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Gene Section

Review

PRKN (arkin RBR E3 ubiquitin protein ligase)

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Abstract

PARK2 (also known as Parkin RBR E3 ubiquitin protein ligase) is one of the largest genes in our genome. It undergoes an extensive alternative splicing both at transcript and protein level, producing multiple transcript variants and distinct protein isoforms. The precise function of PARK2 is still not clear; however, the encoded protein is a component of a multiprotein E3 ubiquitin ligase complex that mediates the targeting of substrates for proteasomal degradation. Mutations in this gene cause Parkinson disease and autosomal recessive juvenile Parkinson disease. Further molecular defects have been linked to other human malignancies. Here, we review some major data on PARK2, concerning the genetic structure, the transcription regulation, the encoded protein and functions, and its implication in human diseases.

Keywords

PARK2, parkin, Parkinson's disease

Identity

Other names: PARK2, PDJ, PRKN, AR-JP, LPRS2, Parkin

HGNC (Hugo): PRKN

Location: 6q26

Local order: PARK2 is flanked towards the telomeric direction by PACRG (or PARK2 co-regulated) gene, which lies in a head-to-head arrangement and shares a common promoter with the adjacent PARK2 (West et al., 2003). In the centromeric direction PARK2 is flanked by AGPAT4 (1-acylglycerol-3-phosphate O-acyltransferase), which encodes a member of the 1-acylglycerol-3-phosphate O-acyltransferase family. According to NCBI MapViewer, further elements overlap or surround the PARK2 genetic region, such as two pseudogenes (KRT8P44 and TRE-TTC15-1) and a set of non-coding RNAs (LOC105378094, LOC105378098, LOC105378097 and LOC105369171).

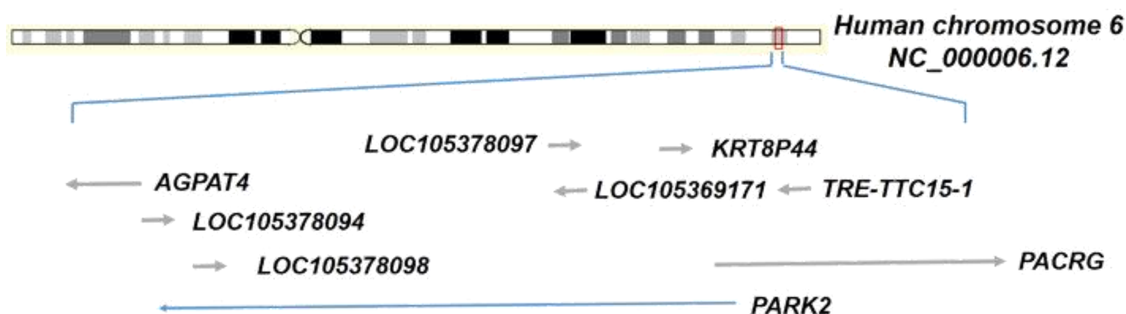

Figure 1 displays the human chromosome 6 (NCBI Reference Sequence NC_000006.12) and relative localization and orientation of PARK2 and flanking genes. PARK2 gene is represented in blue and is transcribed in antisense orientation (reverse strand). Further genes and non-coding RNAs map in this locus.

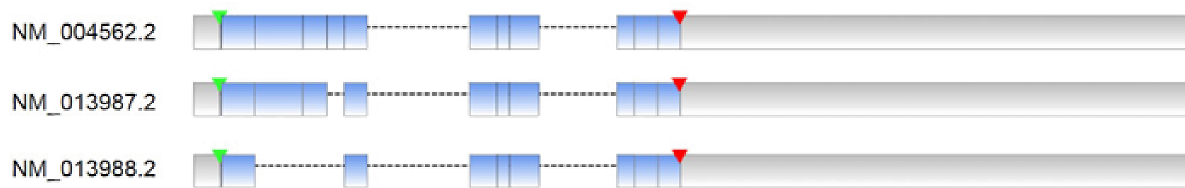

Figure 2 displays the three full-length Reference Sequences of PARK2 gene (NCBI - Nucleotide Database). Corresponding GenBank Accession Numbers are indicated on the left. Exons are represented as coloured boxes (blue for coding regions and grey for non coding), whereas the dashed line indicates intronic regions. The green triangle specifies the start codon, while the red one designates the stop codon.

