenatal growth restriction, postnatal growth failure, hypotonia, developmental delay, characteristic facies (proptosis, infraorbital folds, large, low-set, posteriorly rotated ears, thick vermilion of the upper and lower lips, and gingival hypertrophy), and organomegaly involving the heart, kidneys, liver, spleen, and ovaries. Death usually occurs before age one year.

RMS, at the milder end of the spectrum, is characterized by severe insulin resistance that, although not as severe as that of Donohue syndrome, is nonetheless accompanied by fluctuations in blood glucose levels, diabetic ketoacidosis, and – in the second decade – microvascular complications. Findings can range from severe growth delay and intellectual disability to normal growth and development. Facial features can be milder than those of Donohue syndrome. Complications of longstanding hyperglycemia are the most common cause of death. While death usually occurs in the second decade, some affected individuals live longer.

#### **Diagnosis/testing**

The diagnosis of *INSR*-SIRS is established in a proband with characteristic clinical, laboratory, radiographic, and prenatal ultrasound findings and biallelic *INSR* pathogenic variants identified by molecular genetic testing.

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## Management

*Treatment of manifestations:* Donohue syndrome: no effective treatments for insulin resistance or other manifestations of Donohue syndrome are currently available. Frequent feedings as well as increased protein content of evening feedings can help prevent fasting hypoglycemia.

RMS: Insulin sensitizers are used first to decrease levels of glucose and glycosylated hemoglobin (HbA1c); however, their effect diminishes with time, often requiring dose adjustments and multidrug therapy. When hyperglycemia persists, insulin is started – usually in high doses, especially during the treatment of diabetic ketoacidosis. Standard treatment for hypothyroidism; oral contraceptives, antiandrogen therapies, and gonadotropin-releasing hormone agonists can be used to treat hyperandrogenism; oophorectomy may be needed for enlarged ovaries; nutritional, developmental, and educational support; rigorous workup and treatment of intercurrent infections; beta-blockers for cardiomyopathy; treatment of nephrocalcinosis per nephrologist; treatment of cholestasis per gastroenterologist; treatment of rectal prolapse per surgeon; standard treatments for malignancies; social work and family support.

*Surveillance:* Capillary glucose levels during fasting and after feeding, when clinically indicated, or continuous monitoring; HbA1c, insulin, and C-peptide levels every three months; thyroid function and hyperandrogenism lab assessment every six months or as clinically indicated; ovarian ultrasound every three months until age two years, then every six months or as indicated; nutrition and growth assessment at each visit; assess psychomotor development every three months; assess for recurrent infections at each visit; echocardiogram and cardiac MRI every six months (each test alternating every three months) until age two years, then annually (each test alternating every six months) or as indicated; urine calcium and kidney ultrasound every six months; gynecologic evaluation for endometrial cancer in those with abnormal vaginal bleeding.

*Agents/circumstances to avoid:* In Donohue syndrome, avoid agents that cause hypoglycemia, prolonged fasting, and contact with persons with contagious disease. In RMS avoid agents that cause hypoglycemia, high-carbohydrate diet, and contact with persons with contagious disease.

## Genetic counseling

*INSR-SIRS* is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *INSR* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected with *INSR-SIRS*, a 50% chance of inheriting one pathogenic variant and being heterozygous, and a 25% chance of inheriting neither of the familial *INSR* pathogenic variants.

Heterozygotes are usually asymptomatic but may have features of the allelic disorder type A insulin resistance. Once the *INSR* pathogenic variants have been identified in an affected family member, heterozygote testing for at-risk relatives and prenatal and preimplantation genetic testing are possible. (Of note: Heterozygotes for an *INSR* pathogenic variant are at increased risk for gestational diabetes and require monitoring for glucose intolerance before and during pregnancy.)

## GeneReview Scope

*INSR*-Related Severe Insulin Resistance Syndrome: Included Phenotypes

- Donohue syndrome<sup>1</sup>
- Rabson-Mendenhall syndrome

1. For synonyms, see Nomenclature.

## Diagnosis

### Suggestive Findings

INSR-related severe insulin resistance syndrome (INSR-SIRS) **should be suspected** in individuals with the following clinical, laboratory, and imaging findings of Donohue syndrome or Rabson-Mendenhall syndrome (RMS).

### Clinical Findings

#### Donohue syndrome

- Progressive intrauterine growth restriction (IUGR) from the early third trimester and postnatal poor weight gain, growth deficiency, and reduced subcutaneous fat
- Dysmorphic facial features (Figure 1) characterized by proptosis, infraorbital folds, large, low-set, posteriorly rotated ears, thick vermilion of the upper and lower lips, and gingival hypertrophy [Grasso et al 2013]
- Hypotonia
- Developmental delay
- Integument, including dry skin, hypertrichosis (Figure 2), and acanthosis nigricans
- Prominent nipples (Figure 3)
- Abdominal distention (Figure 4) and organomegaly
- Genital enlargement (males and females) (Figure 4B)
- Rectal hypertrophy and prolapse (Figure 5)

#### RMS

- Dysmorphic facial features that can resemble those of Donohue syndrome [Ben Abdelaziz et al 2016] or can be milder [Musso et al 2004]
- Integument, including hypertrichosis and acanthosis nigricans
- Prominent nipples
- Genital enlargement (males and females)
- Early dental eruption and dental crowding [Bathi et al 2010]
- Growth deficiency (less severe than in Donohue syndrome) [Tuthill et al 2007]
- Developmental delay (in some individuals) [Ben Abdelaziz et al 2016, Sinnarajah et al 2016]

