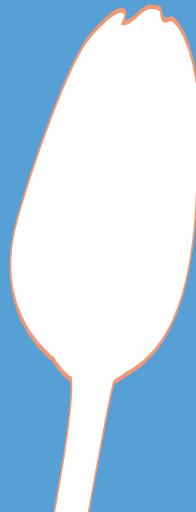


THE NATURE OF SEVERE PRIMARY IGF1



Replace
what's missing™



The long and the short of it

This brochure is meant to help you understand growth. It will help you grow your knowledge about short stature and, more specifically, about a condition called severe primary IGF-1 deficiency.

It's important to recognize that “tall” and “short” are relative terms. What is considered “normal” height has a lot to do with our cultural surroundings and ethnic heritage. Even within a particular culture, the range of what is considered normal for height and weight is wide.

It's also important to know that a child can have “short stature” and be perfectly normal and healthy. **The question to be addressed is whether the child's small size is the result of an underlying medical condition.** A pediatric endocrinologist can examine the child and perform tests to see whether a medical condition is affecting growth. If so, the endocrinologist can suggest treatment options that have demonstrated positive growth results.

Common types of short stature

Most children with short stature fit into one of the following categories.

Familial short stature: Familial short stature means that shortness can run in the family.

Constitutional growth delay (CGD): Children with CGD are small for their age and tend to reach puberty a little later than normal. However, because they are growing at a normal rate, they “catch up” and reach normal adult heights. Children with CGD are sometimes called “late bloomers.”

Idiopathic short stature (ISS): This is a catch-all term sometimes used to describe short stature when no cause for the lack of normal growth has been identified.

Small for gestational age (SGA): In some children, growth problems occur before birth. These problems can continue through childhood.

Endocrine diseases: Hormones are body chemicals that regulate and control how specific cells function. An endocrine disease is one in which the level of a hormone is too high or too low, and this can affect the body activity that the hormone controls. Two endocrine disorders that affect growth are growth hormone deficiency and a deficiency of IGF-1.

- ***Growth hormone deficiency:*** This is a disorder caused by lack of growth hormone, which stimulates the body to grow. To make this diagnosis, the physician considers many factors, including laboratory tests that tell the physician whether the body is able to make growth hormone on its own.
- ***Severe Primary IGF-1 (insulin-like growth factor-1) deficiency (Primary IGFD):*** This term can explain short stature in some children. IGF-1 is a hormone that plays a central role in human growth. Severe primary IGF-1 deficiency is a disorder in which IGF-1 levels are low. See detailed explanations of severe primary IGF-1 deficiency on the following pages.

Systemic diseases: Many chronic diseases, including diseases of the liver, heart, lung, or kidney—affect the whole body. As a result, they also affect the health and well-being of a child and the rate and extent of growth.

Unlocking the steps of normal growth

Step 1

The normal growth process begins when growth hormone is released by the pituitary gland in the brain. Growth hormone travels through the bloodstream, where it attaches itself to special structures on cells called “receptors.”

Step 2]

Think of receptors on cells as tiny locks.
Growth hormone acts like a key. When growth hormone attaches itself to a receptor, it “unlocks” the process that begins growth.

Step 3]

When the receptor works properly, a signal is sent throughout the cell, telling the cell to “start making IGF-1,” which is a key element needed for human growth.

Step 4]

In normal growth,
the cell starts producing the all-important
growth factor, IGF-1.

Step 5]

IGF-1 is released into the bloodstream and travels to other specialized cells in bone, cartilage, the liver, and other tissues, telling these parts of the body to grow.

When normal growth does not occur

Even though adequate growth hormone levels are present...



The growth hormone receptor can malfunction. For example, the key (growth hormone) may attach itself, but the lock (the receptor) won't open, and the growth process can't begin.



An error can occur in the signaling process within the cell. The message to make IGF-1 is not passed along properly and growth may not proceed normally.



A gene might be defective. A gene is a piece of DNA that contains the "code" from an individual's parents, so that their traits can be passed from one generation to the next. If the IGF-1 gene is defective, even if the "message" to make IGF-1 comes through loud and clear, the cell won't make the IGF-1 correctly.



