

RET gene

ret proto-oncogene

Normal Function

The *RET* gene provides instructions for producing a protein that is involved in signaling within cells. This protein appears to be essential for the normal development of several kinds of nerve cells, including nerves in the intestine (enteric neurons) and the portion of the nervous system that controls involuntary body functions such as heart rate (the autonomic nervous system). The RET protein is also necessary for normal kidney development and the production of sperm (spermatogenesis).

The RET protein spans the cell membrane, so that one end of the protein remains inside the cell and the other end projects from the outer surface of the cell. This positioning of the protein allows it to interact with specific factors outside the cell and to receive signals that help the cell respond to its environment. When molecules that stimulate growth and development (growth factors) attach to the RET protein, a complex cascade of chemical reactions inside the cell is triggered. These reactions instruct the cell to undergo certain changes, such as dividing or maturing to take on specialized functions.

Health Conditions Related to Genetic Changes

Nonsyndromic paraganglioma

Mutations in the *RET* gene increase the risk of developing a type of paraganglioma called pheochromocytoma. Paragangliomas are tumors of the nervous system that are usually noncancerous (benign). Pheochromocytomas specifically affect the adrenal glands, which are small hormone-producing glands located on top of each kidney. Pheochromocytomas are a feature of multiple endocrine neoplasia type 2 (described below), but they can also be nonsyndromic, which means they occur without the other signs and symptoms of the syndrome. *RET* gene mutations associated with nonsyndromic pheochromocytoma change single amino acids in the RET protein. As in multiple endocrine neoplasia type 2, the mutations likely result in an overactive RET protein that can trigger cells to grow and divide uncontrollably and can lead to the formation of tumors.

Hirschsprung disease

Mutations in the *RET* gene are the most common genetic cause of Hirschsprung disease, a disorder that causes severe constipation or blockage of the intestine. More than 200 *RET* gene mutations are known to cause this condition. These genetic changes result in a nonfunctional version of the RET protein that cannot interact with growth factors or transmit signals within cells. Without RET protein signaling, enteric nerves do not develop properly. These nerves control contractions that move stool through the intestine, and their absence leads to the intestinal problems characteristic of Hirschsprung disease.

Multiple endocrine neoplasia

More than 25 mutations in the *RET* gene are known to cause a form of multiple endocrine neoplasia called type 2. Multiple endocrine neoplasia typically involves the development of tumors in two or more of the body's hormone-producing glands, called endocrine glands. These tumors can be noncancerous or cancerous. Multiple endocrine neoplasia type 2 is divided into three subtypes: type 2A, type 2B, and familial medullary thyroid carcinoma. These subtypes are distinguished by their characteristic signs and symptoms and risk of specific tumors.

Most of the *RET* gene mutations that cause multiple endocrine neoplasia type 2 change single protein building blocks (amino acids) in the RET protein. Type 2A most often results from a mutation that substitutes the amino acid arginine for the amino acid cysteine at position 634 (written as Cys634Arg or C634R). More than 90 percent of cases of type 2B are caused by a mutation that replaces the amino acid methionine with the amino acid threonine at position 918 (written as Met918Thr or M918T). Several amino acid substitutions can cause familial medullary thyroid carcinoma.

The mutations responsible for multiple endocrine neoplasia type 2 result in an overactive RET protein that can transmit signals without first attaching to growth factors outside the cell. The overactive protein likely triggers cells to grow and divide abnormally, which can lead to the formation of tumors in the endocrine system and other tissues. The overactivating *RET* gene mutations that cause multiple endocrine neoplasia type 2 are very different from the inactivating mutations that cause Hirschsprung disease (described above); these two disorders rarely occur in the same individual.

Lung cancer

MedlinePlus Genetics provides information about Lung cancer

Other cancers

Some gene mutations are acquired during a person's lifetime and are present only in certain cells. These changes, which are called somatic mutations, are not inherited. Somatic changes in the *RET* gene have been identified in several nonhereditary (sporadic) cancers. Chromosomal rearrangements involving the *RET* gene are one of the most common causes of a sporadic form of thyroid cancer called papillary thyroid carcinoma (also known as RET/PTC). Additionally, a nonfamilial form of medullary

thyroid carcinoma (a type of thyroid cancer that can also occur as part of multiple endocrine neoplasia, described above) can be caused by somatic mutations in the *RET* gene.

Other Names for This Gene

- cadherin family member 12
- cadherin-related family member 16
- CDHF12
- CDHR16
- HSCR1
- hydroxyaryl-protein kinase
- MEN2A
- MEN2B
- MTC1
- PTC
- rearranged during transfection
- ret proto-oncogene (multiple endocrine neoplasia and medullary thyroid carcinoma 1, Hirschsprung disease)
- RET-ELE1
- RET/PTC
- RET51
- RET_HUMAN

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of RET ([https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=5979\[geneid\]](https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=5979[geneid]))

Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28%28RET%5BTI%5D%29+OR+%28ret+proto-oncogene%5BTI%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D>)

Catalog of Genes and Diseases from OMIM

- RET PROTOONCOGENE; RET (<https://omim.org/entry/164761>)
- THYROID CANCER, NONMEDULLARY, 1; NMTC1 (<https://omim.org/entry/188550>)

Gene and Variant Databases

- NCBI Gene (<https://www.ncbi.nlm.nih.gov/gene/5979>)
- ClinVar ([https://www.ncbi.nlm.nih.gov/clinvar?term=RET\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar?term=RET[gene]))

