GJA1 Gene

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Gap junction protein alpha 1

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1. Normal Function

The *GJA1* gene provides instructions for making a protein called connexin 43, which is one of 21 connexin proteins. Connexins play a role in cell-to-cell communication by forming channels, or gap junctions, between cells. Gap junctions allow for the transport of nutrients, charged particles (ions), and other small molecules that carry necessary communication signals between cells. In addition, connexin 43 attaches (binds) several signaling molecules that can relay communication signals inside the cell. Connexin 43 is found in many tissues such as the eyes, skin, bone, ears, heart, and brain, and it plays a role in their normal development and function.

2. Health Conditions Related to Genetic Changes

2.1 Craniometaphyseal Dysplasia

A mutation in the *GJA1* gene has been found to cause autosomal recessive craniometaphyseal dysplasia in a small number of people. This condition is characterized by thickening of bones in the skull (cranium) and widening of a region at the end of long bones known as the metaphysis. The mutation is present in both copies of the *GJA1* gene. It changes a single protein building block (amino acid) in the connexin 43 protein: at position 239, the amino acid arginine is replaced with the amino acid glutamine (written as Arg239Gln or R239Q). It is unknown how this change affects the function of the connexin 43 protein or leads to the bone abnormalities characteristic of craniometaphyseal dysplasia.

2.2 Erythrokeratodermia Variabilis et Progressiva

At least two mutations in the *GJA1* gene have been found to cause erythrokeratodermia variabilis et progressiva (EKVP), a skin disorder characterized by areas of hyperkeratosis, which is abnormally thickened skin, and temporarily reddened patches called erythematous areas. The *GJA1* gene mutations that cause this disorder are present in one of the two copies of the gene in each cell. Each of the known mutations changes a single amino acid in the connexin 43 protein. These changes lead to the production of an abnormal version of the protein that is unable to reach the cell surface to become part of gap junctions. Instead, after it is produced, the abnormal protein becomes trapped in a cell structure called the Golgi apparatus. It is unclear how a shortage of connexin 43 at the cell surface affects the structure of gap junctions in the outermost layer of skin (epidermis), or how these changes result in the skin abnormalities characteristic of EKVP.

2.3 Nonsyndromic Hearing Loss

2.4 Oculodentodigital Dysplasia

At least 76 mutations in the *GJA1* gene have been found to cause oculodentodigital dysplasia, a condition characterized by abnormalities of the eyes (oculo-), teeth (dento-), and fingers (digital). The *GJA1* gene mutations that cause this disorder are usually present in one of the two copies of the gene in each cell. Most of these mutations change an amino acid in connexin 43. A different type of change in the *GJA1* gene causes people to have oculodentodigital dysplasia with palmoplantar keratoderma. Palmoplantar keratoderma is a condition that causes skin on the palms of the hands and the soles of the feet to become thick, scaly, and calloused. The mutation that causes this condition deletes two DNA building blocks (nucleotides) to create a premature stop signal in the instructions for making connexin 43. As a result, an abnormally short, nonfunctional protein is produced.

Gap junctions formed with abnormal connexin 43 proteins are often permanently closed, preventing the transport of any molecules. Some mutations prevent connexin 43 proteins from traveling to the cell surface where they are needed to form gap junctions. These disruptions impair communication between cells, which is thought to cause the eye, tooth, and finger abnormalities characteristic of oculodentodigital dysplasia.

2.5 Coloboma

2.6 Critical Congenital Heart Disease

2.7 Heterotaxy Syndrome

2.8 Other Disorders

Mutations in one copy of the *GJA1* gene in each cell can cause isolated syndactyly type III, which is characterized by fusion of the ring and pinky fingers (fourth and fifth fingers) and sometimes shortening of the pinky finger. Syndactyly type III is a characteristic feature in oculodentodigital dysplasia (described above); however, some people have syndactyly type III without other features of oculodentodigital dysplasia, which is known as isolated syndactyly type III. It is unclear why some people with *GJA1* gene mutations develop only the finger abnormalities and others have additional developmental abnormalities characteristic of oculodentodigital dysplasia.

A mutation in one copy of the *GJA1* gene has been found to cause palmoplantar keratoderma and congenital alopecia 1, a condition characterized by skin problems, an absence of hair from birth (congenital alopecia), and often nail abnormalities. The mutation identified in this disorder leads to production of an altered connexin 43 protein. Channels made with the altered protein open more easily than normal, increasing the transport of molecules. Researchers suggest that abnormal signaling in cells that form the skin, hair, and nails results in the features characteristic of palmoplantar keratoderma and congenital alopecia 1.

Other mutations in one copy of the *GJA1* gene in each cell have been found in a small number of people who have died suddenly with no known cause in infancy (sudden infant death syndrome) or early adulthood (sudden unexplained nocturnal death). Doctors suspect that abnormalities of heart function associated with *GJA1* gene mutations may contribute to sudden death. It is thought that other genetic and environmental factors, many of which have not been identified, also play a part in determining the risk of these disorders. Mutations in one copy of the *GJA1* gene may also contribute to heart malformations, although the role of such a genetic change is unclear.

3. Other Names for This Gene

- connexin 43
- connexin43
- CX43
- Cx43α1
- CXA1_HUMAN
- gap junction 43 kDa heart protein
- gap junction protein, alpha 1, 43kDa
- gap junction protein, alpha-like

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