When IGF-1 is deficient,
the body does not grow as it should.

1. Growth
Hormone
Secretion



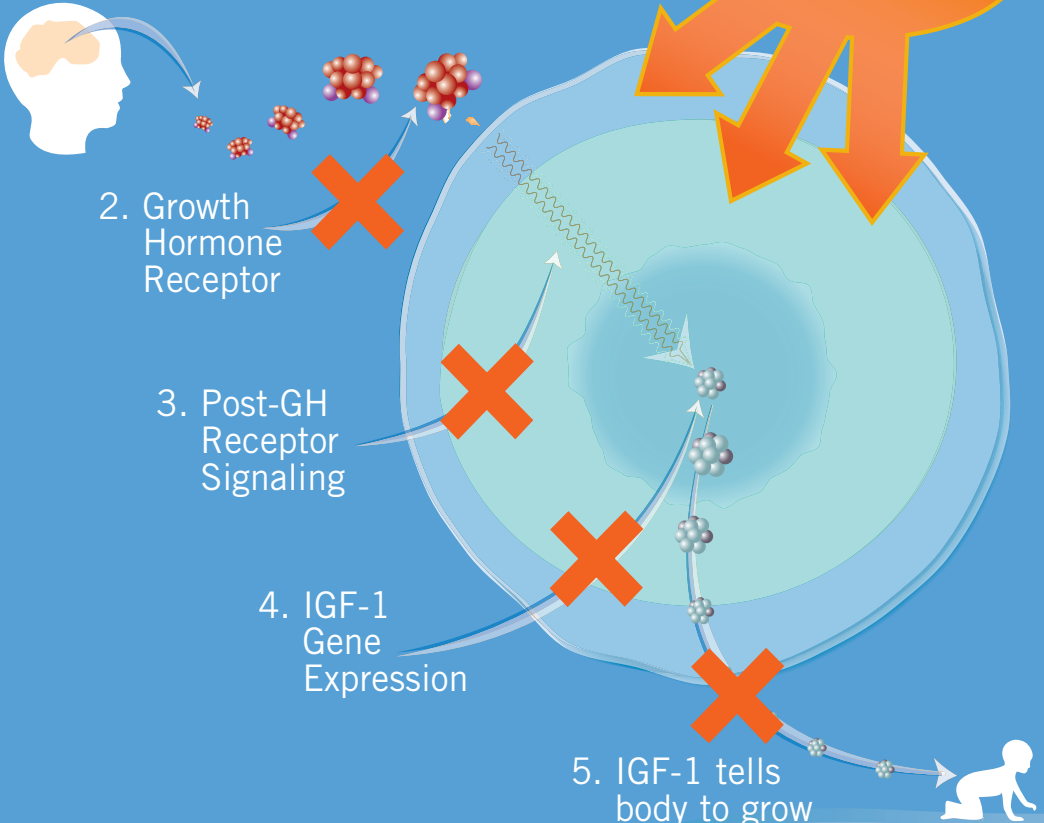
2. Growth
Hormone
Receptor

3. Post-GH
Receptor
Signaling

4. IGF-1
Gene
Expression

5. IGF-1 tells
body to grow

**Severe
Primary IGFD**



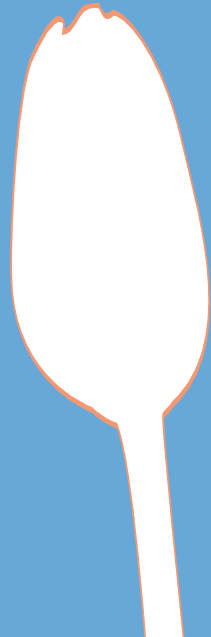
When...

Locks get **blocked**...

Signals get **crossed**...

Or genes have **defects**...

The IGF-1 needed for
growth can be **missing!**



The nature of severe Primary

WHAT IS IGF-1?

For years, researchers and scientists suspected that something in the body other than growth hormone was involved in stimulating growth. But it wasn't until the 1970s and 1980s that this factor was identified and called IGF-1 (insulin-like growth factor-1).

