WDR35 Gene

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WD repeat domain 35.

genes

1. Normal Function

The *WDR35* gene (also known as *IFT121*) provides instructions for making a protein that is involved in the formation and maintenance of cilia, which are microscopic, finger-like projections that stick out from the surface of cells. Cilia participate in signaling pathways that transmit information within and between cells and are important for the development and function of many types of cells and tissues, including cells in the kidneys and liver and the light-sensitive tissue at the back of the eye (the retina). Cilia also play a role in the development of the bones, although the mechanism is not well understood.

The movement of substances within cilia and similar structures called flagella is known as intraflagellar transport. This process is essential for the assembly and maintenance of these cell structures. During intraflagellar transport, cells use molecules called IFT particles to carry materials to and from the tips of cilia. Each IFT particle is made up of two groups of IFT proteins: complex A and complex B. The protein produced from the *WDR35* gene forms part of IFT complex A (IFT-A). During intraflagellar transport, this complex carries materials from the tip to the base of cilia.

The IFT-A complex is essential for proper regulation of the Sonic Hedgehog signaling pathway, which is important for the growth and maturation (differentiation) of cells and the normal shaping (patterning) of many parts of the body, especially during embryonic development. The exact role of the complex in this pathway is unclear.

2. Health Conditions Related to Genetic Changes

2.1. Cranioectodermal Dysplasia

The *WDR35* gene is the most commonly mutated gene in people with cranioectodermal dysplasia; at least eight mutations in this gene have been identified in affected individuals. This condition is characterized by an elongated head (dolichocephaly) with a prominent forehead and other distinctive facial features; short bones; and abnormalities of certain tissues known as ectodermal tissues, which include the teeth, hair, nails, and skin.

The *WDR35* gene mutations involved in cranioectodermal dysplasia reduce the amount of functional WDR35 protein. A shortage or reduction in activity of this component of the IFT-A complex impairs the function of the entire complex, disrupting transport of proteins and materials from the tips of cilia. As a result, assembly and maintenance of cilia is impaired, which leads to a smaller number of cilia and abnormalities in their shape and structure. Although the mechanism is unclear, a loss of normal cilia impedes proper development of bone and other tissues, leading to the features of cranioectodermal dysplasia. Some researchers suggest that disrupted intraflagellar transport prevents signaling through the Sonic Hedgehog pathway, which could impact cell growth and other functions in several tissues throughout the body.

2.2. Asphyxiating Thoracic Dystrophy

2.3. Other Disorders

WDR35 gene mutations can cause short-rib polydactyly type 5, a severe condition with signs and symptoms similar to those of cranioectodermal dysplasia (described above); however, affected individuals do not survive to birth. Bone abnormalities in short-rib polydactyly type 5 include extremely short ribs, short arms and legs, and extra fingers or toes (polydactyly). Additional features include abnormalities in one or more organs, including the heart, kidneys, liver, and intestines. The severity of this condition is thought to be caused by a severe loss of function of the WDR35 protein, which likely disrupts the function of cilia to a greater degree than in cranioectodermal dysplasia.

3. Other Names for This Gene

- CED2
- IFT121
- IFTA1
- intraflagellar transport protein 121 homolog
- KIAA1336
- MGC33196
- naofen
- WD repeat-containing protein 35
- WDR35_HUMAN

References

1. Arts H, Knoers N. Cranioectodermal Dysplasia. 2013 Sep 12 [updated 2018 Apr12]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K,Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University ofWashington, Seattle; 1993-2020. Available fromhttp://www.ncbi.nlm.nih.gov/books/NBK154653/
2. Bacino CA, Dhar SU, Brunetti-Pierri N, Lee B, Bonnen PE. WDR35 mutation insiblings with Sensenbrenner syndrome: a ciliopathy with variable phenotype. Am J Med Genet A. 2012 Nov;158A(11):2917-24. doi: 10.1002/ajmg.a.35608.
3. Liem KF Jr, Ashe A, He M, Satir P, Moran J, Beier D, Wicking C, Anderson KV.The IFT-A complex regulates Shh signaling through cilia structure and membraneprotein trafficking. J Cell Biol. 2012 Jun 11;197(6):789-800. doi:10.1083/jcb.201110049.
4. Mill P, Lockhart PJ, Fitzpatrick E, Mountford HS, Hall EA, Reijns MA, KeighrenM, Bahlo M, Bromhead CJ, Budd P, Aftimos S, Delatycki MB, Savarirayan R, Jackson IJ, Amor DJ. Human and mouse mutations in WDR35 cause short-rib polydactylysyndromes due to abnormal ciliogenesis. Am J Hum Genet. 2011 Apr 8;88(4):508-15. doi: 10.1016/j.ajhg.2011.03.015.