

Autosomal Dominant Hyper-IgE Syndrome

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Autosomal dominant hyper-IgE syndrome (AD-HIES), formerly known as Job syndrome, is a condition that affects several body systems, particularly the immune system. Recurrent infections are common in people with this condition. Affected individuals tend to have frequent bouts of pneumonia, which are caused by certain kinds of bacteria that infect the lungs and cause inflammation. Inflammation is a normal immune system response to injury and foreign invaders (such as bacteria). However, excessive inflammation can damage body tissues. Recurring pneumonia often results in the formation of air-filled cysts (pneumatocoeles) in the lungs. Frequent skin infections and an inflammatory skin disorder called eczema are also very common in AD-HIES. These skin problems cause rashes, blisters, accumulations of pus (abscesses), open sores, and scaling.

Keywords: genetic conditions

1. Introduction

For unknown reasons, people with AD-HIES have abnormally high levels of an immune system protein called immunoglobulin E (IgE) in the blood. IgE normally triggers an immune response against foreign invaders in the body, particularly parasitic worms, and is involved in allergies. However, IgE is not needed for these roles in people with AD-HIES, and it is unclear why affected individuals have such high levels of the protein without having allergies.

AD-HIES also affects other parts of the body, including the bones and teeth. Many people with AD-HIES have skeletal abnormalities such as an unusually large range of joint movement (hyperextensibility), an abnormal curvature of the spine (scoliosis), reduced bone density (osteopenia), and a tendency for bones to fracture easily. A common dental abnormality in this condition is that the primary (baby) teeth do not fall out at the usual time during childhood but are retained as the adult teeth grow in. Other signs and symptoms of AD-HIES can include abnormalities of the arteries that supply blood to the heart muscle (coronary arteries), distinctive facial features, and structural abnormalities of the brain, which do not affect a person's intelligence.

2. Frequency

AD-HIES is rare, affecting fewer than 1 per million people worldwide.

3. Causes

Mutations in the *STAT3* gene cause most cases of AD-HIES. This gene provides instructions for making a protein that plays important roles in several body systems. To carry out its roles, the STAT3 protein attaches to DNA and helps control the activity of particular genes. In the immune system, the STAT3 protein regulates genes that are involved in the maturation of immune system cells, especially certain types of T cells. T cells and other immune system cells help control the body's response to foreign invaders such as bacteria and fungi.

Changes in the *STAT3* gene alter the structure and function of the STAT3 protein, impairing its ability to control the activity of other genes. A shortage of functional STAT3 blocks the maturation of T cells (specifically a subset known as Th17 cells) and other immune cells. The resulting immune system abnormalities make people with AD-HIES highly susceptible to infections, particularly bacterial and fungal infections of the lungs and skin. The STAT3 protein is also involved in the formation of cells that build and break down bone tissue, which could help explain why *STAT3* gene mutations lead to the skeletal and dental abnormalities characteristic of this condition. It is unclear how *STAT3* gene mutations lead to increased IgE levels.

Mutations in the *ZNF341* gene cause a disorder similar to AD-HIES but with a different pattern of inheritance. When the *STAT3* gene is involved, one altered copy of the gene is sufficient to cause the disorder (which is known as autosomal dominant inheritance). In contrast, when the *ZNF341* gene is involved, both copies of the gene are altered (which is known as autosomal recessive inheritance).

The *ZNF341* gene provides instructions for making a protein that appears to control the activity of the *STAT3* gene. *ZNF341* gene mutations, which prevent production of functional ZNF341 protein, result in a shortage of STAT3 protein, leading to immune system problems similar to those caused by *STAT3* gene mutations.

AD-HIES is thought to be caused by mutations in other genes that have not been definitively linked to the condition.

3.1. The genes associated with Autosomal dominant hyper-IgE syndrome

- STAT3
- ZNF341

4. Inheritance

AD-HIES has an autosomal dominant pattern of inheritance, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In about half of cases caused by *STAT3* gene mutations an affected person inherits the mutation from one affected parent. The other half result from new mutations in the gene and occur in people with no history of the disorder in their family.

A similar condition caused by mutations in the *ZNF341* gene has an autosomal recessive pattern of inheritance, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

5. Other Names for This Condition

- AD-HIES
- autosomal dominant HIES
- autosomal dominant hyper-IgE recurrent infection syndrome
- autosomal dominant hyperimmunoglobulin E recurrent infection syndrome
- autosomal dominant Job syndrome
- Buckley syndrome
- Job syndrome
- Job's Syndrome
- Job-Buckley syndrome
- STAT3 deficiency
- STAT3-deficient hyper IgE syndrome

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