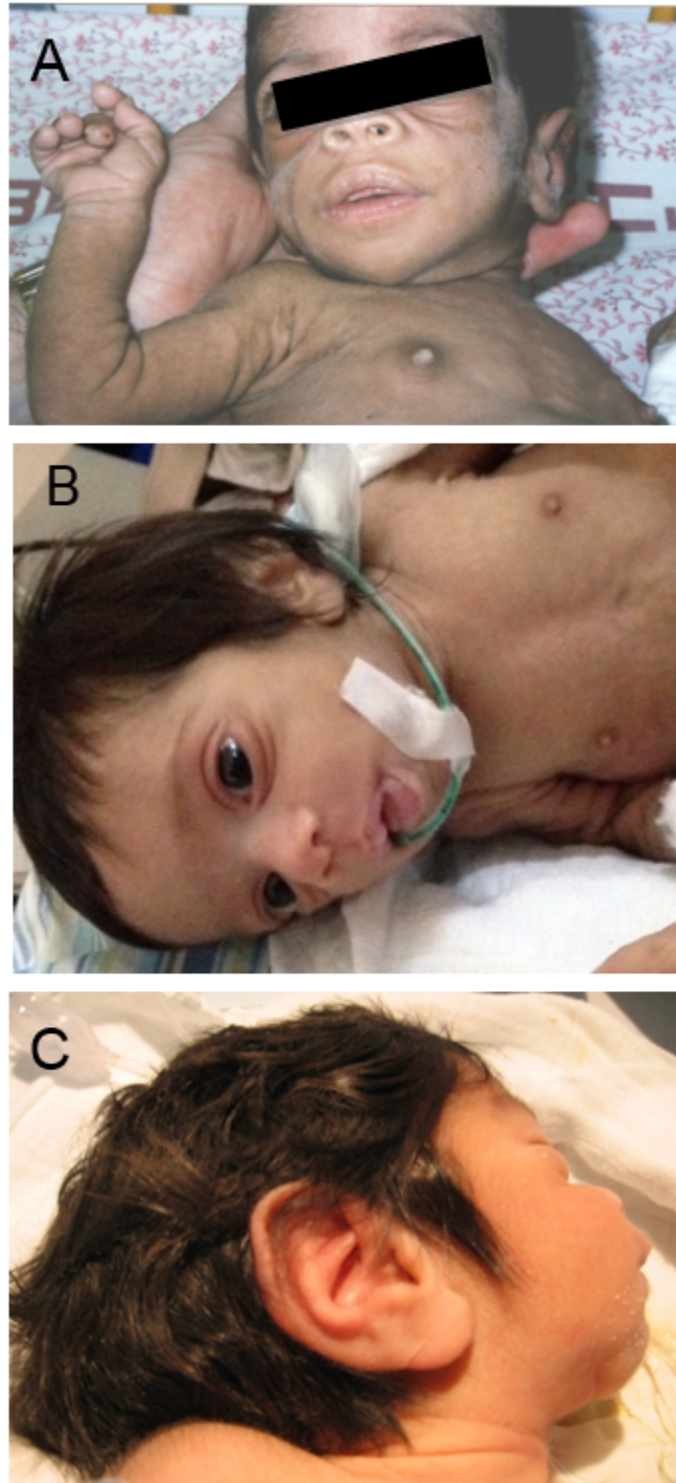
### Laboratory Findings

#### Donohue syndrome

- Severe hyperinsulinemia. Extremely high plasma insulin and C-peptide levels with fluctuating blood glucose levels (typically fasting hypoglycemia and postprandial hyperglycemia)
- Ketoacidosis not reported.

#### RMS

- **Birth to age one year.** Severe hyperinsulinemia, with extremely high plasma insulin and C-peptide levels with fluctuating blood glucose levels (typically fasting hypoglycemia and postprandial hyperglycemia)
- **Age one year and older.** Insulin levels decline steadily, initially resulting in increased glucose levels and fewer hypoglycemic events, and subsequently resulting in increased risk for ketoacidosis.
- Low triglyceride levels, high high-density lipoprotein (HDL) levels [Semple et al 2009]
- High adiponectin levels [Semple et al 2008]



**Figure 1.** Characteristic dysmorphism seen in neonate with Donohue syndrome: gingival overgrowth; large, low-set, posteriorly rotated ears; infraorbital folds; proptosis; thick vermillion of the upper and lower lips

Figures 1A and 1C reproduced from Falik Zaccai et al [2014]

## Imaging Findings

### Donohue syndrome and RMS



**Figure 2.** Hypertrichosis is a feature in all individuals with Donohue syndrome.

Reproduced from Falik Zaccai et al [2014]



**Figure 3.** Prominent nipples are a typical finding in neonates with Donohue syndrome.

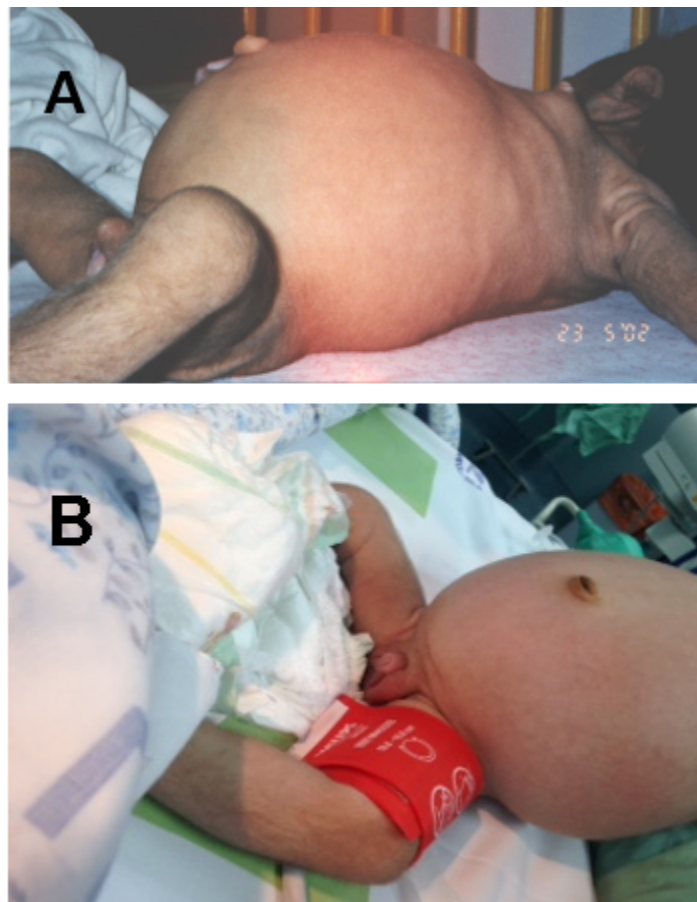
- Hypertrophic cardiomyopathy
- Enlarged kidneys, liver, and spleen
- Nephrocalcinosis
- Enlarged polycystic ovaries

