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## Help Me Understand Genetics

# Gene Families

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U.S. National Library of Medicine  
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Department of Health & Human Services

Published May 23, 2017

# Gene Families

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## What are gene families?

A gene family is a group of genes that share important characteristics. In many cases, genes in a family share a similar sequence of DNA building blocks (nucleotides). These genes provide instructions for making products (such as proteins) that have a similar structure or function. In other cases, dissimilar genes are grouped together in a family because proteins produced from these genes work together as a unit or participate in the same process.

Classifying individual genes into families helps researchers describe how genes are related to each other. Researchers can use gene families to predict the function of newly identified genes based on their similarity to known genes. Similarities among genes in a family can also be used to predict where and when a specific gene is active (expressed). Additionally, gene families may provide clues for identifying genes that are involved in particular diseases.

Sometimes not enough is known about a gene to assign it to an established family. In other cases, genes may fit into more than one family. No formal guidelines define the criteria for grouping genes together. Classification systems for genes continue to evolve as scientists learn more about the structure and function of genes and the relationships between them.

### **For more information about gene families:**

The HUGO Gene Nomenclature Committee (<http://www.genenames.org/cgi-bin/genefamilies/>) (HGNC) has classified many human genes into families. Each grouping is given a name and symbol, and contains a table of the genes in that family.

The Gene Ontology (<http://geneontology.org/>) database lists the protein products of genes by their location within the cell (cellular component), biological process, and molecular function.

The Reactome (<http://www.reactome.org/>) database classifies the protein products of genes based on their participation in specific biological pathways. For example, this resource provides tables of genes involved in controlled cell death (apoptosis), cell division, and DNA repair.

## Blood group antigens

Blood is classified into different groups according to the presence or absence of molecules called antigens on the surface of every red blood cell in a person's body. Antigens determine blood type and can either be proteins or complexes of sugar molecules (polysaccharides). The genes in the blood group antigen family provide instructions for making antigen proteins. Blood group antigen proteins serve a variety of functions within the cell membrane of red blood cells. These protein functions include transporting other proteins and molecules into and out of the cell, maintaining cell structure, attaching to other cells and molecules, and participating in chemical reactions.

Blood group antigens play a role in recognizing foreign cells in the bloodstream. For example, if a person with blood type A receives a blood transfusion with blood type B, the recipient's immune system will recognize the type B cells as foreign and mount an immune response. Antibodies against type B blood cells (anti-B antibodies) are made, which attack and destroy the type B blood cells. This sort of blood type mismatch can lead to illness. Some blood types are associated with more severe immune reactions than others. The blood type of donated cells, or tissues in the case of organ donation, is checked before being given to a recipient in order to prevent this immune response.

There are 29 recognized blood groups, most involving only one gene. Variations (polymorphisms) within the genes that determine blood group give rise to the different antigens for a particular blood group protein. For example, changes in a few DNA building blocks (nucleotides) in the *ABO* gene give rise to the A, B, and O blood types of the *ABO* blood group. The changes that occur in the genes that determine blood group typically affect only blood type and are not associated with adverse health conditions, although exceptions do occur.

Example of a gene in this gene family: *SLC4A1*

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (<http://www.genenames.org/cgi-bin/genefamilies/>) and their member genes.

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### **Learn more about the blood group antigens gene family:**

National Library of Medicine: Blood Groups and Red Cell Antigens (2005): Blood group antigens are surface markers on the red blood cell membrane (<http://www.ncbi.nlm.nih.gov/books/NBK2264/#ch2>)

Emory University: The Genetics of Blood Type (<http://genetics.emory.edu/documents/resources/factsheet43.pdf>)

NCBI: Blood Group Antigen Gene Mutations Database (<http://www.ncbi.nlm.nih.gov/gv/rbc/xslcgi.fcgi?cmd=bgmut/home>)

## Collagen proteoglycans

Genes in this family provide instructions for making the protein component of large molecules called collagen proteoglycans. A proteoglycan is a molecule that is made up of a core protein attached to one or more sugar molecules called glycosaminoglycan (GAG) chains. The collagen proteoglycans gene family is a subset of a larger gene family known as the proteoglycan superfamily.

