SHANK3 gene

SH3 and multiple ankyrin repeat domains 3

Normal Function

The *SHANK3* gene provides instructions for making a protein that is found in many of the body's tissues but is most abundant in the brain. The SHANK3 protein plays a role in the functioning of synapses, which are the connections between nerve cells (neurons) where cell-to-cell communication occurs. Within synapses, the SHANK3 protein acts as a scaffold that supports the connections between neurons, ensuring that the signals sent by one neuron are received by another.

The SHANK3 protein is also involved in the formation and maturation of dendritic spines. Dendrites are specialized extensions from neurons that are essential for the transmission of nerve impulses. Dendritic spines are small outgrowths from dendrites that further help transmit nerve impulses and increase communication between neurons.

Health Conditions Related to Genetic Changes

22q13.3 deletion syndrome

The characteristic signs and symptoms of 22q13.3 deletion syndrome, which is also commonly known as Phelan-McDermid syndrome, are caused by a deletion near the end of the long (q) arm of chromosome 22. The chromosomal region that is typically deleted is thought to contain many genes, including the *SHANK3* gene. As a result of the deletion, people with this condition have only one copy of the *SHANK3* gene in each cell instead of the usual two copies.

Researchers believe that a deletion of the *SHANK3* gene and a reduction in the amount of SHANK3 protein produced is responsible for many of the features of 22q13.3 deletion syndrome. A decrease in the functioning of synapses and cell-to-cell communication between neurons caused by a lack of SHANK3 protein is thought to contribute to the developmental delay, intellectual disability, and absent or severely delayed speech characteristic of people with 22q13.3 deletion syndrome.

Autism spectrum disorder

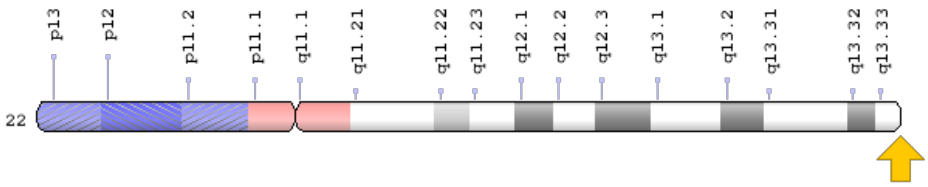
At least 43 *SHANK3* gene mutations have been found in people who have autism spectrum disorder (ASD), which is a varied condition characterized by impaired communication and socialization skills, as well as repetitive behaviors. Most of these mutations disrupt the function of the SHANK3 protein or prevent the protein from being produced. It is unclear how changes in the *SHANK3* gene are related to the risk of developing ASD. Researchers suspect that a disruption in communication

between neurons contributes to the development of this condition. Variations in other genes and environmental factors are also thought to affect the risk of this complex disorder.

Chromosomal Location

Cytogenetic Location: 22q13.33, which is the long (q) arm of chromosome 22 at position 13.33

Molecular Location: base pairs 50,674,642 to 50,733,212 on chromosome 22 (Homo sapiens Annotation Release 109, GRCh38.p12) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- proline-rich synapse-associated protein 2
- ProSAP2
- SPANK-2

Additional Information & Resources

Educational Resources

- Neuroscience (second edition, 2001): Synaptic Transmission
  https://www.ncbi.nlm.nih.gov/books/NBK11001/

Clinical Information from GeneReviews

- Phelan-McDermid Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1198

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28SHANK3%5BTIAB%5D%29+OR+%28PROSAP2%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+2520+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- SH3 AND MULTIPLE ANKYRIN REPEAT DOMAINS 3
  http://omim.org/entry/606230

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_SHANK3.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=SHANK3%5Bgene%5D
- HGNC Gene Symbol Report
  https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:14294
- Monarch Initiative
  https://monarchinitiative.org/gene/NCBIGene:85358
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/85358
- UniProt
  https://www.uniprot.org/uniprot/Q9BYB0

