Erythrokeratodermia variabilis et progressiva

Description

Erythrokeratodermia variabilis et progressiva (EKVP) is a skin disorder that is present at birth or becomes apparent in infancy. Although its signs and symptoms vary, the condition is characterized by two major features. The first is hyperkeratosis, which is rough, thickened skin. These patches are usually reddish-brown and can either affect many parts of the body or occur in only a small area. They tend to be fixed, meaning they rarely spread or go away. However, the patches can vary in size and shape, and in some affected people they get larger over time. The areas of hyperkeratosis are generally symmetric, which means they occur in the same places on the right and left sides of the body.

The second major feature of EKVP is patches of reddened skin called erythematous areas. Unlike the hyperkeratosis that occurs in this disorder, the erythematous areas are usually transient, which means they come and go. They vary in size, shape, and location, and can occur anywhere on the body. The redness is more common in childhood and can be triggered by sudden changes in temperature, emotional stress, or trauma or irritation to the area. It usually fades within hours to days.

Frequency

EKVP is a rare disorder; its prevalence is unknown. More than 200 cases have been reported in the medical literature.

Causes

EKVP can be caused by mutations in several genes, including *GJB3*, *GJB4*, and *GJA1*. These three genes provide instructions for making proteins called connexins 31, 30.3, and 43, respectively. These proteins are part of the connexin family, a group of proteins that form channels called gap junctions on the surface of cells. Gap junctions open and close to regulate the flow of nutrients, charged atoms (ions), and other signaling molecules from one cell to another. They are essential for direct communication between neighboring cells. Gap junctions formed with connexins 31, 30.3, and 43 are found in several tissues, including the outermost layer of skin (the epidermis).

The *GJB3*, *GJB4*, and *GJA1* gene mutations that lead to EKVP alter the structure or location of the connexins produced from these genes. Some *GJB3* or *GJB4* gene

mutations lead to the production of abnormal connexins that can build up in a cell structure called the endoplasmic reticulum (ER), triggering a harmful process known as ER stress. Researchers suspect that ER stress damages cells in the epidermis and leads to their premature death. Other *GJB3* or *GJB4* gene mutations alter the flow of molecules through gap junctions, which may also lead to premature cell death in the epidermis. The mechanisms by which epidermal damage and cell death contribute to hyperkeratosis and erythematous areas are poorly understood.

Mutations in the *GJA1* gene lead to the production of an abnormal connexin 43 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 epidermis, or how these changes result in the skin abnormalities characteristic of EKVP.

In some cases, people with EKVP do not have a known mutation in one of the three connexin genes described above. Mutations in at least one non-connexin gene have been reported in a very small number of affected people. Studies suggest that changes in other genes that have not been identified may also cause EKVP.

Learn more about the genes associated with Erythrokeratodermia variabilis et progressiva

- GJA1
- GJB3
- GJB4
- KRT83

Inheritance

EKVP is most often inherited in an autosomal dominant pattern, which means one copy of an altered gene in each cell is sufficient to cause the disorder. In most cases, an affected person inherits the mutation from one affected parent. Other cases result from new gene mutations and occur in people with no history of the disorder in their family. Very rarely, the mutation is found in some of the body's cells but not others. In these individuals, the condition is described as mosaic EKVP or inflammatory linear verrucous epidermal nevus (ILVEN). In mosaic EKVP, the characteristic skin abnormalities affect a small region of the body and usually occur on just one side. They may follow a pattern on the skin known as the lines of Blaschko.

A few studies have shown that EKVP can also have an autosomal recessive pattern of inheritance. However, this inheritance pattern has been reported in only a small number of affected families. Autosomal recessive inheritance means both copies of a 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.

Other Names for This Condition

- EKV
- EKV-P
- EKVP
- Erythrokeratodermia variabilis
- Erythrokeratodermia variabilis of Mendes da Costa
- Erythrokeratodermia, progressive symmetric
- Progressive symmetrical erythrokeratoderma of Gottron

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Erythrokeratodermia variabilis et progressiva 1 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C4551486/)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Catalog of Genes and Diseases from OMIM

- ERYTHROKERATODERMIA VARIABILIS ET PROGRESSIVA 1; EKVP1 (https://omim.org/entry/133200)
- ERYTHROKERATODERMIA VARIABILIS ET PROGRESSIVA 2; EKVP2 (https://omim.org/entry/617524)
- ERYTHROKERATODERMIA VARIABILIS ET PROGRESSIVA 3; EKVP3 (https://omim.org/entry/617525)
- ERYTHROKERATODERMIA VARIABILIS ET PROGRESSIVA 4; EKVP4 (https://omim.org/entry/617526)
- ERYTHROKERATODERMIA VARIABILIS ET PROGRESSIVA 5; EKVP5 (https://omim.org/entry/617756)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28Erythrokeratodermia+Variabilis%5BMAJR%5D%29+OR+%28Erythrokeratodermia+Variabilis%5BTI%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D)

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