ROBO3 gene

roundabout guidance receptor 3

Normal Function

The *ROBO3* gene provides instructions for making a protein that is critical for the normal development of the nervous system. The protein is active in the developing spinal cord and in the brain (central nervous system). In particular, the ROBO3 protein is active in the brainstem, which connects the upper parts of the brain to the spinal cord. In the brainstem, the ROBO3 protein helps direct nerve cells (neurons) to their proper positions in a process called neuronal migration. The protein also helps guide the growth of axons, which are specialized extensions of neurons that transmit nerve impulses throughout the nervous system. Some axons are very long and connect neurons in the brain to those in the spinal cord and elsewhere in the body.

For the brain and body to communicate effectively, certain bundles of axons must cross from one side of the body to the other in the brainstem. These bundles include the axons of motor neurons, which transmit information about voluntary muscle movement, and the axons of sensory neurons, which transmit information about sensory input (such as touch, pain, and temperature). The ROBO3 protein plays a critical role during brain development to ensure that this crossing over occurs.

Health Conditions Related to Genetic Changes

Horizontal gaze palsy with progressive scoliosis

Variants (also called mutations) in the *ROBO3* gene have been identified in people with a condition called horizontal gaze palsy with progressive scoliosis (HGPPS). At birth, individuals with this condition are unable to move their eyes side-to-side (horizontally). They also develop an abnormal, and often severe, side-to-side curvature of the spine (scoliosis) between infancy and early childhood. The ROBO3 gene variants can cause changes to the structure of the protein in different ways; however, all of the variants appear to cause cells to produce a nonfunctional version of the protein. A lack of functional ROBO3 protein disrupts normal brainstem development.

In people with HGPPS, the axons of motor and sensory neurons do not cross over in the brainstem; they stay on the same side of the body. Researchers believe that this miswiring is the underlying cause of the eye movement abnormalities that are associated with the disorder. The cause of progressive scoliosis in people with HGPPS

is unclear.

Other Names for This Gene

- HGPPS1
- HGPS
- RBIG1 (retinoblastoma inhibiting gene 1)
- RIG1
- Roundabout homolog 3

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of ROBO3 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=64221[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28ROBO3%5BTIAB%5D%29+OR+%28Roundabout+AND+homolog+AND+3%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- ROUNDABOUT GUIDANCE RECEPTOR 3; ROBO3 (https://omim.org/entry/608630)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/64221)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=ROBO3[gene])

References

- Abu-Amero KK, al Dhalaan H, al Zayed Z, Hellani A, Bosley TM. Five newconsanguineous families with horizontal gaze palsy and progressive scoliosis andnovel ROBO3 mutations. J Neurol Sci. 2009 Jan 15;276(1-2):22-6. doi:10.1016/j.jns.2008.08.026. Epub 2008 Oct 1. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18829051)
- Amoiridis G, Tzagournissakis M, Christodoulou P, Karampekios S, Latsoudis H,

Panou T, Simos P, Plaitakis A. Patients with horizontal gaze palsy andprogressive scoliosis due to ROBO3 E319K mutation have both uncrossed and crossedcentral nervous system pathways and perform normally on neuropsychologicaltesting. J Neurol Neurosurg Psychiatry. 2006 Sep;77(9):1047-53. doi:10.1136/jnnp.2006.088435. Epub 2006 Jun 13. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16772357) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2077731/)

- Bosley TM, Salih MA, Jen JC, Lin DD, Oystreck D, Abu-Amero KK, MacDonald DB, al Zayed Z, al Dhalaan H, Kansu T, Stigsby B, Baloh RW. Neurologic features ofhorizontal gaze palsy and progressive scoliosis with mutations in ROBO3. Neurology. 2005 Apr 12;64(7):1196-203. doi: 10.1212/01.WNL.0000156349.01765.2B. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/15824346)
- Chan WM, Traboulsi EI, Arthur B, Friedman N, Andrews C, Engle EC. Horizontalgaze palsy with progressive scoliosis can result from compound heterozygousmutations in ROBO3. J Med Genet. 2006 Mar;43(3):e11. doi:10.1136/jmg.2005.035436. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16525029) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2563249/)
- Jen JC, Chan WM, Bosley TM, Wan J, Carr JR, Rub U, Shattuck D, Salamon G, KudoLC, Ou J, Lin DD, Salih MA, Kansu T, Al Dhalaan H, Al Zayed Z, MacDonald DB,Stigsby B, Plaitakis A, Dretakis EK, Gottlob I, Pieh C, Traboulsi EI, Wang Q, Wang L, Andrews C, Yamada K, Demer JL, Karim S, Alger JR, Geschwind DH, Deller T,Sicotte NL, Nelson SF, Baloh RW, Engle EC. Mutations in a human ROBO gene disrupthindbrain axon pathway crossing and morphogenesis. Science. 2004 Jun4;304(5676):1509-13. doi: 10.1126/science.1096437. Epub 2004 Apr 22. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/15105459) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1618874/)
- Nugent AA, Kolpak AL, Engle EC. Human disorders of axon guidance. Curr OpinNeurobiol. 2012 Oct;22(5):837-43. doi: 10.1016/j.conb.2012.02.006. Epub 2012 Mar5. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/22398400)
- Pinero-Pinto E, Perez-Cabezas V, Tous-Rivera C, Sanchez-Gonzalez JM,Ruiz-Molinero C, Jimenez-Rejano JJ, Benitez-Lugo ML, Sanchez-Gonzalez MC.Mutation in ROBO3 Gene in Patients with Horizontal Gaze Palsy withProgressive Scoliosis Syndrome: A Systematic Review. Int J Environ Res PublicHealth. 2020 Jun 22;17(12):4467. doi: 10.3390/ijerph17124467. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/32580277)
- Sicotte NL, Salamon G, Shattuck DW, Hageman N, Rub U, Salamon N, Drain AE, Demer JL, Engle EC, Alger JR, Baloh RW, Deller T, Jen JC. Diffusion tensor MRIshows abnormal brainstem crossing fibers associated with ROBO3 mutations. Neurology. 2006 Aug 8;67(3):519-21. doi: 10.1212/01.wnl.0000227960.38262.0c. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16894121)
- Sim B, Ng JWZ, Sim DY, Goh J, Kam S, Teo JX, Lim WW, Lieviant J, Lim WK, LimSA, Tang PH, Ling S, Ng SWL, Roca X, Jamuar SS. A novel intronic variant in ROBO3associated with horizontal gaze palsy with progressive scoliosis: case report andliterature review. J AAPOS. 2023 Dec;27(6):359-363. doi:10.1016/j.jaapos.2023.

08.017. Epub 2023 Nov 4. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/37931836)

Genomic Location

The *ROBO3* gene is found on chromosome 11 (https://medlineplus.gov/genetics/chromosome/11/).

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