## Establishing the Diagnosis

The diagnosis of *INSR*-SIRS is **established** in a proband with suggestive findings and biallelic *INSR* pathogenic (or likely pathogenic) variants identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *INSR* variants of uncertain





**Figure 4.** A and B. Abdominal distention

B. Labial hypertrophy and clitoromegaly in a girl age four months with Donohue syndrome

Figure 4A reproduced from Falik Zaccai et al [2014]

significance (or of one known *INSR* pathogenic variant and one *INSR* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

## Option 1

**Single-gene testing.** Sequence analysis of *INSR* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

**A multigene panel** that includes *INSR* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in



**Figure 5.** Rectal hypertrophy and prolapse in an infant with Donohue syndrome.

this *GeneReview*. Of note, given the rarity of *INSR*-SIRS, some panels for diabetes mellitus may not include this gene. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

## Option 2

**Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

**Table 1.** Molecular Genetic Testing Used in *INSR*-Related Severe Insulin Resistance Syndrome

Gene <sup>1</sup>	Method	Proportion of Pathogenic Variants <sup>2</sup> Identified by Method
<i>INSR</i>	Sequence analysis <sup>3</sup>	>90% <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5</sup>	<10% <sup>4</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

## Clinical Characteristics

### Clinical Description

*INSR*-related severe insulin resistance syndrome (*INSR*-SIRS) comprises a phenotypic continuum from the severe phenotype of Donohue syndrome to the milder phenotype of Rabson-Mendenhall syndrome (RMS). To date, fewer than 100 individuals have been identified with *INSR*-SIRS [Termote et al 2016]. The following description of the phenotypic features associated with this condition is based on these reports.

**Table 2.** *INSR*-Related Severe Insulin Resistance Syndrome: Comparison of Phenotypes by Select Features

Feature	Donohue Syndrome	Rabson-Mendenhall Syndrome
<b>Endocrine</b>	<b>Hyperinsulinism</b>	100%
	<b>Diabetic ketoacidosis</b>	+
	<b>Genital enlargement</b>	+
	<b>Hypothyroidism</b>	+
<b>Growth</b>	<b>Intrauterine growth deficiency</b>	100%
	<b>Postnatal growth deficiency</b>	100%
<b>Neurologic</b>	<b>Hypotonia</b>	100%
	<b>Developmental delay</b>	100%
	<b>Intellectual disability</b>	100%
<b>Dysmorphic facial features</b>	100%	100%
<b>Integument abnormalities</b>	100%	100%
<b>Organomegaly</b>	100%	60%-80%
<b>Rectal hypertrophy &amp;/or prolapse</b>	100%	+

Based on Kushchayeva et al [2019], Bamborschke et al [2021], Angelidi et al [2021], Gosavi et al [2021], Iqbal et al [2022], Metwalley et al [2022], Nicolescu et al [2023], Vakili & Rezaei [2023]

+ = reported feature; incidence unknown



## Donohue Syndrome

Donohue syndrome is characterized by severe insulin resistance, growth failure, hypotonia, developmental delay, characteristic facies, and organomegaly.

**Endocrine manifestations.** Insulin resistance with hyperinsulinemia (fasting hypoglycemia and postprandial hyperglycemia) is present from birth. There are currently no effective treatments for the insulin resistance. Postprandial hyperglycemia does not respond to insulin treatment [Semple et al 2010] or glucose-lowering therapies such as metformin [Musso et al 2004].

Enlargement of the external genitalia occurs in both males (enlargement of the penis) and females (labial hypertrophy and clitoral enlargement). Ovarian enlargement is characteristic; ovarian ultrasonography usually reveals multiple peripheral cysts, as seen in idiopathic polycystic ovary syndrome. Cysts may become very large and vulnerable to hemorrhage or torsion, and surgical removal may be required [Semple et al 2011]. Prominent nipples are seen in all individuals.

Central hypothyroidism has been reported [Baqir et al 2012, Falik Zaccai et al 2014].

**Growth deficiency.** Birth weight, length, and head circumference are below the third centile. However, weight and/or length are more affected than head circumference [Dagdeviren Cakir et al 2020]. Neonates continue to have poor weight gain and severe growth deficiency; the average weight at age one year is 4-5 kg [Longo et al 2002]. Reduced subcutaneous fat is present in all individuals.

**Developmental delay / intellectual disability.** Most infants have severe global developmental delay, including speech and motor as well as cognitive impairment [Falik Zaccai et al 2014]. Most individuals do not reach any significant developmental milestones prior to early demise [Falik Zaccai et al 2014, Joshi et al 2021]. Axial hypotonia and muscle atrophy are also observed [Baqir et al 2012]. Intellectual disability is thought to be a consequence of recurrent, severe hypoglycemic episodes [Ben Abdelaziz et al 2016].

**Characteristic facies** include proptosis, infraorbital folds, large, low-set, posteriorly rotated ears, thick vermilion of the upper and lower lips, and gingival hypertrophy [Grasso et al 2013] (see Figure 1). Macroglossia has been reported but may be secondary to prolonged therapy with insulin-like growth factor 1 (IGF-1) [Joshi et al 2021].

**Recurrent infections.** Recurrent bacterial infections including pneumonia and urinary tract infection are a common cause of death; health care-acquired infections may contribute to recurrent infections [Rojek et al 2023].

**Integument.** Hypertrichosis and hyperkeratosis are present at birth in all affected infants. Acanthosis nigricans can be apparent at birth or in early infancy [Musso et al 2004].

**Cardiac manifestations.** Hypertrophic cardiomyopathy is present in 30% of infants and is a major cause of death [Geffner et al 1987, Hovnik et al 2013, Falik Zaccai et al 2014].

**Renal manifestations.** Enlarged kidneys are common. Abnormalities of the renin-aldosterone system are reported, resulting in hypokalemia, hyperaldosteronism, and hyperreninemia [Grasso et al 2013]. Hypercalciuria and nephrocalcinosis are often seen during the first months of life and in some instances can be detected prenatally [Simpkin et al 2014]. Kidney function as measured by glomerular filtration rate and plasma creatinine concentration is normal [Grasso et al 2013, Simpkin et al 2014].

