RAG1 gene

recombination activating 1

Normal Function

The *RAG1* gene provides instructions for making a member of a group of proteins called the RAG complex. This complex is active in immune system cells (lymphocytes) called B cells and T cells. These cells have special proteins on their surface that recognize foreign invaders and help protect the body from infection. These proteins need to be diverse to be able to recognize a wide variety of substances. The genes from which these proteins are made contain segments known as variable (V), diversity (D), and joining (J) segments. During protein production within lymphocytes, these gene segments are rearranged in different combinations to increase variability of the resulting proteins. The RAG complex is involved in this process, which is known as V(D)J recombination.

During V(D)J recombination, the RAG complex attaches (binds) to a section of DNA called a recombination signal sequence (RSS), which is next to a V, D, or J segment. The RAG complex makes small cuts in the DNA between the segment and the RSS so the segment can be separated and moved to a different area in the gene. This process of DNA rearrangement within B cells and T cells is repeated multiple times in different areas so that the V, D, and J segments are arranged in various combinations. The variety of proteins produced throughout life following V(D)J recombination provides greater recognition of foreign invaders and allows the body to fight infection efficiently.

Health Conditions Related to Genetic Changes

Omenn syndrome

At least 70 mutations in the *RAG1* gene have been found to cause an immune system disorder called Omenn syndrome. This condition is a type of severe combined immunodeficiency (SCID), which is a group of disorders characterized by an almost total lack of immune protection from foreign invaders such as bacteria, viruses, and fungi. Omenn syndrome is characterized by a reduced ability to fight infections and autoimmunity, in which the immune system attacks the body's own tissues and organs. Without treatment, Omenn syndrome is often fatal in infancy.

Most of the *RAG1* gene mutations that cause Omenn syndrome change single protein building blocks (amino acids) in the RAG1 protein. These changes can impair RAG complex formation and function, including its ability to bind to DNA. As a result, V(D)J recombination is diminished and the diversity of proteins on the surface of B cells and T cell is severely limited, impairing the cells' ability to recognize foreign invaders and fight infections. The abnormal B and T cells result in the frequent, life-

threatening infections of Omenn syndrome. The decrease in lymphocyte function leads to a reduction in the numbers of B cells, but the number of T cells is typically normal. The abnormal T cells attack the body's own cells and tissues, accounting for the autoimmune features of Omenn syndrome.

Other disorders

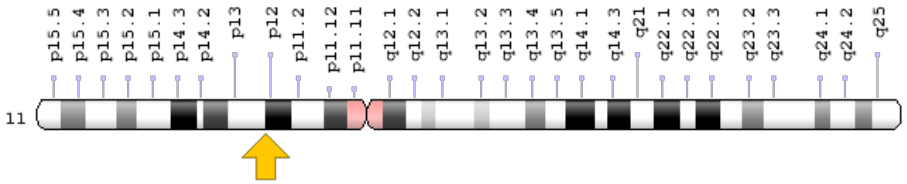
RAG1 gene mutations can cause other disorders of the immune system (immunodeficiencies). Mutations that completely eliminate the production or function of the RAG1 protein cause a form of SCID that is associated with few or no B cells and T cells. Individuals with this form of SCID have recurrent, persistent infections beginning in infancy, which are usually fatal within the first year of life.

RAG1 gene mutations that result in the production of RAG1 proteins that retain some normal function cause another form of immunodeficiency. This condition is characterized by somewhat reduced numbers of B and T cells, but affected individuals typically do not develop severe infections until late childhood. People with this form of immunodeficiency may also have areas of inflammation (granulomas) in various tissues that can cause tissue damage.

Chromosomal Location

Cytogenetic Location: 11p12, which is the short (p) arm of chromosome 11 at position 12

Molecular Location: base pairs 36,510,366 to 36,579,762 on chromosome 11 (Homo sapiens Annotation Release 109, GRCh38.p12) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- MGC43321
- RAG-1
- recombination activating gene 1
- recombination activating protein 1
- RING finger protein 74

- RNF74
- V(D)J recombination-activating protein 1

Additional Information & Resources

Educational Resources

- Immunobiology: The Immune System in Health and Disease (fifth edition, 2001): The Rearrangement of Antigen-receptor Gene Segments Controls Lymphocyte Development
  https://www.ncbi.nlm.nih.gov/books/NBK27113/
- Immunobiology: The Immune System in Health and Disease: (fifth edition, 2001): Lymphocyte Development Occurs in Specialized Environments and is Regulated by the Somatic Rearrangement of the Antigen-receptor Genes
  https://www.ncbi.nlm.nih.gov/books/NBK27123/#A801
- Madame Curie Bioscience Database: V(D)J Rearrangement
  https://www.ncbi.nlm.nih.gov/books/NBK6600/#A77542
- Molecular Biology of the Cell (fourth edition, 2002): The Generation of Antibody Diversity
  https://www.ncbi.nlm.nih.gov/books/NBK26860/

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28RAG1%5BTIAB%5D%29+OR+%28recombination+activating+1%5BTIAB%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+1080+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- COMBINED CELLULAR AND HUMORAL IMMUNE DEFECTS WITH GRANULOMAS
  http://omim.org/entry/233650
- RECOMBINATION-ACTIVATING GENE 1
  http://omim.org/entry/179615
- SEVERE COMBINED IMMUNODEFICIENCY, AUTOSOMAL RECESSIVE, T CELL-NEGATIVE, B CELL-NEGATIVE, NK CELL-POSITIVE
  http://omim.org/entry/601457

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_RAG1.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=RAG1%5Bgene%5D
- HGNC Gene Symbol Report
  https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:9831
- Monarch Initiative
  https://monarchinitiative.org/gene/NCBIGene:5896
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/5896
- UniProt
  https://www.uniprot.org/uniprot/P15918

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