References

- Alberti L, Carniti C, Miranda C, Roccato E, Pierotti MA. RET and NTRK1 proto-oncogenes in human diseases. *J Cell Physiol.* 2003 May;195(2):168-86. doi:10.1002/jcp.10252. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/12652644>)
- Arighi E, Borrello MG, Sariola H. RET tyrosine kinase signaling in development and cancer. *Cytokine Growth Factor Rev.* 2005 Aug-Oct;16(4-5):441-67. doi:10.1016/j.cytogfr.2005.05.010. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/15982921>)
- Baynash AG, Hosoda K, Giaid A, Richardson JA, Emoto N, Hammer RE, Yanagisawa M. Interaction of endothelin-3 with endothelin-B receptor is essential for development of epidermal melanocytes and enteric neurons. *Cell.* 1994 Dec30;79(7):1277-85. doi: 10.1016/0092-8674(94)90018-3. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/8001160>)
- Burnichon N, Vescovo L, Amar L, Libe R, de Reynies A, Venisse A, Jouanno E, Laurendeau I, Parfait B, Bertherat J, Plouin PF, Jeunemaitre X, Favier J, Gimenez-Roqueplo AP. Integrative genomic analysis reveals somatic mutations in pheochromocytoma and paraganglioma. *Hum Mol Genet.* 2011 Oct 15;20(20):3974-85. doi: 10.1093/hmg/ddr324. Epub 2011 Jul 22. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/21784903>)
- Chatterjee S, Kapoor A, Akiyama JA, Auer DR, Lee D, Gabriel S, Berrios C, Pennacchio LA, Chakravarti A. Enhancer Variants Synergistically Drive Dysfunction of a Gene Regulatory Network in Hirschsprung Disease. *Cell.* 2016 Oct6;167(2):355-368.e10. doi: 10.1016/j.cell.2016.09.005. Epub 2016 Sep 29. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/27693352>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5113733/>)
- Eng C, Plitt G. Multiple Endocrine Neoplasia Type 2. 1999 Sep 27 [updated 2023 Aug 10]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. *GeneReviews*(R) [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from <http://www.ncbi.nlm.nih.gov/books/NBK1257/> Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/20301434>)
- Ichihara M, Murakumo Y, Takahashi M. RET and neuroendocrine tumors. *Cancer Lett.* 2004 Feb 20;204(2):197-211. doi: 10.1016/S0304-3835(03)00456-7. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/15013219>)
- Koch CA. Molecular pathogenesis of MEN2-associated tumors. *Fam Cancer.* 2005;4(1):3-7. doi: 10.1007/s10689-004-7022-3. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/15013219>)

m.nih.gov/15883703)

- Kouvaraki MA, Shapiro SE, Perrier ND, Cote GJ, Gagel RF, Hoff AO, Sherman SI, Lee JE, Evans DB. RET proto-oncogene: a review and update of genotype-phenotype correlations in hereditary medullary thyroid cancer and associated endocrine tumors. *Thyroid*. 2005 Jun;15(6):531-44. doi: 10.1089/thy.2005.15.531. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/16029119>)
- Marx SJ. Molecular genetics of multiple endocrine neoplasia types 1 and 2. *Nat Rev Cancer*. 2005 May;5(5):367-75. doi: 10.1038/nrc1610. Erratum In: *Nat Rev Cancer*. 2005 Aug;5(8):663. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/15864278>)
- Neumann HP, Bausch B, McWhinney SR, Bender BU, Gimm O, Franke G, Schipper J, Klisch J, Althoefer C, Zerres K, Januszewicz A, Eng C, Smith WM, Munk R, Manz T, Glaesker S, Apel TW, Treier M, Reineke M, Walz MK, Hoang-Vu C, Brauckhoff M, Klein-Franke A, Klose P, Schmidt H, Maier-Woelfle M, Peczkowska M, Szmigielski C, Eng C; Freiburg-Warsaw-Columbus Pheochromocytoma Study Group. Germ-line mutations in nonsyndromic pheochromocytoma. *N Engl J Med*. 2002 May 9;346(19):1459-66. doi:10.1056/NEJMoa020152. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/12000816>)
- Panta GR, Du L, Nwariaku FE, Kim LT. Direct phosphorylation of proliferative and survival pathway proteins by RET. *Surgery*. 2005 Aug;138(2):269-74. doi:10.1016/j.surg.2005.04.007. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/16153436>)
- Putzer BM, Drost M. The RET proto-oncogene: a potential target for molecular cancer therapy. *Trends Mol Med*. 2004 Jul;10(7):351-7. doi:10.1016/j.molmed.2004.06.002. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/15242684>)
- Santoro M, Carlomagno F, Melillo RM, Fusco A. Dysfunction of the RET receptor in human cancer. *Cell Mol Life Sci*. 2004 Dec;61(23):2954-64. doi:10.1007/s00018-004-4276-8. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/15583857>)
- Tomuschat C, Puri P. RET gene is a major risk factor for Hirschsprung disease: a meta-analysis. *Pediatr Surg Int*. 2015 Aug;31(8):701-10. doi:10.1007/s00383-015-3731-y. Epub 2015 Jul 12. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/26164711>)

Genomic Location

The *RET* gene is found on chromosome 10 (<https://medlineplus.gov/genetics/chromosome/10/>).

Last updated May 1, 2018