**Liver/gastrointestinal manifestations.** Cholestasis is common in the neonatal period [Hovnik et al 2013, Kawashima et al 2013]. Hepatomegaly occurs without liver dysfunction. Rectal prolapse or hypertrophy can be present, which sometimes requires colostomy [Weber et al 2014].

**Dental findings** include macrodontia and dental crowding.

**Prognosis.** Death usually occurs during the first year of life. The major causes of death are complications of hypoglycemia, recurrent bacterial infections [Elders et al 1982, de Bock et al 2012], and cardiomyopathy [Grasso et al 2013].

## **Rabson-Mendenhall Syndrome (RMS)**

RMS, at the milder end of the spectrum, is characterized by severe insulin resistance with fluctuations in blood glucose levels, diabetic ketoacidosis, and microvascular complications. Findings can range from severe growth deficiency and intellectual disability to normal growth and development. Facial features can be milder than those of Donohue syndrome.

**Endocrine manifestations.** Insulin resistance with hyperinsulinemia is less severe than that of Donohue syndrome. Fluctuations in blood glucose levels occur with fasting hypoglycemia and postprandial hyperglycemia from birth. After age one year, insulin levels decline steadily, initially resulting in increased glucose levels and fewer hypoglycemic events, and subsequently resulting in increased risk for ketoacidosis. Morbidity in older individuals with RMS results from microvascular complications of prolonged hyperglycemia and hyperinsulinemia (e.g., proliferative retinopathy, peripheral neuropathy, and renal vascular complications) [Musso et al 2004, Carrasco de la Fuente et al 2010, Jiang et al 2011].

Enlargement of the external genitalia in both males and females typically appears later in childhood in individuals with RMS compared to those with Donohue syndrome. Enlarged ovaries are reported in some individuals and may be complicated by multiple cysts and development of tumors [Parker & Semple 2013]. Prominent nipples are also seen.

Thyroid abnormalities reported in RMS include high prevalence of thyroid nodules and thyromegaly [Kushchayeva et al 2019].

**Growth** is variable in individuals with RMS, from severe growth deficiency that includes reduction of weight, length, and head circumference [Dagdeviren Cakir et al 2020] to normal growth [Musso et al 2004]. In those with growth deficiency, linear growth does not improve with human growth hormone treatment even when the child's growth hormone levels are low [Musso et al 2004, Kim et al 2012, Brown et al 2013].

**Developmental delay / intellectual disability.** Developmental delay can range from severe to normal development [de Kerdanet et al 2015, Ben Abdelaziz et al 2016]. More than 50% of individuals with RMS are reported to have mild intellectual disability [Ben Abdelaziz et al 2016, Angelidi et al 2021].

**Dysmorphic facial features** in individuals with RMS can be more subtle than facial features characteristic of Donohue syndrome (e.g., proptosis, infraorbital folds, large, low-set, posteriorly rotated ears, thick vermilion of the upper and lower lips, and gingival hypertrophy). The face can show increased vertical growth, increased gonial angle, macroglossia, macrodontia, dental crowding, dental prematurity, and dysplastic dentition [Joshi et al 2021]. Early dental eruption, dental crowding, and low anterior hair line may be the only unique facial features [Jiang et al 2011].

**Recurrent infections.** Recurrent episodes of bacterial pneumonia are the most common infections in individuals with RMS [Iqbal et al 2022].

**Integument.** Cutaneous changes (hirsutism and acanthosis nigricans) typically appear later in childhood in individuals with RMS.

**Cardiac manifestations.** Hypertrophic cardiomyopathy is common and typically observed during the first decade of life. Neonatal hypertrophic cardiomyopathy was also reported in some individuals [Aftab et al 2022].

**Renal manifestations.** Enlarged kidneys are common. Hypercalcemia, nephrocalcinosis, and medullary sponge kidney are also reported as features of RMS [Chrzanowska et al 2023]. Nephrocalcinosis was reported in the vast majority of individuals [Simpkin et al 2014].

**Liver/gastrointestinal manifestations.** Hepatosplenomegaly occurs without liver or spleen dysfunction. Rectal prolapse was reported in some affected individuals [Joshi et al 2021].

**Malignancy.** Rare malignancies have been reported. Endometrial carcinoma was reported in a woman age 24 years treated with recombinant human IGF-1 (rhIGF-1) for severe insulin resistance [Jo et al 2013]. Ovarian granulosa cell tumor was reported in a girl age 35 months with severe insulin resistance treated with rhIGF-1 for 16 months [Weber et al 2014] and in a young girl who was untreated [Brisigotti et al 1993]. Because two of these individuals were treated with rhIGF-1, it is possible that the tumors resulted from an adverse effect of this treatment.

**Prognosis.** Complications of prolonged hyperglycemia and hyperinsulinemia are the major causes of death in individuals with RMS, usually during the second decade of life [Semple et al 2010]. However, survival can be into the third decade [Longo et al 2002, Musso et al 2004].

## Genotype-Phenotype Correlations

There are no known genotype-phenotype correlations in *INSR*-SIRS.

## Nomenclature

Leprechaunism is a synonym of Donohue syndrome.

## Prevalence

Donohue syndrome is extremely rare, estimated at 1:1,000,000 [Desbois-Mouthon et al 1997].

To date, 96 individuals with Donohue syndrome and RMS have been molecularly diagnosed and reported [Ardon et al 2014, Ben Abdelaziz et al 2016, Termote et al 2016, Moore et al 2017, Chen et al 2018, Dagdeviren Cakir et al 2020, Al-Kandari et al 2021, Dos Santos et al 2021, Joshi et al 2021, Lai et al 2021, Zhou et al 2021, Novoa et al 2022, Chrzanowska et al 2023, Rojas Velazquez et al 2024]; about ten additional individuals have Donohue syndrome and RMS based on clinical diagnosis.

