PRKN gene

parkin RBR E3 ubiquitin protein ligase

Normal Function

The *PRKN* gene, one of the largest human genes, provides instructions for making a protein called parkin. Parkin plays a role in the cell machinery that breaks down (degrades) unneeded proteins by tagging damaged and excess proteins with molecules called ubiquitin. Ubiquitin serves as a signal to move unneeded proteins into specialized cell structures known as proteasomes, where the proteins are degraded. The ubiquitin-proteasome system acts as the cell's quality control system by disposing of damaged, misshapen, and excess proteins. This system also regulates the availability of proteins that are involved in several critical cell activities, such as the timing of cell division and growth. Because of its activity in the ubiquitin-proteasome system, parkin belongs to a group of proteins called E3 ubiquitin ligases.

Parkin appears to be involved in the maintenance of mitochondria, the energy-producing centers in cells. However, little is known about its role in mitochondrial function. Research suggests that parkin may help trigger the destruction of mitochondria that are not working properly.

Studies of the structure and activity of parkin have led researchers to propose several additional activities for this protein. Parkin may act as a tumor suppressor protein, which means it prevents cells from growing and dividing too rapidly or in an uncontrolled way. Parkin may also regulate the supply and release of sacs called synaptic vesicles from nerve cells. Synaptic vesicles contain chemical messengers that transmit signals from one nerve cell to another.

Health Conditions Related to Genetic Changes

Parkinson disease

Researchers have identified more than 200 *PRKN* gene mutations that cause Parkinson disease, a condition characterized by progressive problems with movement and balance. Mutations in this gene are associated with the juvenile form of Parkinson disease, which appears before age 20, and some cases of the more common, late-onset form that begins after age 50.

Some *PRKN* gene mutations lead to an abnormally small parkin protein that is nonfunctional and is rapidly broken down (degraded) within cells. Other mutations insert, delete, or change DNA building blocks (nucleotides) in the *PRKN* gene, leading to a defective version of the parkin protein or preventing the production of this protein. The *PRKN* gene mutations associated with Parkinson disease usually lead to a loss of parkin activity.

It is unclear how *PRKN* gene mutations cause Parkinson disease. The loss of parkin activity probably disturbs the ubiquitin-proteasome system, which allows unneeded proteins to accumulate. A buildup of these proteins could disrupt normal cell activities such as the supply and release of synaptic vesicles, particularly those that contain a chemical messenger called dopamine. As parkin is normally abundant in the brain, its loss could lead to the impairment or death of nerve cells, including those that produce dopamine. Loss of dopamine-producing nerve cells is a characteristic feature of Parkinson disease.

Mutations in the *PRKN* gene may also disrupt the regulation of mitochondria. Researchers speculate that mitochondrial dysfunction in dopamine-producing nerve cells may play an important role in causing the signs and symptoms of Parkinson disease.

Leprosy

Lung cancer

Ovarian cancer

Cancers

The *PRKN* gene spans part of a region on chromosome 6 known as FRA6E. This region is known as a fragile area because it is unstable and prone to breakage and rearrangement. Changes involving the FRA6E region have been reported in several forms of human cancer, including glioblastoma (a form of brain cancer), colorectal cancer, lung cancer, and ovarian cancer. In some of these cancerous tumors, segments of the FRA6E region, including part or all of the *PRKN* gene, are abnormally deleted or duplicated. These genetic changes are described as somatic because they occur only in tumor cells and are not inherited. As a result of these alterations, parkin activity is reduced or absent in these cells. Because parkin is thought to act as a tumor suppressor, a shortage of this protein's function could allow cells to grow and divide in an uncontrolled manner, leading to tumor formation.

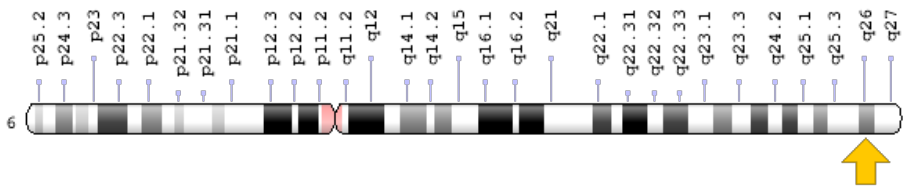
Other disorders

Studies suggest that common variations (polymorphisms) in the *PRKN* gene (and a neighboring gene called *PACRG*) can increase the risk of contracting Hansen disease, also known as leprosy. This disease affects the nerves and skin and is caused by the bacterium *Mycobacterium leprae*. It remains unclear how *PRKN* polymorphisms increase susceptibility to Hansen disease. Researchers believe that the ubiquitin-proteasome system may play a role in controlling infection. Polymorphisms in the *PRKN* gene may subtly alter parkin's function, making the ubiquitin-proteasome system less efficient.

Chromosomal Location

Cytogenetic Location: 6q26, which is the long (q) arm of chromosome 6 at position 26

Molecular Location: base pairs 161,347,417 to 162,727,802 on chromosome 6 (Homo sapiens Annotation Release 109, GRCh38.p12) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- AR-JP
- PARK2
- parkin
- Parkinson disease (autosomal recessive, juvenile) 2, parkin
- parkinson protein 2, E3 ubiquitin protein ligase (parkin)
- PDJ
- PRKN2_HUMAN
- ubiquitin E3 ligase

Additional Information & Resources

Educational Resources

- Annual Reviews Collection: Overview of the Ubiquitin-Proteasome Degradation System
  https://www.ncbi.nlm.nih.gov/books/NBK2229/#A103
- Biochemistry (fifth edition, 2002): Protein Turnover is Tightly Regulated
  https://www.ncbi.nlm.nih.gov/books/NBK22397/
- National Institute of Allergy and Infectious Diseases: Leprosy (Hansen's Disease)
  https://www.niaid.nih.gov/diseases-conditions/leprosy-hansens-disease
- The Cell: A Molecular Approach (second edition, 2000): The Ubiquitin-Proteasome Pathway
  https://www.ncbi.nlm.nih.gov/books/NBK9957/#A1233

Clinical Information from GeneReviews

- Parkin Type of Early-Onset Parkinson Disease
  https://www.ncbi.nlm.nih.gov/books/NBK1478
- Parkinson Disease Overview
  https://www.ncbi.nlm.nih.gov/books/NBK1223

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28PARK2%5BTIAB%5D%29+OR+%28parkin+AND+protein%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+720+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- LEPROSY, SUSCEPTIBILITY TO, 2
  http://omim.org/entry/607572
- PARKIN
  http://omim.org/entry/602544

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/PARK2ID46408ch6q26.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=PRKN%5Bgene%5D
- HGNC Gene Symbol Report
  https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:8607
- Monarch Initiative
  https://monarchinitiative.org/gene/NCBIGene:5071
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/5071
- PDGene
  http://www.pdgene.org/view?gene=PARK2
- UniProt
  https://www.uniprot.org/uniprot/O60260

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