Sources for This Summary

- Boeckers TM, Bockmann J, Kreutz MR, Gundelfinger ED. ProSAP/Shank proteins - a family of higher order organizing molecules of the postsynaptic density with an emerging role in human neurological disease. J Neurochem. 2002 Jun;81(5):903-10. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12065602
- Bonaglia MC, Giorda R, Mani E, Aceti G, Anderlid BM, Baroncini A, Pramparo T, Zuffardi O. Identification of a recurrent breakpoint within the SHANK3 gene in the 22q13.3 deletion syndrome. J Med Genet. 2006 Oct;43(10):822-8. Epub 2005 Nov 11.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16284256
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2563164/
- Durand CM, Betancur C, Boeckers TM, Bockmann J, Chaste P, Fauchereau F, Nygren G, Rastam M, Gillberg IC, Anckarsäter H, Sponheim E, Goubran-Botros H, Delorme R, Chabane N, Mouren-Simeoni MC, de Mas P, Bieth E, Rogé B, Héron D, Burglen L, Gillberg C, Leboyer M, Bourgeron T. Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. Nat Genet. 2007 Jan;39(1):25-7. Epub 2006 Dec 17.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17173049
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2082049/
- Gauthier J, Spiegelman D, Piton A, Lafrenière RG, Laurent S, St-Onge J, Lapointe L, Hamdan FF, Cossette P, Mottron L, Fombonne E, Joober R, Marineau C, Drapeau P, Rouleau GA. Novel de novo SHANK3 mutation in autistic patients. Am J Med Genet B Neuropsychiatr Genet. 2009 Apr 5; 150B(3):421-4. doi: 10.1002/ajmg.b.30822.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18615476

- Leblond CS, Nava C, Polge A, Gauthier J, Huguet G, Lumbroso S, Giuliano F, Stordeur C, Depienne C, Mouzat K, Pinto D, Howe J, Lemière N, Durand CM, Guibert J, Ey E, Toro R, Peyre H, Mathieu A, Amsellem F, Rastam M, Gillberg IC, Rappold GA, Holt R, Monaco AP, Maestrini E, Galan P, Heron D, Jacquette A, Afenjar A, Rastetter A, Brice A, Devillard F, Assouline B, Laffargue F, Lespinasse J, Chiesa J, Rivier F, Bonneau D, Regnault B, Zelenika D, Delepine M, Lathrop M, Sanlaville D, Schluth-Bolard C, Edery P, Perrin L, Tabet AC, Schmeisser MJ, Boeckers TM, Coleman M, Sato D, Szatmari P, Scherer SW, Rouleau GA, Betancur C, Leboyer M, Gillberg C, Delorme R, Bourgeron T. Meta-analysis of SHANK Mutations in Autism Spectrum Disorders: a gradient of severity in cognitive impairments. PLoS Genet. 2014 Sep 4;10(9):e1004580. doi: 10.1371/journal.pgen.1004580. eCollection 2014 Sep 4.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25188300
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4154644/
- Moessner R, Marshall CR, Sutcliffe JS, Skaug J, Pinto D, Vincent J, Zwaigenbaum L, Fernandez B, Roberts W, Szatmari P, Scherer SW. Contribution of SHANK3 mutations to autism spectrum disorder. Am J Hum Genet. 2007 Dec;81(6):1289-97. Epub 2007 Oct 16.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17999366
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2276348/
- Monteiro P, Feng G. SHANK proteins: roles at the synapse and in autism spectrum disorder. Nat Rev Neurosci. 2017 Mar;18(3):147-157. doi: 10.1038/nrn.2016.183. Epub 2017 Feb 9. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28179641
- OMIM: SH3 AND MULTIPLE ANKYRIN REPEAT DOMAINS 3
  http://omim.org/entry/606230
- Sala C, Vicidomini C, Bigi I, Mossa A, Verpelli C. Shank synaptic scaffold proteins: keys to understanding the pathogenesis of autism and other synaptic disorders. J Neurochem. 2015 Dec; 135(5):849-58. doi: 10.1111/jnc.13232. Epub 2015 Sep 3. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26338675
- Uchino S, Waga C. SHANK3 as an autism spectrum disorder-associated gene. Brain Dev. 2013 Feb;35(2):106-10. doi: 10.1016/j.braindev.2012.05.013. Epub 2012 Jun 29. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22749736
- Wilson HL, Wong AC, Shaw SR, Tse WY, Stapleton GA, Phelan MC, Hu S, Marshall J, McDermid HE. Molecular characterisation of the 22q13 deletion syndrome supports the role of haploinsufficiency of SHANK3/PROSAP2 in the major neurological symptoms. J Med Genet. 2003 Aug;40(8):575-84.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12920066
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1735560/

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/gene/SHANK3

Reviewed: June 2017
Published: June 11, 2019

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services