## Genetically Related (Allelic) Disorders

**Type A insulin resistance** (OMIM 610549). Heterozygous or, less commonly, biallelic pathogenic variants in *INSR* are known to be associated with type A insulin resistance, especially when the pathogenic variant is in the intracellular domain [Takahashi et al 1997, Longo et al 2002, Jiang et al 2011, Zhou et al 2021]. Type A insulin resistance is characterized by hyperandrogenism (manifest as hirsutism, acne, and amenorrhea) and signs of insulin resistance (e.g., acanthosis nigricans and diabetes) without obesity, and most commonly comes to attention around the time of puberty due to findings that resemble polycystic ovarian syndrome. Of note, males can also be affected. The insulin resistance, which is milder than that of *INSR*-related severe insulin resistance syndrome, can be treated. Growth and cognitive abilities are normal [Musso et al 2004, Semple et al 2010].

## Differential Diagnosis

The differential diagnosis of *INSR*-related severe insulin resistance syndrome (*INSR*-SIRS) includes many rare disorders with hirsutism, severe growth deficiency, and developmental delay with other syndromic features, some of which are summarized in Table 3.

**Table 3.** Selected Disorders of Interest in the Differential Diagnosis of *INSR*-Related Severe Insulin Resistance Syndrome

Gene(s) / Genetic Mechanism	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/ <i>INSR</i> -SIRS	Distinguishing from <i>INSR</i> -SIRS
11p15.5 hypomethylation, maternal UPD7, & other causes <sup>1</sup>	Silver-Russell syndrome (SRS)	See footnote 1.	<ul style="list-style-type: none"> <li>IUGR &amp; postnatal growth deficiency<sup>2</sup></li> <li>↑ risk for hypoglycemia</li> </ul>	<ul style="list-style-type: none"> <li>Dysmorphic features unlike those in DS/RMS</li> <li>Limb, body, &amp;/or facial asymmetry</li> <li>Hypoglycemia assoc w/ fasting only</li> <li>Hyperinsulinemia is not a feature in SRS.</li> </ul>
<i>ABCC8</i> <i>CACNA1D</i> <i>GCK</i> <i>GLUD1</i> <i>HADH</i> <i>HK1</i> <i>HNF1A</i> <i>HNF4A</i> <i>KCNJ11</i> <i>PMM2</i> <i>SLC16A1</i> <i>UCP2</i>	Familial hyperinsulinism (FHI)	AD AR	<ul style="list-style-type: none"> <li>Congenital hyperinsulinemia</li> <li>Hypoglycemia (ranging from severe neonatal-onset disease to childhood-onset disease w/mild symptoms in FHI)<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>Dysmorphism &amp; growth deficiency are not characteristic of FHI.</li> <li>Insulin levels are usually much higher in DS/RMS.</li> </ul>
<i>AGPAT2</i> <i>BSCL2</i> <i>CAV1</i> <i>CAVIN1 (PTRF)</i>	Berardinelli-Seip congenital lipodystrophy (BSCL) (OMIM PS608594)	AR	<ul style="list-style-type: none"> <li>Congenital hyperinsulinemia</li> <li>Insulin resistance<sup>4</sup></li> <li>Hepatomegaly (due to hepatic steatosis &amp; skeletal muscle hypertrophy in BSCL)</li> <li>Hypertrophic cardiomyopathy<sup>5</sup></li> </ul>	<ul style="list-style-type: none"> <li>Dysmorphic features (due to absence of subcutaneous fat) in BSCL are unlike those in DS/RMS.</li> <li>Hyperlipidemia &amp; liver steatosis in BSCL</li> </ul>

Table 3. continued from previous page.

Gene(s) / Genetic Mechanism	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/INSR-SIRS	Distinguishing from INSR-SIRS
<i>IGF1R</i>	Resistance to insulin-like growth factor 1 (OMIM 270450)	AR AD	<ul style="list-style-type: none"> <li>IUGR &amp; postnatal growth deficiency</li> <li>Mildly impaired glucose tolerance<sup>6</sup></li> <li>Delayed psychomotor development</li> <li>Mild dysmorphic features</li> </ul>	<ul style="list-style-type: none"> <li>No hyperinsulinemia</li> <li>Only mildly impaired glucose tolerance</li> </ul>

AD = autosomal dominant; AR = autosomal recessive; DS = Donohue syndrome; INSR-SIRS = INSR-related severe insulin resistance syndrome; IUGR = intrauterine growth restriction; MOI = mode of inheritance; RMS = Rabson-Mendenhall syndrome; UPD = uniparental disomy

1. Silver-Russell syndrome (SRS) is a genetically heterogeneous condition. Genetic testing confirms clinical diagnosis in ~60% of affected individuals. Accurate assessment of SRS recurrence requires identification of the causative genetic mechanism in the proband.
2. The birth weight of infants with SRS is typically  $\geq 2$  standard deviations (SD) below the mean, and postnatal growth  $\geq 2$  SD below the mean for length or height.
3. Familial hyperinsulinism (FHI) is characterized by hypoglycemia that ranges from difficult-to-manage severe neonatal-onset disease to childhood-onset disease with mild symptoms and difficult-to-diagnose hypoglycemia. Neonatal-onset disease manifests within hours to two days after birth. In the newborn period, presenting symptoms (including seizures, hypotonia, poor feeding, and apnea) may be nonspecific. In severe FHI, serum glucose concentrations are typically extremely low and thus easily recognized. Childhood-onset disease manifests during the first months or years of life, and in milder FHI, diagnosis may be difficult to establish due to variable and/or mild hypoglycemia.
4. Approximately 25%-35% of affected individuals develop diabetes mellitus between ages 15 and 20 years.
5. Hypertrophic cardiomyopathy is reported in 20%-25% of affected individuals.
6. Klammt et al [2011]

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with INSR-related severe insulin resistance syndrome (INSR-SIRS), the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. INSR-Related Severe Insulin Resistance Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
<b>Endocrine</b>	<ul style="list-style-type: none"> <li>Assessment by pediatric endocrinologist</li> <li>Blood glucose monitoring (during fasting &amp; after feeding) or continuous glucose monitoring</li> <li>Measurement of insulin &amp; C-peptide levels</li> <li>Thyroid function tests</li> <li>Ovarian ultrasound (in females)</li> </ul>	
<b>Nutrition/Feeding</b>	Assessment by nutritionist	To assess feeding & diet required to achieve normal glucose levels & optimal growth
<b>Development</b>	Developmental assessment	



Table 4. continued from previous page.

