HDAC8 Gene

Subjects: Genetics & Heredity
Contributor: Dean Liu

Histone deacetylase 8

genes

1. Introduction

The *HDAC8* gene provides instructions for making an enzyme called histone deacetylase 8. This enzyme is involved in regulating the structure and organization of chromosomes during cell division.

Before cells divide, they must copy all of their chromosomes. The copied DNA from each chromosome is arranged into two identical structures called sister chromatids. Sister chromatids are attached to one another during the early stages of cell division by a group of proteins called the cohesin complex. Later in cell division, the cohesin complex must be removed so the sister chromatids can separate, allowing one from each pair to move into each newly forming cell. Histone deacetylase 8 carries out a chemical reaction that helps remove the cohesin complex so it can be recycled for future cell divisions.

Researchers believe that histone deacetylase 8, as a regulator of the cohesin complex, also plays important roles in stabilizing cells' genetic information, repairing damaged DNA, and controlling the activity of certain genes that are essential for normal development.

2. Health Conditions Related to Genetic Changes

2.1. Cornelia de Lange Syndrome

At least 28 mutations in the *HDAC8* gene have been identified in people with Cornelia de Lange syndrome, a developmental disorder that affects many parts of the body. Researchers estimate that mutations in this gene account for about 5 percent of all cases of this condition.

Most *HDAC8* gene mutations change single protein building blocks (amino acids) in histone deacetylase 8 or add or delete a small number of amino acids in the enzyme. All of these mutations appear to reduce or eliminate the enzyme's activity, which likely alters the activity of the cohesin complex and impairs its ability to regulate genes that are critical for normal development. Although researchers do not fully understand how these changes cause

Cornelia de Lange syndrome, they suspect that altered gene regulation probably underlies many of the developmental problems characteristic of the condition.

Studies suggest that mutations in the *HDAC8* gene cause a somewhat different pattern of signs and symptoms than those associated with mutations in the *NIPBL* gene, which are the most common known cause of Cornelia de Lange syndrome. Affected individuals with *HDAC8* gene mutations often have less severe growth problems, fewer abnormalities of the arms and hands, and different characteristic facial features than those with *NIPBL* gene mutations. They are more likely to have delayed closure of the "soft spot" on the head (the anterior fontanelle) in infancy, widely spaced eyes, and dental abnormalities. Like affected individuals with *NIPBL* gene mutations, those with *HDAC8* gene mutations may have significant intellectual disability.

2.2. Other Disorders

A mutation in the *HDAC8* gene has also been identified in a large Dutch family with a form of X-linked intellectual disability. (X-linked refers to the fact that the *HDAC8* gene is on the X chromosome, one of the two sex chromosomes.) Signs and symptoms in affected males include severe intellectual disability, short stature, obesity, breast enlargement (gynecomastia), reduced production of sex hormones (hypogonadism), an unusually small head, small hands, and distinctive facial features. Affected females tend to have less severe signs and symptoms, including learning disabilities and unusual facial features.

The identified mutation leads to a version of histone deacetylase 8 that is missing a segment. The abnormally short protein probably alters gene regulation during development, which causes the various health problems described in this family.

The condition in this family has been described as Wilson-Turner syndrome, which is a form of X-linked intellectual disability. However, researchers speculate that it may actually be part of the same disease spectrum as Cornelia de Lange syndrome (described above).

3. Other Names for This Gene

- CDA07
- CDLS5
- HD8
- HDACL1
- histone deacetylase-like 1
- MRXS6

- RPD3
- WTS

References

1. Deardorff MA, Bando M, Nakato R, Watrin E, Itoh T, Minamino M, Saitoh K,Komata M, Katou Y, Clark D, Cole KE, De Baere E, Decroos C, Di Donato N, Ernst S,Francey LJ, Gyftodimou Y, Hirashima K, Hullings M, Ishikawa Y, Jaulin C, Kaur M, Kiyono T, Lombardi PM, Magnaghi-Jaulin L, Mortier GR, Nozaki N, Petersen MB,Seimiya H, Siu VM, Suzuki Y, Takagaki K, Wilde JJ, Willems PJ, Prigent C,Gillessen-Kaesbach G, Christianson DW, Kaiser FJ, Jackson LG, Hirota T, KrantzID, Shirahige K. HDAC8 mutations in Cornelia de Lange syndrome affect the cohesinacetylation cycle. Nature. 2012 Sep 13;489(7415):313-7. doi: 10.1038/nature11316.
2. Decroos C, Bowman CM, Moser JA, Christianson KE, Deardorff MA, ChristiansonDW. Compromised structure and function of HDAC8 mutants identified in Cornelia deLange Syndrome spectrum disorders. ACS Chem Biol. 2014 Sep 19;9(9):2157-64. doi: 10.1021/cb5003762.
3. Harakalova M, van den Boogaard MJ, Sinke R, van Lieshout S, van Tuil MC, DuranK, Renkens I, Terhal PA, de Kovel C, Nijman IJ, van Haelst M, Knoers NV, vanHaaften G, Kloosterman W, Hennekam RC, Cuppen E, Ploos van Amstel HK. X-exomesequencing identifies a HDAC8 variant in a large pedigree with X-linkedintellectual disability, truncal obesity, gynaecomastia, hypogonadism and unusualface. J Med Genet. 2012 Aug;49(8):539-43. doi: 10.1136/jmedgenet-2012-100921.
4. Kaiser FJ, Ansari M, Braunholz D, Concepción Gil-Rodríguez M, Decroos C, WildeJJ, Fincher CT, Kaur M, Bando M, Amor DJ, Atwal PS, Bahlo M, Bowman CM, BradleyJJ, Brunner HG, Clark D, Del Campo M, Di Donato N, Diakumis P, Dubbs H, DymentDA, Eckhold J, Ernst S, Ferreira JC, Francey LJ, Gehlken U, Guillén-Navarro E,Gyftodimou Y, Hall BD, Hennekam R, Hudgins L, Hullings M, Hunter JM, Yntema H,Innes AM, Kline AD, Krumina Z, Lee H, Leppig K, Lynch SA, Mallozzi MB, Mannini L,McKee S, Mehta SG, Micule I; Care4Rare Canada Consortium, Mohammed S, Moran E,Mortier GR, Moser JA, Noon SE, Nozaki N, Nunes L, Pappas JG, Penney LS,Pérez-Aytés A, Petersen MB, Puisac B, Revencu N, Roeder E, Saitta S, ScheuerleAE, Schindeler KL, Siu VM, Stark Z, Strom SP, Thiese H, Vater I, Willems P,Williamson K, Wilson LC; University of Washington Center for Mendelian Genomics, Hakonarson H, Quintero-Rivera F, Wierzba J, Musio A, Gillessen-Kaesbach G, Ramos FJ, Jackson LG, Shirahige K, Pié J, Christianson DW, Krantz ID, Fitzpatrick DR,Deardorff MA. Loss-of-function HDAC8 mutations cause a phenotypic spectrum ofCornelia de Lange syndrome-like features, ocular hypertelorism, large fontanelle and X-linked inheritance. Hum Mol Genet. 2014 Jun 1;23(11):2888-900. doi:10.1093/hmg/ddu002.

5. Mordaunt DA, McLauchlan A. HDAC8-deficiency causes an X-linked dominantdisorder with a wide range of severity. Clin Genet. 2015 Jul;88(1):98. doi:10.1111/cge.12588.

Retrieved from https://encyclopedia.pub/entry/history/show/12518