The many different types of proteoglycans are classified according to their core protein. The core protein produced by members of the collagen proteoglycans gene family is collagen. Collagens are a family of proteins that strengthen and support connective tissues, such as skin, bone, cartilage, tendons, and ligaments. Collagen proteoglycans are major components of the extracellular matrix, which is an intricate lattice of proteins and other molecules that forms in the spaces between cells. The collagen proteoglycans bind to a variety of other proteins in the extracellular matrix, including other forms of collagen.

Examples of genes in this gene family: *COL9A1*, *COL9A2*, *COL9A3*

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (<http://www.genenames.org/cgi-bin/genefamilies/>) and their member genes.

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### Learn more about the collagen proteoglycan gene family:

Essentials of Glycobiology (first edition, 1999): Proteoglycans and Glycosaminoglycans (<http://www.ncbi.nlm.nih.gov/books/NBK20693/>)

## Complement

Genes in the complement family provide instructions for making proteins involved in the complement system, an essential part of the body's immune response. The complement system is composed of more than 20 proteins that work together to destroy foreign invaders (such as bacteria and viruses), trigger inflammation, and remove debris from cells and tissues. This system must be carefully regulated so it targets only unwanted materials and does not attack the body's healthy cells.

Several diseases have been associated with changes in complement genes. Each of these genetic changes typically results in a shortage (deficiency) of a single complement system protein. These deficiencies disrupt the normal activity or regulation of the complement system, often leading to an increased risk of bacterial infection or recurrent episodes of severe swelling (angioedema). Complement system defects have also been found in autoimmune disorders such as systemic lupus erythematosus. Autoimmune disorders occur when the immune system malfunctions and attacks the body's own tissues and organs.

Examples of genes in this gene family: *C8A*, *C8B*, *CFH*, *CFHR5*, *CFI*, *ITGB2*

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### Learn more about the complement gene family:

MedlinePlus Encyclopedia: Complement (<https://medlineplus.gov/ency/article/003456.htm>)

Merck Manual Professional Version: Complement System (<http://www.merckmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/complement-system>)

Immunobiology (fifth edition, 2001): The Complement System and Innate Immunity (<http://www.ncbi.nlm.nih.gov/books/NBK27100/>)



## Cytochrome p450

Enzymes produced from the cytochrome P450 genes are involved in the formation (synthesis) and breakdown (metabolism) of various molecules and chemicals within cells. Cytochrome P450 enzymes play a role in the synthesis of many molecules including steroid hormones, certain fats (cholesterol and other fatty acids), and acids used to digest fats (bile acids). Additional cytochrome P450 enzymes metabolize external substances, such as medications that are ingested, and internal substances, such as toxins that are formed within cells. There are approximately 60 CYP genes in humans.

Cytochrome P450 enzymes are primarily found in liver cells but are also located in cells throughout the body. Within cells, cytochrome P450 enzymes are located in a structure involved in protein processing and transport (endoplasmic reticulum) and the energy-producing centers of cells (mitochondria). The enzymes found in mitochondria are generally involved in the synthesis and metabolism of internal substances, while enzymes in the endoplasmic reticulum usually metabolize external substances, primarily medications and environmental pollutants.

Common variations (polymorphisms) in cytochrome P450 genes can affect the function of the enzymes. The effects of polymorphisms are most prominently seen in the breakdown of medications. Depending on the gene and the polymorphism, drugs can be metabolized quickly or slowly. If a cytochrome P450 enzyme metabolizes a drug slowly, the drug stays active longer and less is needed to get the desired effect. A drug that is quickly metabolized is broken down sooner and a higher dose might be needed to be effective. Cytochrome P450 enzymes account for 70 percent to 80 percent of enzymes involved in drug metabolism.

Each cytochrome P450 gene is named with CYP, indicating that it is part of the cytochrome P450 gene family. The gene is also given a number associated with a specific group within the gene family, a letter representing the gene's subfamily, and a number assigned to the specific gene within the subfamily. For example, the cytochrome P450 gene that is in group 27, subfamily A, gene 1 is written as *CYP27A1*.

