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

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 \textit{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.

\textbf{Nonsyndromic paraganglioma}

Mutations in the \textit{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, 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.

\textbf{Lung cancer}

\textbf{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 \textit{RET} gene have been identified in several nonhereditary (sporadic) cancers. Chromosomal rearrangements involving the \textit{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) can be caused by somatic mutations in the \textit{RET} gene.
**Chromosomal Location**

Cytogenetic Location: 10q11.21, which is the long (q) arm of chromosome 10 at position 11.21

Molecular Location: base pairs 43,077,027 to 43,130,351 on chromosome 10 (Homo sapiens Annotation Release 109, GRCh38.p12) (NCBI)

Credit: Genome Decoration Page/NCBI

**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-ELE1
- ret proto-oncogene (multiple endocrine neoplasia and medullary thyroid carcinoma 1, Hirschsprung disease)
- RET/PTC
- RET51
- RET_HUMAN
Additional Information & Resources

Clinical Information from GeneReviews

- Hirschsprung Disease Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1439
- Multiple Endocrine Neoplasia Type 2
  https://www.ncbi.nlm.nih.gov/books/NBK1257

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?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

- REARRANGED DURING TRANSFECTION PROTOONCOGENE
  http://omim.org/entry/164761
- THYROID CANCER, NONMEDULLARY, 1
  http://omim.org/entry/188550

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/RETID76.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=RET%5Bgene%5D
- HGNC Gene Family: Cadherin related
  https://www.genenames.org/cgi-bin/genefamilies/set/24
- HGNC Gene Family: Receptor tyrosine kinases
  https://www.genenames.org/cgi-bin/genefamilies/set/321
- HGNC Gene Symbol Report
  https://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=9967
- Monarch Initiative
  https://monarchinitiative.org/gene/NCBIGene:5979
- NCBI Gene
- UniProt
  https://www.uniprot.org/uniprot/P07949
Sources for This Summary

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12652644

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  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/8001160

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