SLC12A3 gene

solute carrier family 12 member 3

Normal Function

The *SLC12A3* gene provides instructions for making a protein known as NCC. This protein is a sodium chloride co-transporter, which means that it moves charged atoms (ions) of sodium (Na^+) and chlorine (Cl^-) across cell membranes.

The NCC protein is essential for normal kidney function. It is part of the mechanism by which kidneys reabsorb salt (sodium chloride or NaCl) from the urine back into the bloodstream. The retention of salt affects the body's fluid levels and helps maintain blood pressure.

Health Conditions Related to Genetic Changes

Gitelman syndrome

More than 140 mutations in the *SLC12A3* gene have been identified in people with Gitelman syndrome. Most of these mutations change single protein building blocks (amino acids) in the NCC co-transporter protein. These mutations prevent the protein from reaching the cell membrane or alter the protein's ability to transport sodium and chloride ions. Other mutations in the *SLC12A3* gene insert or delete genetic material or lead to the production of an abnormally short, nonfunctional version of the NCC protein.

Mutations in the *SLC12A3* gene impair the kidneys' ability to reabsorb salt, leading to the loss of excess salt in the urine (salt wasting). Abnormalities of salt transport also affect the reabsorption of other ions, including ions of potassium, magnesium, and calcium. The resulting imbalance of ions in the body underlies the major features of Gitelman syndrome.

Other disorders

Some research suggests that normal variants (polymorphisms) in the *SLC12A3* gene may help explain differences in blood pressure between people. Certain rare polymorphisms also appear to protect against high blood pressure (hypertension). Changes in the *SLC12A3* gene may affect blood pressure by altering the kidneys' ability to reabsorb salt into the bloodstream. However, some studies have not found any association between variants in the *SLC12A3* gene and blood pressure.

Other Names for This Gene

- Na-Cl symporter
- NaCl electroneutral thiazide-sensitive cotransporter
- NCCT
- S12A3_HUMAN
- solute carrier family 12 (sodium/chloride transporter), member 3
- solute carrier family 12 (sodium/chloride transporters), member 3
- thiazide-sensitive Na-Cl cotransporter
- thiazide-sensitive sodium-chloride cotransporter
- TSC

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of SLC12A3 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=6559[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28SLC12A3%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

- SOLUTE CARRIER FAMILY 12 (SODIUM/CHLORIDE TRANSPORTER), MEMBER 3; SLC12A3 (https://omim.org/entry/600968)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/6559)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=SLC12A3[gene])

References

- Aoi N, Nakayama T, Sato N, Kosuge K, Haketa A, Sato M, Soma M. Case-controlstudy of the role of the Gitelman's syndrome gene in essential hypertension.Endocr J. 2008 May;55(2):305-10. doi: 10.1507/endocrj.k07e-021. Epub 2008 Mar 25. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18362449)

- Cruz DN, Simon DB, Nelson-Williams C, Farhi A, Finberg K, Burleson L, Gill JR, Lifton RP. Mutations in the Na-Cl cotransporter reduce blood pressure in humans. Hypertension. 2001 Jun;37(6):1458-64. doi: 10.1161/01.hyp.37.6.1458. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/11408395)
- De Jong JC, Van Der Vliet WA, Van Den Heuvel LP, Willems PH, Knoers NV, Bindels RJ. Functional expression of mutations in the human NaCl cotransporter: evidence for impaired routing mechanisms in Gitelman's syndrome. J Am SocNephrol. 2002 Jun;13(6):1442-8. doi: 10.1097/01.asn.0000017904.77985.03. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/12039972)
- Ji W, Foo JN, O'Roak BJ, Zhao H, Larson MG, Simon DB, Newton-Cheh C, State MW,Levy D, Lifton RP. Rare independent mutations in renal salt handling genescontribute to blood pressure variation. Nat Genet. 2008 May;40(5):592-599. doi:10.1038/ng.118. Epub 2008 Apr 6. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18391953) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3766631/)
- Lemmink HH, Knoers NV, Karolyi L, van Dijk H, Niaudet P, Antignac C,Guay-Woodford LM, Goodyer PR, Carel JC, Hermes A, Seyberth HW, Monnens LA, vanden Heuvel LP. Novel mutations in the thiazide-sensitive NaCl cotransporter genein patients with Gitelman syndrome with predominant localization to theC-terminal domain. Kidney Int. 1998 Sep;54(3):720-30. doi:10.1046/j.1523-1755.1998.00070.x. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/9734597)
- Lo YF, Nozu K, Iijima K, Morishita T, Huang CC, Yang SS, Sytwu HK, Fang YW, Tseng MH, Lin SH. Recurrent deep intronic mutations in the SLC12A3 generesponsible for Gitelman's syndrome. Clin J Am Soc Nephrol. 2011 Mar;6(3):630-9.doi: 10.2215/CJN.06730810. Epub 2010 Nov 4. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/21051746) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3082423/)
- Mastroianni N, De Fusco M, Zollo M, Arrigo G, Zuffardi O, Bettinelli A,Ballabio A, Casari G. Molecular cloning, expression pattern, and chromosomallocalization of the human Na-Cl thiazide-sensitive cotransporter (SLC12A3).Genomics. 1996 Aug 1;35(3):486-93. doi: 10.1006/geno.1996.0388. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/8812482)
- Riveira-Munoz E, Chang Q, Godefroid N, Hoenderop JG, Bindels RJ, Dahan K, Devuyst O; Belgian Network for Study of Gitelman Syndrome. Transcriptional andfunctional analyses of SLC12A3 mutations: new clues for the pathogenesis ofGitelman syndrome. J Am Soc Nephrol. 2007 Apr;18(4):1271-83. doi:10.1681/ASN.2006101095. Epub 2007 Feb 28. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17329572)
- Sabath E, Meade P, Berkman J, de los Heros P, Moreno E, Bobadilla NA, VazquezN, Ellison DH, Gamba G. Pathophysiology of functional mutations of thethiazide-sensitive Na-Cl cotransporter in Gitelman disease. Am J Physiol RenalPhysiol. 2004 Aug;287(2):F195-203. doi: 10.1152/ajprenal.00044.2004. Epub 2004Apr 6. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/15068971)
- Simon DB, Nelson-Williams C, Bia MJ, Ellison D, Karet FE, Molina AM, Vaara I, Iwata F, Cushner HM, Koolen M, Gainza FJ, Gitleman HJ, Lifton RP. Gitelman';

svariant of Bartter's syndrome, inherited hypokalaemic alkalosis, is caused bymutations in the thiazide-sensitive Na-Cl cotransporter. Nat Genet. 1996Jan;12(1): 24-30. doi: 10.1038/ng0196-24. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/8528245)

Genomic Location

The *SLC12A3* gene is found on chromosome 16 (https://medlineplus.gov/genetics/chromosome/16/).

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