Diseases caused by mutations in cytochrome P450 genes typically involve the buildup of substances in the body that are harmful in large amounts or that prevent other necessary molecules from being produced.

Examples of genes in this gene family: *CYP1B1*, *CYP2C9*, *CYP2C19*, *CYP4V2*, *CYP11B1*, *CYP11B2*, *CYP17A1*, *CYP19A1*, *CYP21A2*, *CYP27B1*

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (<http://www.genenames.org/cgi-bin/genefamilies/>) and their member genes.

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## Learn more about the cytochrome p450 gene family:

Biochemistry (fifth edition, 2002): The Cytochrome P450 System is Widespread and Performs a Protective Function (<http://www.ncbi.nlm.nih.gov/books/NBK22339/#A3663>)

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Indiana University: Cytochrome P450 Drug-Interaction Table (<http://medicine.iupui.edu/clinpharm/ddis/clinical-table/>)

Human Cytochrome P450 (CYP) Allele Nomenclature Database (<http://www.cypalleles.ki.se/>)

## Endogenous ligands

Genes in this family provide instructions for making specialized proteins called endogenous ligands. A ligand is a protein that attaches (binds) to another protein called a receptor; receptor proteins have specific sites into which the ligands fit like keys into locks. Endogenous ligands are those that are produced in the body, not those introduced into the body, such as certain drugs.

Together, ligands and their receptors trigger signals that affect cell development and function. Alterations in ligands can impair cell signaling and change the normal activities of cells. Because ligands mediate many different functions in the body, mutations in genes in the endogenous ligands gene family can have a variety of effects.

Examples of genes in this gene family: *AMH*, *APP*, *AVP*, *BDNF*, *EDN3*, *FN1*, *GDF3*, *GH1*, *HTT*, *PROK2*, *PSAP*, *RB1*, *TGFB1*, *TGFB2*, *TSHB*, *VWF*, *WNT3*

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**Learn more about the endogenous ligands gene family:**

Molecular Cell Biology (fourth edition, 2000): Receptor Proteins Exhibit Ligand-Binding and Effector Specificity (<http://www.ncbi.nlm.nih.gov/books/NBK21517/#A5720>)

## Human leukocyte antigens

The HLA gene family provides instructions for making a group of related proteins known as the human leukocyte antigen (HLA) complex. The HLA complex helps the immune system distinguish the body's own proteins from proteins made by foreign invaders such as viruses and bacteria.

HLA is the human version of the major histocompatibility complex (MHC), a gene family that occurs in many species. In humans, the MHC complex consists of more than 200 genes located close together on chromosome 6. Genes in this complex are categorized into three basic groups: class I, class II, and class III.

Humans have three main MHC class I genes, known as *HLA-A*, *HLA-B*, and *HLA-C*. The proteins produced from these genes are present on the surface of almost all cells. On the cell surface, these proteins are bound to protein fragments (peptides) that have been exported from within the cell. MHC class I proteins display these peptides to the immune system. If the immune system recognizes the peptides as foreign (such as viral or bacterial peptides), it responds by triggering the infected cell to self-destruct.

There are six main MHC class II genes in humans: *HLA-DPA1*, *HLA-DPB1*, *HLA-DQA1*, *HLA-DQB1*, *HLA-DRA*, and *HLA-DRB1*. MHC class II genes provide instructions for making proteins that are present almost exclusively on the surface of certain immune system cells. Like MHC class I proteins, these proteins display peptides to the immune system.

The proteins produced from MHC class III genes have somewhat different functions; they are involved in inflammation and other immune system activities. The functions of some MHC genes are unknown.

HLA genes have many possible variations, allowing each person's immune system to react to a wide range of foreign invaders. Some HLA genes have hundreds of identified versions (alleles), each of which is given a particular number (such as HLA-B27). Closely related alleles are categorized together; for example, at least 40 very similar alleles are subtypes of HLA-B27. These subtypes are designated as *HLA-B\*2701* to *HLA-B\*2743*.

