Autosomal dominant hyper-IgE syndrome

Autosomal dominant hyper-IgE syndrome (AD-HIES), also 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. These infections often result in the formation of air-filled cysts (pneumatoceles) in the lungs. Recurrent 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.

AD-HIES is characterized by 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 plays a role in allergies. It is unclear why people with AD-HIES have such high levels of IgE.

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. Dental abnormalities are also common in this condition. 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.

Frequency

This condition is rare, affecting fewer than 1 per million people.

Genetic Changes

Mutations in the *STAT3* gene cause most cases of AD-HIES. This gene provides instructions for making a protein that plays an important role 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 T cells. These 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.

When AD-HIES is not caused by *STAT3* gene mutations, the genetic cause of the condition is unknown.

Inheritance Pattern

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

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-Buckley syndrome
- Job syndrome
- Job's Syndrome
- STAT3 deficiency
- STAT3-deficient hyper IgE syndrome

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Hyperimmunoglobulin E syndrome
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C3489795/

Other Diagnosis and Management Resources

- GeneReview: Autosomal Dominant Hyper IgE Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK25507
- MedlinePlus Encyclopedia: Hyperimmunoglobulin E syndrome
  https://medlineplus.gov/ency/article/001311.htm

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Hyperimmunoglobulin E syndrome
  https://medlineplus.gov/ency/article/001311.htm
- Health Topic: Immune System and Disorders
  https://medlineplus.gov/immunesystemanddisorders.html
- Health Topic: Lung Diseases
  https://medlineplus.gov/lungdiseases.html
- Health Topic: Skin Conditions
  https://medlineplus.gov/skinconditions.html

Genetic and Rare Diseases Information Center

- Autosomal dominant hyper IgE syndrome
  https://rarediseases.info.nih.gov/diseases/6800/autosomal-dominant-hyper-ige-syndrome
- Hyper IgE syndrome
  https://rarediseases.info.nih.gov/diseases/10956/hyper-ige-syndrome

Additional NIH Resources

- National Institute of Allergy and Infectious Diseases
  https://www.niaid.nih.gov/diseases-conditions/hyper-immunoglobulin-e-syndrome-hies-or-jobs-syndrome
- National Institute of Allergy and Infectious Diseases: Primary Immune Deficiency Diseases
  https://www.niaid.nih.gov/diseases-conditions/primary-immune-deficiency-diseases-pidds

Educational Resources

- Disease InfoSearch: Hyperimmunoglobulin E recurrent infection syndrome, autosomal dominant
  http://www.diseaseinfosearch.org/Hyperimmunoglobulin+E+recurrent+infection+syndrome%2C+autosomal+dominant/3560
- Disease InfoSearch: Hyperimmunoglobulin E syndrome
  http://www.diseaseinfosearch.org/Hyperimmunoglobulin+E+syndrome/8588
- MalaCards: hyper-ige recurrent infection syndrome, autosomal dominant
  http://www.malacards.org/card/hyper_ige_recurrent_infection_syndrome_autosomal_dominant
- Orphanet: Autosomal dominant hyper-IgE syndrome
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=2314

Patient Support and Advocacy Resources

- Immune Deficiency Foundation
  https://primaryimmune.org/
- International Patient Organization for Primary Immunodeficiencies
  https://ipopi.org/
- National Organization for Rare Diseases: Autosomal Dominant Hyper IgE Syndrome
  https://rarediseases.org/rare-diseases/autosomal-dominant-hyper-ige-syndrome/
- Resource List from the University of Kansas Medical Center: Immune Deficiency Conditions
  http://www.kumc.edu/gec/support/immune.html

GeneReviews

- Autosomal Dominant Hyper IgE Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK25507

ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22Job+syndrome%22+OR+%22Job%27s+Syndrome%22

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28Job+syndrome%5BTIAB%5D%29+OR+%28Job+syndrome%5BMAJR%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D

OMIM

- HYPER-IgE RECURRENT INFECTION SYNDROME, AUTOSOMAL DOMINANT
  http://omim.org/entry/147060

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