DNA/RNA

Description

PARK2 is one of the largest genes in the human genome, and spans more than 1.38 Mb of genomic DNA in the long arm of chromosome 6 (reverse strand). Based on the first isolated transcript, the genomic organization and exon/intron boundary sequences of PARK2 were established of 12 exons.

Transcription

Currently, the NCBI RefSeq database annotates 3 representative transcripts as full-length PARK2 mRNAs (Figure 2). However, Homo sapiens cDNA sequences deposited in GenBank and UniGene repositories, coaligned on the genomic sequence and clustered in a minimal non-redundant way, support at least 21 different alternatively spliced mRNAs composed by 17 exons (Figure 3) (La Cognata et al., 2014; Scuderi et al., 2014). Each of these splice variants is indicated in Table 1.

Pseudogene

No known pseudogenes.

Protein

Description

The canonical PARK2 protein (Accession number BAA25751.1) (465 aa) comprises an N-terminal ubiquitin-like (UBQ) domain and two C-terminal in-between ring fingers (IBR) domains (Kitada et al., 1998).

Domain	Start	Stop	E-value
UBQ	1	72	2.95e-16
IBR	313	377	4.49e-14
IBR	401	457	0.142

The UBQ domain targets specific protein substrates for degradation by the proteasome, whereas IBR domains occur between pairs of ring fingers and play a role in protein quality control (Figure 4). The predicted PARK2 protein isoforms, encoded by the alternative splice transcripts currently known, structurally diverge from the canonic one for the presence or absence of the UBQ domain and for one or both IBR domains. Moreover, when UBQ domain is present, it often differs in length from the canonical one (La Cognata et al, 2014: Scuderi et al., 2014).

Expression

PARK2 is widely expressed in a variety of tissue types, including nervous system areas (brain, substantia nigra, mesencephalon, cerebellum, frontal cortex, striatum) (Shimura et al., 2001; Schlossmacher et al., 2002; LaVoie et al., 2005; Sun et al., 2013) and peripheral regions (skeletal muscle, heart and testicular tissue) (Kitada et al., 1998; Rosen et al., 2006), as well as in immortalized cell lines (neuroblastoma, kidney, epithelial, breast cancer and colon cancer cell lines) (Yamamoto et al., 2005; Henn et al., 2007; Poulogiannis et al., 2010; Tay et al., 2010).

Gene	#mRNA	Acc.Num.	Transcript Length
PARK2	1.	NM_004562.2	4073 bp
	2.	AF381282.1	1157 bp
	3.	AF381284.1	1158 bp
	4.	BC022014.2	1575 bp
	5.	NM_013987.2	3989 bp
	6.	NM_013988.2	3626 bp
	7.	AK294684.1	1115 bp
	8.	GU345837.1	1298 bp
	9.	GU345838.1	1340 bp
	10.	GU345840.1	1313 bp
	11.	GU357501.1	936 bp
	12.	GU357502.1	873 bp
	13.	GU361466.1	1279 bp
	14.	GU361467.1	1229 bp
	15.	GU361468.1	1010 bp
	16.	GU361469.1	1559 bp
	17.	GU361470.1	1561 bp
	18.	GU361471.1	634 bp
	19.	KC357594.1	454 bp
	20.	KC357595.1	1627 bp
	21.	KC774171.1	1282 bp