More than 100 diseases have been associated with different alleles of HLA genes. For example, the HLA-B27 allele increases the risk of developing an inflammatory joint disease called ankylosing spondylitis. Many other disorders involving abnormal immune function and some forms of cancer have also been associated with specific HLA alleles. However, it is often unclear what role HLA genes play in the risk of developing these diseases.

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (<http://www.genenames.org/cgi-bin/genefamilies/>) and their member genes.

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## Learn more about the human leukocyte antigens gene family:

Merck Manual for Health Care Professionals: Human Leukocyte Antigen (HLA) System (<http://www.merckmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/human-leukocyte-antigen-hla-system>)

Immunobiology (fifth edition 2001): The Major Histocompatibility Complex and its Functions (<http://www.ncbi.nlm.nih.gov/books/NBK27156/>)

Cold Spring Harbor Laboratory: Chromosome 6: HLA Genes and the Human Immune System (<https://www.dnalc.org/view/15401-Chromosome-6-HLA-genes-and-the-human-immune-system-Matt-Ridley.html>)

The Anthony Nolan Trust: HLA Informatics Group (<https://www.anthonynolan.org/clinicians-and-researchers/anthony-nolan-research-institute/hla-informatics-group>)

EMBL-EBI: IMGT/HLA Database (<http://www.ebi.ac.uk/ipd/imgt/hla/>)

## Homeoboxes

Homeobox genes are a large family of similar genes that direct the formation of many body structures during early embryonic development. In humans, the homeobox gene family contains an estimated 235 functional genes and 65 pseudogenes (structurally similar genes that do not provide instructions for making proteins). Homeobox genes are present on every human chromosome, and they often appear in clusters. Many classes and subfamilies of homeobox genes have been described, although these groupings are used inconsistently.

Homeobox genes contain a particular DNA sequence that provides instructions for making a string of 60 protein building blocks (amino acids) known as the homeodomain. Most homeodomain-containing proteins act as transcription factors, which means they bind to and control the activity of other genes. The homeodomain is the part of the protein that attaches (binds) to specific regulatory regions of the target genes.

Genes in the homeobox family are involved in a wide range of critical activities during development. These activities include directing the formation of limbs and organs along the anterior-posterior axis (the imaginary line that runs from head to tail in animals) and regulating the process by which cells mature to carry out specific functions (differentiation). Some homeobox genes act as tumor suppressors, which means they help prevent cells from growing and dividing too rapidly or in an uncontrolled way.

Because homeobox genes have so many important functions, mutations in these genes are responsible for a variety of developmental disorders. For example, mutations in the HOX group of homeobox genes typically cause limb malformations. Changes in PAX homeobox genes often result in eye disorders, and changes in MSX homeobox genes cause abnormal head, face, and tooth development. Additionally, increased or decreased activity of certain homeobox genes has been associated with several forms of cancer later in life.

Examples of genes in this gene family: *ALX4*, *ARX*, *HOXA13*, *HOXB13*, *OTX2*, *PAX3*, *PAX6*, *POU3F4*, *SHOX*, *SIX3*

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**Learn more about the homeoboxes gene family:**

National Human Genome Research Institute, NIH: Homeodomain Resource (<http://research.nhgri.nih.gov/homeodomain/>)

Arizona State University: Homeobox Genes and the Homeobox (<http://embryo.asu.edu/pages/homeobox-genes-and-homeobox-0>)

## Keratins

Genes in the KRT family provide instructions for making proteins called keratins. Keratins are a group of tough, fibrous proteins that form the structural framework of epithelial cells, which are cells that line the surfaces and cavities of the body. Epithelial cells make up tissues such as the hair, skin, and nails. These cells also line the internal organs and are an important part of many glands.

Keratins are best known for providing strength and resilience to cells that form the hair, skin, and nails. These proteins allow tissues to resist damage from friction and minor trauma, such as rubbing and scratching. Keratins are also involved in several other critical cell functions, including cell movement (migration), regulation of cell size, cell growth and division (proliferation), wound healing, and transport of materials within cells.