In the process of human growth, IGF-1 plays an important role. In fact, studies show that IGF-1 plays an even greater role in regulating height than growth hormone alone.¹

WHEN IGF-1 IS SUFFICIENT...AND DEFICIENT

When children have enough IGF-1, they grow normally, based on family history and assuming general good health, proper diet, and adequate sleep.

When children **don't** have enough IGF-1, they don't grow as tall as most children their age. This lack of normal growth can happen even when levels of growth hormone in the body are normal or high. When a child doesn't experience

IGFD

normal growth, and other criteria listed below are met, endocrinologists call the condition severe Primary IGF-1 deficiency, or severe Primary IGFD for short. It is estimated that 6,000 children in the United States have severe Primary IGFD.²

DIAGNOSING SEVERE PRIMARY IGFD

How does your doctor know when it's severe Primary IGFD?

- The child is shorter than 99.8% of other children of the same age and sex
- Levels of IGF-1 in the body are lower than those in 99.8% of other children of the same age and sex
- Levels of growth hormone in the body are normal or even high

The term “severe” may cause concern, but remember that doctors and insurance companies use the term mainly for classification purposes. It's also important to be aware that “severe” does not eliminate the prospect for help and growth.

Replace what's missing with



increlex[™]

(mecasermin [rDNA origin] injection)

A product is available to replace IGF-1 if the body can't produce enough for normal growth. This product is called Increlex, and it is a synthetic

form of the IGF-1 that is made by the body. Thanks to DNA technology, IGF-1 made in the laboratory is identical to the IGF-1 that the body produces naturally.

For children with severe Primary IGFD, replacing IGF-1 is a therapy option that has recently become available. Years of research and clinical trials were conducted before Increlex was approved by the Food and Drug Administration. As with most drugs, certain side effects have been associated with Increlex use in some patients, including low blood sugar (hypoglycemia) and enlarged tonsils (tonsillar hypertrophy). Your pediatric endocrinologist can explain all the benefits and risks and determine if Increlex is right for you. Ask your pediatric endocrinologist about Increlex trial results, or visit www.increlex.com.

Increlex™





Once your physician prescribes Increlex, TerciCare provides an extra measure of care

TerciCare was established to handle insurance issues and procedures directly with your insurance carrier. Once your physician has prescribed Increlex, TerciCare can help you coordinate and manage the exchange of information among you, your healthcare professional's office, and your health insurance company. In addition, TerciCare can:

- Provide Increlex therapy and supplies, including, if appropriate, a starter kit
- Keep you informed of your coverage status
- Answer any questions you may have about insurance or the process of obtaining coverage

It's all part of an extra measure of care that TerciCare and the people who bring you Increlex provide. For more information about the TerciCare program, call

1-866-TERCICA (1-866-837-2422)

and press option 3 to speak to a case manager.

Please see attached full Prescribing Information.

Talk to your physician about whether Increlex™
is right for your child

Visit the Increlex Web site: www.increlex.com



PI glues here

References:

1. Lupu F, Terwilliger JD, Lee K, Segre GV, Efstratiadis A. Roles of growth hormone and insulin-like growth factor 1 in mouse postnatal growth. *Dev Biol.* 2001;229:141-162.
2. Data on file. Brisbane, Calif: Tercica, Inc; 2005.



increlex™
(mecasermin [rDNA origin] injection)

Missing definitions? Find answers here.

Gene: A piece of DNA that contains the “code” from an individual’s parents, so that some of their traits—hair color, color of eyes, etc—can be passed from one generation to the next

Growth hormone: A specialized hormone, released by the pituitary gland, that plays a key role in the growth process and stimulates the production of IGF-1

Hormones: Chemicals, produced by glands in the body, that circulate in the blood and control many body functions, including growth, puberty, and reproduction

IGF-1: (insulin-like growth factor-1): A hormone that plays a central role in statural growth. IGF-1 affects almost every cell, especially those in muscle, cartilage, bone, liver, kidneys, nerves, skin, and lungs

Pituitary gland: The “master gland,” located at the base of the brain, that controls growth and metabolism (how the body uses energy)

Receptor: A structure on the surface of a cell that binds with substances such as hormones and allows them to do their jobs

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