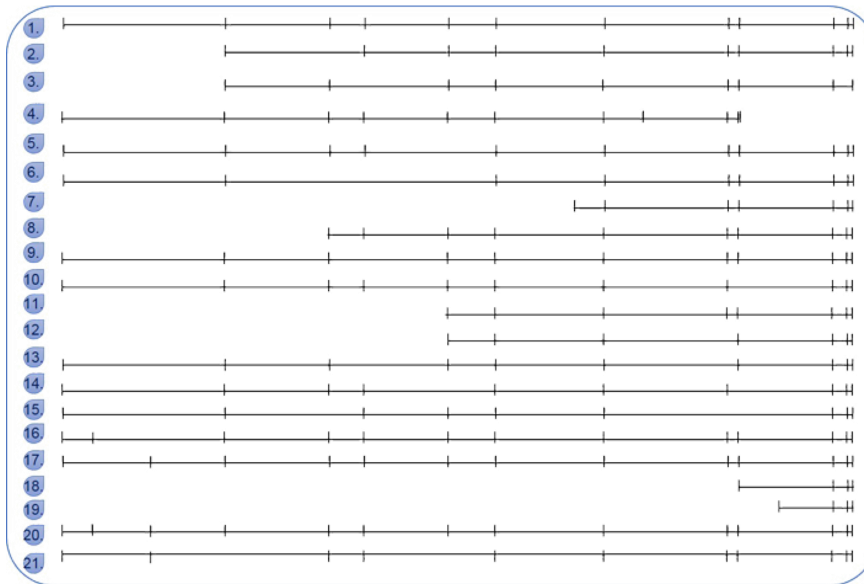

Figure 3 displays the structures of the currently known PARK2 mRNA splicing variants listed in Unigene Cluster Hs.132954 (La Cognata et al., 2014). Each mRNA variant is indicated with a number corresponding to that indicated in the Table 1.

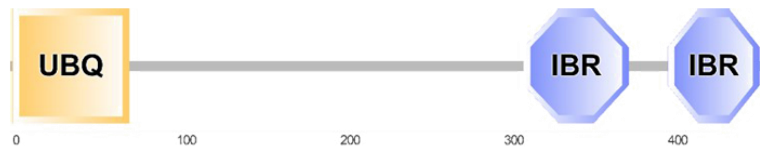

Figure 4 shows the domain composition of PARK2 protein, obtained from SMART Genome tool (http://smart.embl.de/). UBQ is the N-term ubiquitin domain, while IBRs are the C-term in-between ring fingers domains. In Table 2 are reported the aminoacidic start and stop positions and the E-value of the domain prediction.

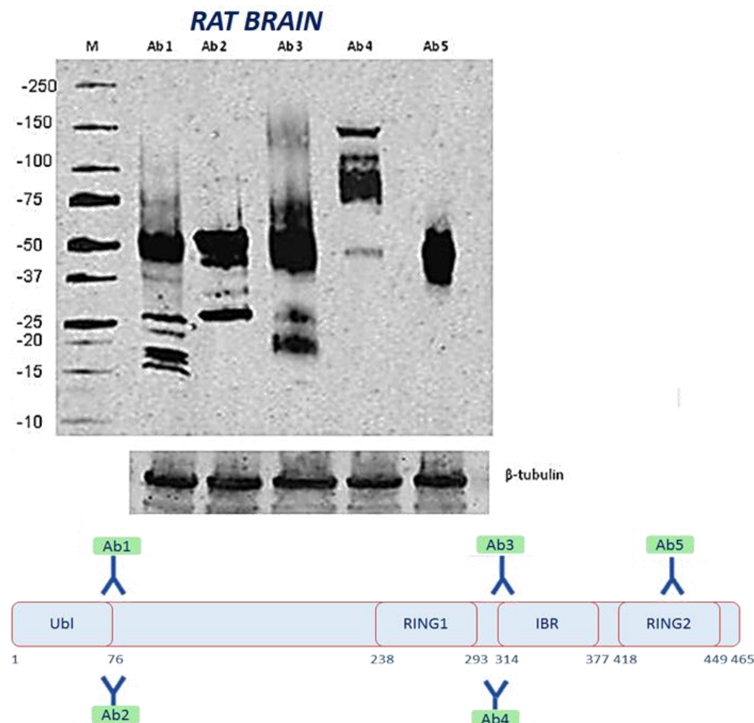

Figure 5 (adapted from Scuderi et al., 2014) shows a representative immunoblot of parkin protein isoforms in homogenized rat brain, visualized by using five different antibodies (Ab1, Ab2, Ab3, Ab4, Ab5). Immunoblot for β-tubulin is used as control. The right panel of the figure shows the localization of the epitopes recognized by the five antibodies on the canonical parkin protein.