Humans have at least 54 functional keratin genes, which are divided into type I and type II keratins. Most of the type I keratin genes, designated *KRT9* through *KRT20*, are located in a cluster on chromosome 17. The type II keratin genes, designated *KRT1* through *KRT8*, are found in another cluster on chromosome 12.

Different combinations of keratin proteins are found in different tissues. In each tissue, a type I keratin pairs with a type II keratin to form a structure called a heterodimer. Heterodimers interact with one another to form strong, flexible fibers called keratin intermediate filaments. These filaments assemble into a dense network, which forms the structural framework of cells.

Mutations in at least 20 KRT genes have been found to cause human diseases affecting the skin, hair, nails, and related tissues. The most well-studied of these diseases include epidermolysis bullosa simplex (EBS) and pachyonychia congenita. Mutations in KRT genes alter the structure of keratins, which prevent them from forming an effective network of keratin intermediate filaments. Without this network, cells become fragile and are easily damaged, making tissues less resistant to friction and minor trauma. Even normal activities such as walking can cause skin cells to break down, resulting in the formation of painful blisters and calluses.

Examples of genes in this gene family: *KRT3*, *KRT4*, *KRT5*, *KRT6A*, *KRT6B*, *KRT6C*, *KRT10*, *KRT12*, *KRT13*, *KRT14*, *KRT16*, *KRT17*, *KRT81*, *KRT83*, *KRT86*

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## Learn more about the keratins gene family:

- Molecular Biology of the Cell (fourth edition, 2002): Keratin Filaments in Epithelial Cells (Image) (<http://www.ncbi.nlm.nih.gov/books/NBK26862/figure/A2988/>)
- The Cell: A Molecular Approach (second edition, 2000): Intermediate Filaments (<http://www.ncbi.nlm.nih.gov/books/NBK9834/>)

## Mitochondrial respiratory chain complex

Genes in the mitochondrial respiratory chain complex gene family provide instructions for proteins involved in oxidative phosphorylation, also called the respiratory chain. Oxidative phosphorylation is an important cellular process that uses oxygen and simple sugars to create adenosine triphosphate (ATP), the cell's main energy source. Five protein complexes, made up of several proteins each, are involved in this process. The complexes are named complex I, complex II, complex III, complex IV, and complex V.

Oxidative phosphorylation occurs in mitochondria, which are specialized, energy-producing structures inside cells. Within mitochondria, the five protein complexes are embedded in a tightly folded membrane called the inner mitochondrial membrane. During oxidative phosphorylation, the protein complexes carry out chemical reactions that drive the production of ATP. Specifically, they create an unequal electrical charge on either side of the inner mitochondrial membrane through a step-by-step transfer of negatively charged particles called electrons. This difference in electrical charge provides the energy for ATP production.

Most DNA is contained in a cell's nucleus and is called nuclear DNA. Mitochondria also contain a small amount of DNA, known as mitochondrial DNA. The mitochondrial respiratory chain complex gene family includes genes found in nuclear DNA as well as genes found in mitochondrial DNA. Mutations in either nuclear or mitochondrial genes in the mitochondrial respiratory chain complex gene family can cause disease.

Examples of genes in this gene family: *MT-ATP6*, *MT-CYB*, *SDHA*, *SDHB*, *SDHC*, *SDHD*

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (<http://www.genenames.org/cgi-bin/genefamilies/>) and their member genes.

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**Learn more about the mitochondrial respiratory chain complex gene family:**

Biochemistry (5th Edition, 2002): Oxidative Phosphorylation in Eukaryotes Takes Place in Mitochondria (<http://www.ncbi.nlm.nih.gov/books/NBK22422/#A2570>)

Molecular Cell Biology (4th Edition, 2000): Electrons Flow from FADH<sub>2</sub> and NADH to O<sub>2</sub> via a Series of Multiprotein Complexes (<http://www.ncbi.nlm.nih.gov/books/NBK21528/#A4383>)

## Myosins

Genes in this family provide instructions for making related proteins called myosins. Myosins are often referred to as molecular motors because they use energy to move. They interact with another protein called actin; actin proteins are organized into filaments to form a network (the cytoskeleton) that gives structure to cells and can act as a track for myosin to move along. Some myosin proteins attach (bind) to other proteins and transport them within and between cells along the actin track.