System/Concern	Evaluation	Comment
<b>Cardiac</b>	<ul style="list-style-type: none"> <li>• Eval by pediatric cardiologist</li> <li>• Echocardiography</li> <li>• Cardiac MRI if indicated</li> </ul>	<ul style="list-style-type: none"> <li>• To assess for hypertrophic cardiomyopathy</li> <li>• Note: Novel blood biomarkers incl BNP, NT-proBNP, hs-CRP, hs-cTnT, &amp; uric acid are currently being evaluated.</li> </ul>
<b>Renal</b>	<ul style="list-style-type: none"> <li>• Eval by pediatric nephrologist</li> <li>• Serum electrolytes</li> <li>• 24-hour urinary calcium</li> <li>• Renal ultrasound</li> </ul>	To assess for abnormal renin-aldosterone system & for nephrocalcinosis
<b>Liver/GI function</b>	<ul style="list-style-type: none"> <li>• Liver function tests per gastroenterologist</li> <li>• Abdominal ultrasound to assess liver/spleen</li> <li>• Eval by pediatric gastroenterologist</li> </ul>	To assess for cholestatic liver disease
	Assess for rectal prolapse.	
<b>Dental</b>	Consider eval by oral & maxillofacial specialist in those w/dental crowding.	
<b>Genetic counseling</b>	By genetics professionals <sup>1</sup>	To inform affected persons & their families re nature, MOI, & implications of <i>INSR</i> -SIRS to facilitate medical & personal decision making
<b>Family support &amp; resources</b>	By clinicians, wider care team, & family support organizations	<p>Assessment of family &amp; social structure to determine need for:</p> <ul style="list-style-type: none"> <li>• Community or online resources such as <a href="#">Parent to Parent</a></li> <li>• Social work involvement for parental support</li> <li>• Home nursing referral</li> </ul>

BNP = brain natriuretic peptide; GI = gastrointestinal; hs-CRP = high-sensitivity C-reactive protein; hs-cTnT = high-sensitivity cardiac troponin T; *INSR*-SIRS = *INSR*-related severe insulin resistance syndrome; MOI = mode of inheritance; NT-proBNP = N-terminal pro-brain natriuretic peptide

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Treatment of Manifestations

There is no cure for *INSR*-SIRS. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

**Table 5.** INSR-Related Severe Insulin Resistance Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
<b>Insulin resistance &amp; hyperglycemia</b>	<b>Donohue syndrome:</b> Frequent feedings (e.g., breastfeeding, nasogastric tube, &/or IV glucose) as well as ↑ protein content of evening feedings to prevent hypoglycemia	No effective treatments for insulin resistance or other manifestations of Donohue syndrome are currently available. Medications (e.g., insulin, metformin) are not effective.
	<b>RMS:</b> <ul style="list-style-type: none"> <li>• First-line therapy is insulin sensitizers, which ↓ the levels of HbA1c.<sup>1</sup></li> <li>• When hyperglycemia persists, insulin is started, usually in high doses.<sup>2</sup></li> <li>• When doses &gt;200 units/day are required, the U500 (500 units/mL) concentration of soluble human insulin is recommended as part of a multiple-injection regime.</li> </ul>	<ul style="list-style-type: none"> <li>• The effect of insulin sensitizers diminishes over time, often requiring dose adjustments &amp; multidrug therapy.<sup>3</sup></li> <li>• In many persons, this treatment is well tolerated &amp; permits large incremental increases in dose w/o excessive discomfort.</li> <li>• U500 can also be administered continuously by subcutaneous insulin pump.<sup>4</sup></li> </ul>
<b>Diabetic ketoacidosis (DKA)</b>	Very high doses of insulin ( $\leq 500$ U/hr) have been used. <sup>5</sup>	Although DKA is a major cause of morbidity & mortality in RMS, treatment used for DKA has only been reported for a few persons.
<b>Hypothyroidism</b>	Standard treatment per endocrinologist	
<b>Hyperandrogenism</b>	<ul style="list-style-type: none"> <li>• Oral contraceptives &amp; antiandrogens such as flutamide &amp; spironolactone as well as finasteride, a 5-alpha reductase inhibitor that ↓ conversion of testosterone to dihydrotestosterone<sup>6</sup></li> <li>• A GnRH agonist to suppress gonadotrophins is also likely to be beneficial.<sup>7</sup></li> </ul>	In some females, removal of the ovaries is necessary to control hyperandrogenism. <sup>8</sup>
<b>Enlarged ovaries</b>	Gonadectomy may be considered when enlarged ovaries cause respiratory distress or interfere w/development, &/or imaging suggests granulosa cell tumor.	
<b>Nutrition/Feeding/ Growth</b>	Nutritional support	There is no known treatment for short stature.
<b>Developmental delay / Intellectual disability</b>	Developmental & educational support as indicated	
<b>Recurrent infections</b>	Rigorous workup & treatment of intercurrent infections	
<b>Cardiomyopathy</b>	Beta-blockers per cardiologist	
<b>Nephrocalcinosis</b>	Treatment per nephrologist	
<b>Cholestasis</b>	Treatment per gastroenterologist	
<b>Rectal prolapse</b>	Treatment per gastroenterologist &/or surgeon	
<b>Malignancies</b>	Standard treatments per oncologist	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
<b>Family/Community</b>	<ul style="list-style-type: none"> <li>Ensure appropriate social work involvement to connect families w/local resources, respite, &amp; support.</li> <li>Coordinate care to manage multiple subspecialty appointments, medications, &amp; supplies.</li> </ul>	Ongoing assessment of need for palliative care involvement &/or home nursing

GnRH = gonadotropin-releasing hormone; HbA1c = glycosylated hemoglobin; RMS = Rabson-Mendenhall syndrome

1. Musso et al [2004], Moreira et al [2010]

2. Chong et al [2013]

3. Carrasco de la Fuente et al [2010]

4. Semple et al [2010]

5. Chong et al [2013], Moore et al [2017]

6. Bathi et al [2010], Wei & Burren [2017]

7. Brown et al [2017]

8. Musso et al [2004]

## Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended [Kushchayeva et al 2019, Perge et al 2020, Huang-Doran et al 2021, Jansen et al 2022].

