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 \textit{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 \textit{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 \textit{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 \textit{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 \textit{PRKN} gene (and a neighboring gene called \textit{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 \textit{Mycobacterium leprae}. It remains unclear how \textit{PRKN} polymorphisms increase susceptibility to Hansen disease. Researchers believe that the ubiquitin-proteasome system may play a role in controlling infection. Polymorphisms in the \textit{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 Updated Annotation Release 109.20200522, GRCh38.p13) (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
Sources for This Summary

- Abou-Sleiman PM, Muqit MM, Wood NW. Expanding insights of mitochondrial dysfunction in Parkinson's disease. Nat Rev Neurosci. 2006 Mar;7(3):207-19. Review. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16495942

- Dawson TM, Dawson VL. The role of parkin in familial and sporadic Parkinson's disease. Mov Disord. 2010;25 Suppl 1:S32-9. doi: 10.1002/mds.22798. Review. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20187240 
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4115293/

- Denison SR, Callahan G, Becker NA, Phillips LA, Smith DI. Characterization of FRA6E and its potential role in autosomal recessive juvenile parkinsonism and ovarian cancer. Genes Chromosomes Cancer. 2003 Sep;38(1):40-52. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12874785

- Denison SR, Wang F, Becker NA, Schüle B, Kock N, Phillips LA, Klein C, Smith DI. Alterations in the common fragile site gene Parkin in ovarian and other cancers. Oncogene. 2003 Nov 13;22(51):8370-8. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/14614640

- Kay DM, Stevens CF, Hamza TH, Montimurro JS, Zabetian CP, Factor SA, Samii A, Griffith A, Roberts JW, Molho ES, Higgins DS, Gancher S, Moses L, Zareparsi S, Pookaj P, Bird T, Nutt J, Schellenberg GD, Payami H. A comprehensive analysis of deletions, multiplications, and copy number variations in PARK2. Neurology. 2010 Sep 28;75(13):1189-94. doi: 10.1212/WNL.0b013e3181f4d832. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20876472 
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3013490/

- Mira MT, Alcaïs A, Nguyen VT, Moraes MO, Di Flumeri C, Vu HT, Mai CP, Nguyen TH, Nguyen NB, Pham XK, Sarno EN, Alter A, Montpetit A, Moraes ME, Moraes JR, Doré C, Gallant CJ, Lepage P, Verner A, Van De Vosse E, Hudson TJ, Abel L, Schurr E. Susceptibility to leprosy is associated with PARK2 and PACRG. Nature. 2004 Feb 12;427(6975):636-40. Epub 2004 Jan 25. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/14737177

- Narendra DP, Youle RJ. Targeting mitochondrial dysfunction: role for PINK1 and Parkin in mitochondrial quality control. Antioxid Redox Signal. 2011 May 15;14(10):1929-38. doi: 10.1089/ars.2010.3799. Epub 2011 Mar 3. Review. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21194381 
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3078490/

- Picchio MC, Martin ES, Cesari R, Calin GA, Yendamuri S, Kuroki T, Pentimalli F, Sarti M, Yoder K, Kaiser LR, Fishel R, Croce CM. Alterations of the tumor suppressor gene Parkin in non-small cell lung cancer. Clin Cancer Res. 2004 Apr 15;10(8):2720-4. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15102676

- Pramstaller PP, Schlossmacher MG, Jacques TS, Scaravilli F, Eskelson C, Pepivani I, Hedrich K, Adel S, Gonzales-McNeal M, Hilker R, Kramer PL, Klein C. Lewy body Parkinson's disease in a large pedigree with 77 Parkin mutation carriers. Ann Neurol. 2005 Sep;58(3):411-22. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16130111

- Schurr E, Alcaïs A, de Léséleuc L, Abel L. Genetic predisposition to leprosy: A major gene reveals novel pathways of immunity to Mycobacterium leprae. Semin Immunol. 2006 Dec;18(6):404-10. Epub 2006 Sep 14. Review. 
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16973374
• Shimura H, Hattori N, Kubo Si, Mizuno Y, Asakawa S, Minoshima S, Shimizu N, Iwai K, Chiba T, Tanaka K, Suzuki T. Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase. Nat Genet. 2000 Jul;25(3):302-5. 
Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/10888878

• Veeriah S, Taylor BS, Meng S, Fang F, Yilmaz E, Vivanco I, Janakiraman M, Schultz N, Hanrahan AJ, Pao W, Ladanyi M, Sander C, Heguy A, Holland EC, Paty PB, Mischel PS, Liau L, Cloughesy TF, Mellinghoff IK, Solit DB, Chan TA. Somatic mutations of the Parkinson's disease-associated gene PARK2 in glioblastoma and other human malignancies. Nat Genet. 2010 Jan;42(1):77-82. doi: 10.1038/ng.491. Epub 2009 Nov 29. 
Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19946270
Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4002225/

• von Coelln R, Dawson VL, Dawson TM. Parkin-associated Parkinson's disease. Cell Tissue Res. 2004 Oct;318(1):175-84. Epub 2004 Jul 30. Review. 
Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15503153

Reprinted from Genetics Home Reference: 
https://ghr.nlm.nih.gov/gene/PRKN

Reviewed: May 2012
Published: August 17, 2020

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services