Some myosins are involved in muscle contraction. These myosins interact with other myosin proteins, forming thick filaments. In muscle cells, thick filaments made up of myosin and thin filaments made up of actin compose structures called sarcomeres, which are the basic units of muscle contraction. The overlapping thick and thin filaments bind to each other and release, which allows the filaments to move relative to one another so that muscles can contract. Mutations in genes that provide instructions for making muscle myosins can cause severe abnormalities in the muscles used for movement (skeletal muscles) or in the heart (cardiac) muscle. Cardiac muscle abnormalities can lead to heart failure and sudden death.

Myosin proteins are involved in many cellular functions. Their ability to transport materials and create force through contractions make them important in the process of cell division. Myosins are also involved in cell movement. Some myosins are found in specialized structures in the inner ear known as stereocilia. These myosins are thought to help properly organize the stereocilia. Abnormalities in these myosins can cause deafness.

Examples of genes in this gene family: *MYH3*, *MYH6*, *MYH7*, *MYH9*, *MYH11*, *MYO5A*, *MYO5B*, *MYO7A*

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (<http://www.genenames.org/cgi-bin/genefamilies/>) and their member genes.

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**Learn more about the myosins gene family:**

Biochemistry (fifth edition, 2002): Myosins Move Along Actin Filaments (<http://www.ncbi.nlm.nih.gov/books/NBK22418/>)

Molecular Biology of the Cell (fourth edition, 2002): Actin-Based Motor Proteins Are Part of the Myosin Superfamily (<http://www.ncbi.nlm.nih.gov/books/NBK26888/#A3042>)

Molecular Cell Biology (fourth edition, 2000): Myosin: The Actin Motor Protein (<http://www.ncbi.nlm.nih.gov/books/NBK21724/>)

## Transfer RNAs

Genes in the tRNA gene family provide instructions for making molecules called transfer RNAs (tRNAs). Transfer RNAs are a particular type of RNA, which is a chemical cousin of DNA. These molecules help assemble protein building blocks (amino acids) into functioning proteins. Each tRNA attaches to a particular amino acid. During protein assembly, the tRNA recognizes a specific three-letter sequence (a codon) in the genetic blueprint for making proteins and inserts the amino acid into the appropriate location in the growing protein.

There are two classes of tRNA: cytoplasmic and mitochondrial. Cytoplasmic tRNAs are found in the fluid inside cells (the cytoplasm). These tRNAs help produce proteins from genes located in the DNA in the nucleus of the cell (nuclear DNA). Although most DNA is nuclear, cellular structures called mitochondria have a small amount of their own DNA, called mitochondrial DNA. Proteins produced from genes located in mitochondrial DNA are assembled by mitochondrial tRNAs.

Mutations in tRNA genes reduce the ability of the tRNA to add amino acids to proteins, slowing protein production. Mutations that affect mitochondrial tRNAs impair the ability of mitochondria to provide energy for cells or to control blood sugar levels. These mutations can cause a variety of signs and symptoms, including muscle weakness, seizures, neurological problems, hearing loss, and diabetes. Mutations in genes that provide instructions for cytoplasmic tRNAs do not appear to cause disease.

Examples of genes in this gene family: *MT-TE*, *MT-TH*, *MT-TK*, *MT-TL1*, *MT-TS1*, *MT-TV*

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (<http://www.genenames.org/cgi-bin/genefamilies/>) and their member genes.

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**Learn more about the transfer RNAs gene family:**

Biochemistry (fifth edition, 2002): Protein Synthesis Requires the Translation of Nucleotide Sequences into Amino Acid Sequences (<http://www.ncbi.nlm.nih.gov/books/NBK22421/>)

The Cell: A Molecular Approach (second edition, 2000): Translation of mRNA (<http://www.ncbi.nlm.nih.gov/books/NBK9849/>)

Molecular Biology of the Cell (fourth edition, 2002): From RNA to Protein (<http://www.ncbi.nlm.nih.gov/books/NBK26829/>)



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Published on May 23, 2017