Keratoderma with Woolly Hair

Subjects: Genetics & Heredity
Contributor: Camila Xu

Keratoderma with woolly hair is a group of related conditions that affect the skin and hair and in many cases increase the risk of potentially life-threatening heart problems.

Keywords: genetic conditions

1. Introduction

People with these conditions have hair that is unusually coarse, dry, fine, and tightly curled. In some cases, the hair is also sparse. The woolly hair texture typically affects only scalp hair and is present from birth. Starting early in life, affected individuals also develop palmoplantar keratoderma, a condition that causes skin on the palms of the hands and the soles of the feet to become thick, scaly, and calloused.

Cardiomyopathy, which is a disease of the heart muscle, is a life-threatening health problem that can develop in people with keratoderma with woolly hair. Unlike the other features of this condition, signs and symptoms of cardiomyopathy may not appear until adolescence or later. Complications of cardiomyopathy can include an abnormal heartbeat (arrhythmia), heart failure, and sudden death.

Keratoderma with woolly hair comprises several related conditions with overlapping signs and symptoms. Researchers have recently proposed classifying keratoderma with woolly hair into four types, based on the underlying genetic cause. Type I, also known as Naxos disease, is characterized by palmoplantar keratoderma, woolly hair, and a form of cardiomyopathy called arrhythmogenic right ventricular cardiomyopathy (ARVC). Type II, also known as Carvajal syndrome, has hair and skin abnormalities similar to type I but features a different form of cardiomyopathy, called dilated left ventricular cardiomyopathy. Type III also has signs and symptoms similar to those of type I, including ARVC, although the hair and skin abnormalities are often milder. Type IV is characterized by palmoplantar keratoderma and woolly and sparse hair, as well as abnormal fingernails and toenails. Type IV does not appear to cause cardiomyopathy.

2. Frequency

Keratoderma with woolly hair is rare; its prevalence worldwide is unknown.

Type I (Naxos disease) was first described in families from the Greek island of Naxos. Since then, affected families have been found in other Greek islands, Turkey, and the Middle East. This form of the condition may affect up to 1 in 1,000 people from the Greek islands.

Type II (Carvajal syndrome), type III, and type IV have each been identified in only a small number of families worldwide.

3. Causes

Mutations in the *JUP*, *DSP*, *DSC2*, and *KANK2* genes cause keratoderma with woolly hair types I through IV, respectively. The *JUP*, *DSP*, and *DSC2* genes provide instructions for making components of specialized cell structures called desmosomes. Desmosomes are located in the membrane surrounding certain cells, including skin and heart muscle cells. Desmosomes help attach cells to one another, which provides strength and stability to tissues. They also play a role in signaling between cells.

Mutations in the *JUP*, *DSP*, or *DSC2* gene alter the structure and impair the function of desmosomes. Abnormal or missing desmosomes prevent cells from sticking to one another effectively, which likely makes the hair, skin, and heart muscle more fragile. Over time, as these tissues are exposed to mechanical stress (for example, friction on the surface of the skin or the constant contraction and relaxation of the heart muscle), they become damaged and can no longer function

normally. This mechanism probably underlies the skin, hair, and heart problems that occur in keratoderma with woolly hair. Some studies suggest that abnormal cell signaling may also contribute to cardiomyopathy in people with this group of conditions.

Unlike the other genes associated with keratoderma with woolly hair, the *KANK2* gene provides instructions for making a protein that is not part of desmosomes. Instead, it regulates other proteins called steroid receptor coactivators (SRCs), whose function is to help turn on (activate) certain genes. SRCs play important roles in tissues throughout the body, including the skin. Studies suggest that mutations in the *KANK2* gene disrupt the regulation of SRCs, which leads to abnormal gene activity. However, it is unclear how these changes underlie the skin and hair abnormalities in keratoderma with woolly hair type IV.

3.1. The genes associated with Keratoderma with woolly hair

- DSC2
- DSP
- JUP
- KANK2

4. Inheritance

Most cases of keratoderma with woolly hair have 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 usually do not show signs and symptoms of the condition.

5. Other Names for This Condition

- KWWH

References

1. McKoy G, Protonotarios N, Crosby A, Tsatsopoulou A, Anastasakis A, Coonar A,Norman M, Baboonian C, Jeffery S, McKenna WJ. Identification of a deletion inplakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). Lancet. 2000 Jun17;355(9221):2119-24.
2. Norgett EE, Hatsell SJ, Carvajal-Huerta L, Cabezas JC, Common J, Purkis PE,Whittock N, Leigh IM, Stevens HP, Kelsell DP. Recessive mutation in desmoplakindisrupts desmoplakin-intermediate filament interactions and causes dilatedcardiomyopathy, woolly hair and keratoderma. Hum Mol Genet. 2000 Nov1;9(18):2761-6.
3. Petrof G, Mellerio JE, McGrath JA. Desmosomal genodermatoses. Br J Dermatol.2012 Jan;166(1):36-45. doi: 10.1111/j.1365-2133.2011.10640.x. Review.
4. Polivka L, Bodemer C, Hadj-Rabia S. Combination of palmoplantar keratodermaand hair shaft anomalies, the warning signal of severe arrhythmogeniccardiomyopathy: a systematic review on genetic desmosomal diseases. J Med Genet. 2016 May;53(5):289-95. doi: 10.1136/jmedgenet-2015-103403.Review.
5. Ramot Y, Molho-Pessach V, Meir T, Alper-Pinus R, Siam I, Tams S, Babay S,Zlotogorski A. Mutation in KANK2, encoding a sequestering protein for steroidreceptor coactivators, causes keratoderma and woolly hair. J Med Genet. 2014Jun;51(6):388-94. doi: 10.1136/jmedgenet-2014-102346.
6. Ramot Y, Zlotogorski A. The twisting tale of woolly hair: a trait with manycauses. J Med Genet. 2015 Apr;52(4):217-23. doi: 10.1136/jmedgenet-2014-102630.
7. Simpson MA, Mansour S, Ahnood D, Kalidas K, Patton MA, McKenna WJ, Behr ER,Crosby AH. Homozygous mutation of desmocollin-2 in arrhythmogenic rightventricular cardiomyopathy with mild palmoplantar keratoderma and woolly hair.Cardiology. 2009;113(1):28-34. doi: 10.1159/000165696.