DUX4 Gene

Subjects: Genetics & Heredity
Contributor: Vivi Li

Double Homeobox 4

genes

1. Normal Function

The *DUX4* gene is located near the end of chromosome 4 in a region known as D4Z4. This region consists of 11 to more than 100 repeated segments, each of which is about 3,300 DNA base pairs (3.3 kb) long. The entire D4Z4 region is normally hypermethylated, which means that it has a large number of methyl groups (consisting of one carbon atom and three hydrogen atoms) attached to the DNA. The addition of methyl groups turns off (silences) genes, so hypermethylated regions of DNA tend to have fewer genes that are turned on (active).

Each of the repeated segments in the D4Z4 region contains a copy of the *DUX4* gene; the copy closest to the end of chromosome 4 is called *DUX4*, while the other copies are described as "*DUX4*-like" or *DUX4L*. Hypermethylation of the D4Z4 region keeps the *DUX4*-like genes silenced all the time. No protein is produced from these genes. The *DUX4* gene is also silenced in most adult cells and tissues, although it is active during early development and in the testes of adult males. Little is known about the function of the protein produced from the active *DUX4* gene; it appears to help control the activity of other genes.

The *DUX4* gene (the copy closest to the end of chromosome 4) is located next to a regulatory region of DNA known as a pLAM sequence, which is necessary for the production of the DUX4 protein. Some copies of chromosome 4 have a functional pLAM sequence, while others do not. Copies of chromosome 4 with a functional pLAM sequence are described as 4qA or "permissive." Those without a functional pLAM sequence are described as 4qB or "non-permissive." Without a functional pLAM sequence, no DUX4 protein is made. Because there are two copies of chromosome 4 in each cell, individuals may have two "permissive" copies of chromosome 4, two "non-permissive" copies, or one of each.

2. Health Conditions Related to Genetic Changes

2.1 Facioscapulohumeral Muscular Dystrophy

Changes in the D4Z4 region of chromosome 4, which contains the *DUX4* gene, cause facioscapulohumeral muscular dystrophy. This disorder is characterized by muscle weakness and wasting (atrophy) that worsens slowly

over time. Two types of the disorder have been described: type 1 (FSHD1) and type 2 (FSHD2). Both types result from hypomethylation of the D4Z4 region, in which the DNA has fewer methyl groups attached than normal. In FSHD1, hypomethylation occurs because the D4Z4 region is abnormally shortened (contracted), containing between 1 and 10 repeats instead of the usual 11 to 100 repeats. In FSHD2, hypomethylation most often results from mutations in a gene called *SMCHD1*, which normally hypermethylates the D4Z4 region.

Hypomethylation of the D4Z4 region prevents the *DUX4* gene from being silenced in cells and tissues where it is usually turned off, such as adult muscle cells. However, hypomethylation of the D4Z4 region results in facioscapulohumeral muscular dystrophy only when it occurs with a "permissive" chromosome 4. The "permissive" chromosome contains a working pLAM sequence, which allows protein to be produced from the abnormally active *DUX4* gene. Researchers believe that the protein influences the activity of other genes, particularly in muscle cells. However, it is unknown how presence of the DUX4 protein damages or destroys these cells, leading to progressive muscle weakness and atrophy.

3. Other Names for This Gene

- double homeobox 4-like
- double homeobox protein 10
- double homeobox protein 4
- double homeobox protein 4/10

References

1. Geng LN, Yao Z, Snider L, Fong AP, Cech JN, Young JM, van der Maarel SM, RuzzoWL, Gentleman RC, Tawil R, Tapscott SJ. DUX4 activates germline genes,retroelements, and immune mediators: implications for facioscapulohumeraldystrophy. Dev Cell. 2012 Jan 17;22(1):38-51. doi: 10.1016/j.devcel.2011.11.013.
2. Lemmers RJ, Tawil R, Petek LM, Balog J, Block GJ, Santen GW, Amell AM, van derVliet PJ, Almomani R, Straasheijm KR, Krom YD, Klooster R, Sun Y, den Dunnen JT, Helmer Q, Donlin-Smith CM, Padberg GW, van Engelen BG, de Greef JC, Aartsma-RusAM, Frants RR, de Visser M, Desnuelle C, Sacconi S, Filippova GN, Bakker B,Bamshad MJ, Tapscott SJ, Miller DG, van der Maarel SM. Digenic inheritance of an SMCHD1 mutation and an FSHD-permissive D4Z4 allele causes facioscapulohumeralmuscular dystrophy type 2. Nat Genet. 2012 Dec;44(12):1370-4. doi:10.1038/ng.2454.

3. Lemmers RJ, van der Vliet PJ, Klooster R, Sacconi S, Camaño P, Dauwerse JG,Snider L, Straasheijm KR, van Ommen GJ, Padberg GW, Miller DG, Tapscott SJ, TawilR, Frants RR, van der Maarel SM. A unifying genetic model for facioscapulohumeralmuscular dystrophy. Science. 2010 Sep 24;329(5999):1650-3. doi:10.1126/science.1189044.
4. Sacconi S, Salviati L, Desnuelle C. Facioscapulohumeral muscular dystrophy.Biochim Biophys Acta. 2015 Apr;1852(4):607-14. doi: 10.1016/j.bbadis.2014.05.021.
5. Tawil R, van der Maarel SM, Tapscott SJ. Facioscapulohumeral dystrophy: thepath to consensus on pathophysiology. Skelet Muscle. 2014 Jun 10;4:12. doi:10.1186/2044-5040-4-12.
6. Yao Z, Snider L, Balog J, Lemmers RJ, Van Der Maarel SM, Tawil R, Tapscott SJ.DUX4-induced gene expression is the major molecular signature in FSHD skeletalmuscle. Hum Mol Genet. 2014 Oct 15;23(20):5342-52. doi: 10.1093/hmg/ddu251.