**Table 6.** INSR-Related Severe Insulin Resistance Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
<b>Endocrine</b>	Capillary glucose levels	During fasting & after feeding or when clinically indicated; or continuous glucose monitoring
	<ul style="list-style-type: none"> <li>HbA1c</li> <li>Insulin &amp; C-peptide levels</li> </ul>	Every 3 mos
	<ul style="list-style-type: none"> <li>Thyroid function tests</li> <li>Endocrinology lab assessment for hyperandrogenism</li> </ul>	Every 6 mos or when clinically indicated
	Ovarian ultrasound to assess for enlarged ovaries	Every 3 mos until age 2 yrs, then every 6 mos or when clinically indicated
<b>Nutrition/Feeding/Growth</b>	Nutrition & growth assessment	At each visit
<b>Development</b>	Assess psychomotor development.	Every 3 mos
<b>Immune function</b>	Assess for recurrent infections.	At each visit
<b>Cardiac</b>	<ul style="list-style-type: none"> <li>Echocardiography</li> <li>Cardiac MRI</li> </ul>	Every 6 mos (each test alternating every 3 mos) until age 2 yrs; then annually (each test alternating every 6 mos) in those age ≥2 yrs or per clinical indication
<b>Renal</b>	<ul style="list-style-type: none"> <li>Urine calcium to assess for hypercalciuria</li> <li>Kidney ultrasound to assess for nephrocalcinosis</li> </ul>	Every 6 mos
<b>Malignancies</b>	Gynecologic eval to assess for endometrial cancer	In those w/abnormal vaginal bleeding

HbA1c = glycosylated hemoglobin

## Agents/Circumstances to Avoid

In individuals with Donohue syndrome, avoid the following:

- Agents that cause hypoglycemia
- Prolonged fasting
- Contact with persons with a contagious disease

In individuals with RMS, avoid the following:

- Agents that cause hyperglycemia
- High-carbohydrate diet
- Contact with persons with a contagious disease

## Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

There are no controlled trials in *INSR-SIRS*; thus, the two therapies discussed in this section are for individuals with *INSR* pathogenic variants based on clinical experience, case series, and expert opinion.

### Recombinant Human Insulin-like Growth Factor 1 (rhIGF-1)

The rationale for using rhIGF-1 to treat severe insulin resistance syndromes is based on observations of its direct effects on carbohydrate metabolism. In humans, infusion of rhIGF-1 suppresses hepatic glucose production, stimulates peripheral glucose uptake in muscle, and – despite a significant reduction in circulating insulin levels – causes hypoglycemia. The insulin-like growth factor 1 receptor (IGF1R) and the insulin receptor (INSR) share 60% homology and very similar intracellular activity [Weber et al 2014].

**Treatment regimen.** Although many case reports of severe insulin resistance syndromes describe treatment with rhIGF-1, there is no standard protocol regarding this treatment. In fact, the treatment regimens either differed [McDonald et al 2007, de Kerdanet et al 2015] or were not reported.

Three treatment regimens for rhIGF-1 therapy in children with severe insulin resistance were reported: subcutaneous injections two to four times a day, continuous subcutaneous infusion via insulin pump, and intravenous infusion [Backeljauw et al 1994]. Anecdotal experience suggests that the use of continuous rhIGF-1 infusion is more beneficial than divided doses. Doses ranged from 80 to 1,120 µg/kg per day [McDonald et al 2007].

**Outcome of treatment.** In most treated children:

- The metabolic state improved and levels of glucose, insulin, and glycosylated hemoglobin decreased.
- Growth parameters improved [Nakae et al 1998].
- Renal tubular dysfunction improved [Hovnik et al 2013].

In some children treated with rhIGF-1, the degree of cardiomyopathy improved and survival was prolonged [McDonald et al 2007, de Kerdanet et al 2015, Carmody et al 2016], whereas in others no improvement was observed [Musso et al 2004, Grasso et al 2013].

**Potential side effects** include severe hypoglycemia and soft tissue overgrowth.

Given a lack of evidence, it is unclear whether the following two instances were side effects of the treatment or the hyperinsulinemia itself:

- Endometrial carcinoma in a woman age 24 years treated with rhIGF-1 for severe insulin resistance (called Donohue syndrome by the authors, but clinically more likely RMS) [Jo et al 2013]
- Granulosa cell tumor of the ovary in a girl age 35 months with severe insulin resistance treated with rhIGF-1 for 16 months [Weber et al 2014]

To summarize the experience with rhIGF-1 treatment in severe insulin resistance syndromes: (1) its benefit is not well established; and (2) it is more likely to be effective in individuals with less severe insulin resistance, as the few individuals with prolonged survival with rhIGF-1 treatment had milder phenotypes [Carmody et al 2016]. To date, rhIGF-1 appears to be the best treatment option; it is thus reasonable to consider in any individual with severe syndromic insulin resistance.

## Metreleptin (Recombinant Human Leptin)

Metreleptin is approved by the FDA for treatment of congenital or acquired generalized lipodystrophy.

Leptin replacement normalized blood lipids (i.e., reduced triglycerides and increased high-density lipoproteins [HDL]) and reduced insulin and glucose levels in syndromes with leptin deficiency. Syndromes with leptin deficiency are characterized by insulin resistance, hyperglycemia, dyslipidemia, endocrine disruptions, and fatty liver disease [Paz-Filho et al 2015] and include lipodystrophy syndromes, hypothalamic amenorrhea, anorexia nervosa, and congenital leptin deficiency.

After one year of treatment with metreleptin (along with other medications including insulin, metformin, and pioglitazone), individuals with RMS showed improvement in all of the following: serum glucose levels, glycosylated hemoglobin (HbA1c) levels, insulinemia, insulin dose required, caloric intake, and body fat mass [Cochran et al 2004, Brown et al 2013].

Metreleptin alters the natural history of rising HbA1c in RMS, leading to lower HbA1c throughout long-term follow up. Improved glycemia with metreleptin is likely attributable to appetite suppression and lower body mass index (BMI). Lower BMI after metreleptin may also worsen growth hormone resistance in RMS, resulting in a null effect on IGF-1 and growth despite improved glycemia [Okawa et al 2022].

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://european-clinical-trials-register.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

## Mode of Inheritance

*INSR*-related severe insulin resistance syndrome (*INSR*-SIRS) is inherited in an autosomal recessive manner.

