MAP3K1 gene

mitogen-activated protein kinase kinase kinase 1

Normal Function

The *MAP3K1* gene provides instructions for making a protein that helps regulate signaling pathways that control various processes in the body, including the processes of determining sexual characteristics before birth. The MAP3K1 protein attaches (binds) to other molecules called RHOA, MAP3K4, FRAT1, and AXIN1. The binding of MAP3K1 to these molecules, which are called cofactors, helps MAP3K1 control the activity of the signaling pathways.

Health Conditions Related to Genetic Changes

Swyer syndrome

Mutations in the *MAP3K1* gene are thought to account for up to 18 percent of cases of Swyer syndrome, a condition affecting sexual development also known as 46,XY complete gonadal dysgenesis or 46,XY pure gonadal dysgenesis.

People usually have 46 chromosomes in each cell. Two of the 46 chromosomes, known as X and Y, are called sex chromosomes because they help determine whether a person will develop male or female sex characteristics. Girls and women typically have two X chromosomes (46,XX karyotype), while boys and men usually have one X chromosome and one Y chromosome (46,XY karyotype).

The *MAP3K1* gene mutations that cause Swyer syndrome increase cofactor binding, which decreases signaling that leads to male sexual differentiation and enhances signaling that leads to female sexual differentiation. As a result, affected individuals with a typically male 46,XY karyotype will not develop male gonads (testes) but will develop female reproductive structures (a uterus and fallopian tubes).

Breast cancer

Langerhans cell histiocytosis

Other disorders

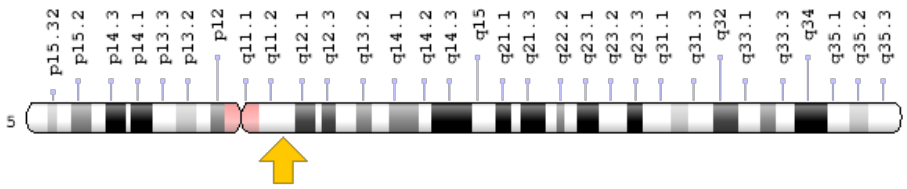
MAP3K1 gene mutations have also been identified in people with 46,XY disorder of sex development, which is also known as partial gonadal dysgenesis. These mutations likely have similar but less pronounced effects on signaling related to sexual development than those that cause Swyer syndrome (described above). Affected individuals may have external genitalia that do not look clearly male or

clearly female (ambiguous genitalia) or other abnormalities of the genitals and reproductive organs.

Chromosomal Location

Cytogenetic Location: 5q11.2, which is the long (q) arm of chromosome 5 at position 11.2

Molecular Location: base pairs 56,815,543 to 56,896,152 on chromosome 5 (Homo sapiens Updated Annotation Release 109.20190607, GRCh38.p13) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- M3K1_HUMAN
- MAP/ERK kinase kinase 1
- MAPK/ERK kinase kinase 1
- MAPKKK1
- MEK kinase 1
- MEKK
- MEKK 1
- MEKK1
- mitogen-activated protein kinase kinase kinase 1, E3 ubiquitin protein ligase
- SRXY6

Additional Information & Resources

Educational Resources

- Endotext: Sex Determination https://www.ncbi.nlm.nih.gov/books/NBK279001/#_sex-differentiation_toc-sex-determination_

Clinical Information from GeneReviews

- Nonsyndromic Disorders of Testicular Development
  https://www.ncbi.nlm.nih.gov/books/NBK1547

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28MAP3K1%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+1440+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- 46,XY SEX REVERSAL 6
  http://omim.org/entry/613762
- MITOGEN-ACTIVATED KINASE KINASE KINASE 1
  http://omim.org/entry/600982

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_MAP3K1.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=MAP3K1%5Bgene%5D
- HGNC Gene Symbol Report
  https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:6848
- Monarch Initiative
  https://monarchinitiative.org/gene/NCBIGene:4214
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/4214
- UniProt
  https://www.uniprot.org/uniprot/Q13233

Sources for This Summary

- Jara L, Gonzalez-Hormazabal P, Cerceño K, Di Capua GA, Reyes JM, Blanco R, Bravo T, Peralta O, Gomez F, Waugh E, Margarit S, Ibañez G, Romero C, Pakomio J, Roizen G. Genetic variants in FGFR2 and MAP3K1 are associated with the risk of familial and early-onset breast cancer in a South-American population. Breast Cancer Res Treat. 2013 Jan;137(2):559-69. doi: 10.1007/s10549-012-2359-z. Epub 2012 Dec 7.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23225170
- Loke J, Pearlman A, Radi O, Zuffardi O, Giussani U, Pallotta R, Camerino G, Ostrer H. Mutations in MAP3K1 tilt the balance from SOX9/FGF9 to WNT/β-catenin signaling. Hum Mol Genet. 2014 Feb 15;23(4):1073-83. doi: 10.1093/hmg/ddt502. Epub 2013 Oct 16.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24135036

- OMIM: MITOGEN-ACTIVATED KINASE KINASE KINASE 1
  http://omim.org/entry/600982
- Nelson DS, van Halteren A, Quispel WT, van den Bos C, Bovée JV, Patel B, Badalian-Very G, van Hummelen P, Ducar M, Lin L, MacConaill LE, Egeler RM, Rollins BJ. MAP2K1 and MAP3K1 mutations in Langerhans cell histiocytosis. Genes Chromosomes Cancer. 2015 Jun;54(6):361-8. doi: 10.1002/gcc.22247. Epub 2015 Mar 31.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25899310
- Pearlman A, Loke J, Le Caignec C, White S, Chin L, Friedman A, Warr N, Willan J, Brauer D, Farmer C, Brooks E, Oddoux C, Riley B, Shajahan S, Camerino G, Homfray T, Crosby AH, Couper J, David A, Greenfield A, Sinclair A, Ostrer H. Mutations in MAP3K1 cause 46,XY disorders of sex development and implicate a common signal transduction pathway in human testis determination. Am J Hum Genet. 2010 Dec 10;87(6):898-904. doi: 10.1016/j.ajhg.2010.11.003.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21129722
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2997363/
- Zheng Q, Ye J, Wu H, Yu Q, Cao J. Association between mitogen-activated protein kinase kinase kinase 1 polymorphisms and breast cancer susceptibility: a meta-analysis of 20 case-control studies. PLoS One. 2014 Mar 4;9(3):e90771. doi: 10.1371/journal.pone.0090771. eCollection 2014.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24595411
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3942489/

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/gene/MAP3K1

Reviewed: March 2015
Published: September 10, 2019

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