## Risk to Family Members

### Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *INSR* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *INSR* pathogenic variant and to allow reliable recurrence risk assessment.



- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Maassen et al 2003, Kawashima et al 2013]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes are usually asymptomatic but may have features of the allelic disorder type A insulin resistance (see Genetically Related Disorders). Females who are heterozygous for an *INSR* pathogenic variant are at increased risk for gestational diabetes (see **Family planning**).

### Sibs of a proband

- If both parents are known to be heterozygous for an *INSR* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected with *INSR*-SIRS, a 50% chance of inheriting one pathogenic variant and being heterozygous, and a 25% chance of inheriting neither of the familial *INSR* pathogenic variants.
- Heterozygotes are usually asymptomatic but may have features of the allelic disorder type A insulin resistance (see Genetically Related Disorders). Females who are heterozygotes for an *INSR* pathogenic variant are at increased risk for gestational diabetes (see **Family planning**).

**Offspring of a proband.** Individuals with *INSR*-SIRS are not known to reproduce.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being heterozygous for an *INSR* pathogenic variant.

## Heterozygote Detection

Heterozygote testing for at-risk relatives requires prior identification of the *INSR* pathogenic variants in the family.

Heterozygotes are usually asymptomatic but may have features of the allelic disorder type A insulin resistance. Females who are heterozygous for an *INSR* pathogenic variant are at increased risk for gestational diabetes (see **Family planning**).

## Related Genetic Counseling Issues

### Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are heterozygous or are at risk of being heterozygous.
- Heterozygote testing should be considered for the reproductive partners of known heterozygotes, particularly if both partners are of the same ancestry. The prevalence of heterozygotes for the pathogenic variant c.167T>C is high among Druze in Israel [Falik Zaccai et al 2014].
- Females who are heterozygous for an *INSR* pathogenic variant are at increased risk for gestational diabetes and require monitoring for glucose intolerance before and during pregnancy [Kleijer et al 2006]. See ElSayed et al [2023] for management recommendations.

## Prenatal Testing and Preimplantation Genetic Testing

Once the *INSR* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).*

- **MedlinePlus**  
[Donohue syndrome](#)
- **National Organization for Rare Disorders (NORD)**  
[Leprechaunism](#)

## Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table A.** *INSR*-Related Severe Insulin Resistance Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>INSR</i>	19p13.2	Insulin receptor	<a href="#">INSR database</a>	<a href="#">INSR</a>	<a href="#">INSR</a>

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

**Table B.** OMIM Entries for *INSR*-Related Severe Insulin Resistance Syndrome ([View All in OMIM](#))

147670	INSULIN RECEPTOR; INSR
246200	DONOHUE SYNDROME
262190	PINEAL HYPERPLASIA, INSULIN-RESISTANT DIABETES MELLITUS, AND SOMATIC ABNORMALITIES

## Molecular Pathogenesis

*INSR* encodes the insulin receptor, a member of the superfamily of transmembrane receptor tyrosine kinases. The *INSR* preprotein, consisting of 1,382 amino acids, is proteolytically processed to generate the alpha and beta subunits of *INSR*, a heterotetrameric glycoprotein. The 731-amino acid alpha subunit, which is external to the plasma membrane, contains the insulin-binding region. The alpha subunit is linked by disulfide bonds to the 620-amino acid beta subunit, which includes a 194-amino acid extracellular domain, a 23-amino acid membrane-spanning segment, and a 403-amino acid cytoplasmic segment that has intrinsic tyrosine kinase activity [Seino et al 1989].

When insulin binds to the alpha subunit, the beta subunit undergoes autophosphorylation, which activates the insulin-signaling pathway regulating glucose uptake and release as well as the synthesis and storage of carbohydrates, lipids, and protein.

Taylor et al [1991] described five classes of *INSR* pathogenic variants that:

- Impair synthesis of the receptors;
- Impair transport of receptors to the cell membrane;
- Decrease receptor affinity for insulin;
- Reduce the tyrosine kinase activity of the receptor intracellular domain;
- Accelerate receptor degradation [Porter & Barrett 2005].

In severe insulin resistance, reduced intracellular insulin signaling causes hyperglycemia. The hypoglycemia in *INSR*-related severe insulin resistance syndrome is thought to be a consequence of late action of insulin-like growth factor 1 (IGF-1) [Kawashima et al 2013]. Insulin resistance causes alterations in the expression of genes encoding growth factors and apoptosis [Iovino et al 2014].

**Mechanism of disease causation.** Loss of function

**Table 7.** Notable *INSR* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000208.4 NP_000199.2	c.167T>C	p.Ile56Thr	Founder variant in the Druze from Israel [Falik Zaccai et al 2014]
	c.3003_3012del10insGGAAG	p.Ser1001ArgfsTer37	Identified in 3 persons from 2 unrelated families of Tunisian origin [Siala-Sahnoun et al 2016]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

## Chapter Notes

### Author Notes

Author research interests:

- Searching for genes responsible for various rare genetic disorders and investigating the clinical, biochemical, and molecular basis for each disorder by studying the related protein function and biologic pathway. Diseases currently of particular interest include neurogenetic diseases, aplasia of distal phalanges with juvenile breast hypertrophy (MDN), osteogenesis imperfecta, and hereditary spastic paraparesis and cardiomyopathies.
- Identification of new pathogenic variants, genes, and proteins involved in NER-type DNA repair mechanisms and understanding their cellular function and their role in premature aging and cancer. In addition, the establishment of new diagnostic procedures for the screening of causative pathogenic variants in affected individuals in Israel and the Middle East.
- Development of methods of genetic counseling tailored to kindreds at high risk for genetic disorders, in an attempt to raise awareness and to prevent and minimize the births of affected individuals. Also, early identification of affected newborns is critical for provision of prompt and effective treatment.
- Genetics of pain. Our interest in this field is manifested in the study of women with vulvodynia (pain during sexual intercourse). This phenomenon is evident within families, and genetic associations have been found. With the collaboration of Professor J Bornstein, we are studying possible genetic associations

that relate to biochemical pathways involved in pain regulation among a large cohort of women affected with vulvodynia.

Dr Falik Zaccai's [web page](#)

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