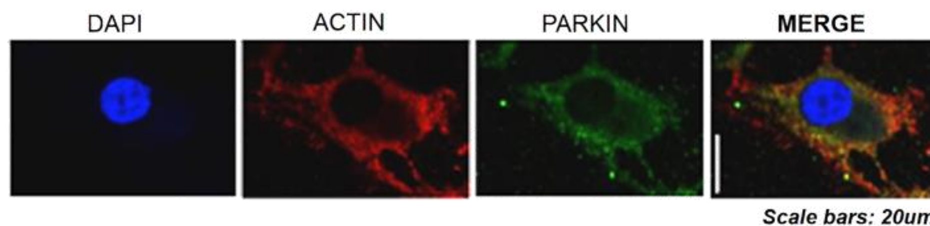

Figure 6 (adapted from Maugeri et al., 2015) shows the immunolocalization of parkin protein in glioblastoma cell lines (A172 cells). β-actin (red) was used as control and nuclei were stained with DAPI (blue).

In addition, distinct expression patterns of the PARK2 spliced isoforms have emerged in human leukocytes (Kasap et al., 2009), glioma and lung adenocarcinoma cell lines (D'Amico et al., 2015; Maugeri et al., 2015) and aged brain (Pawlyk et al., 2003). The differential expression of PARK2 splice isoforms have also observed in rat and mouse central and peripheral tissues and developmental stages (Horowitz et al., 1999; D'Agata et al., 2000; Gu et al., 2000; Stichel et al., 2000; Huynh et al., 2001).

Localisation

Subcellular localisation: PARK2 is mainly cytoplasmatic (Figure 5). Positive signals have been detected in endoplasmic reticulum (Imai et al., 2002), perinuclear region, microtubules (Ren et al., 2003), nucleus and plasma membrane. PARK2 protein also colocalizes with Lewy bodies (Schlossmacher et al., 2002), the pathological hallmark of Parkinson's Disease and dementia.

Function

PARK2 protein acts as an E3 ubiquitin protein ligase and is responsible of substrates recognition for proteasome-mediated degradation. It tags various types of proteins, including cytosolic (SNCAIP (Synphilin-1), GPR37 (Pael-R), SEPT5 (CDCrel-1) and 2a, SNCA ID: 46121> (α-synuclein), p22, Synaptogamina XI) (Imai et al., 2000; Shimura et al., 2000; Zhang et al., 2000; Chung et al., 2001; Staropoli et al., 2003), nuclear (Cyclin E, Cyclin D) (Ikeuchi et al., 2009; Gong et al., 2014) and mitochondrial ones (MFN1 and MFN2, VDAC, TOMM70A, TOMM40 and TOMM0, BAK1, RHOT1 (MIRO1) and RHOT2 (MIRO2), FIS1) (Narendra et al., 2008; Chan et al., 2011; Yoshii et al., 2011; Cookson, 2012; Jin et al., 2012).
The number of targets is such high that parkin protein results involved in numerous molecular pathways (proteasome-degradation, mitochondrial homeostasis, mitophagy, mitochondrial DNA stability, regulation of cellular cycle).

Homology

PARK2 gene shows a great evolutionary conservation across species, especially mammals. Mouse and rat species represent the most common animals used to model and study human pathologies. Human PARK2 protein shows a protein similarity of about 50% with rat, while it is more similar with the mouse parkin (90% of similarity) (protein similarity is calculated used Genomicus - PhyloView tool) (Figure 8).

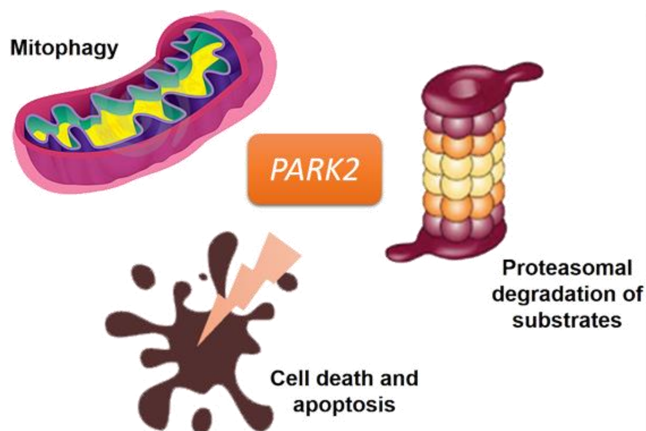

Figure 7 shows the major pathways in which PARK2 protein is involved: proteasome-degradation of substrates, mitochondrial homeostasis and mitophagy, and regulation of cellular cycle and cell death.

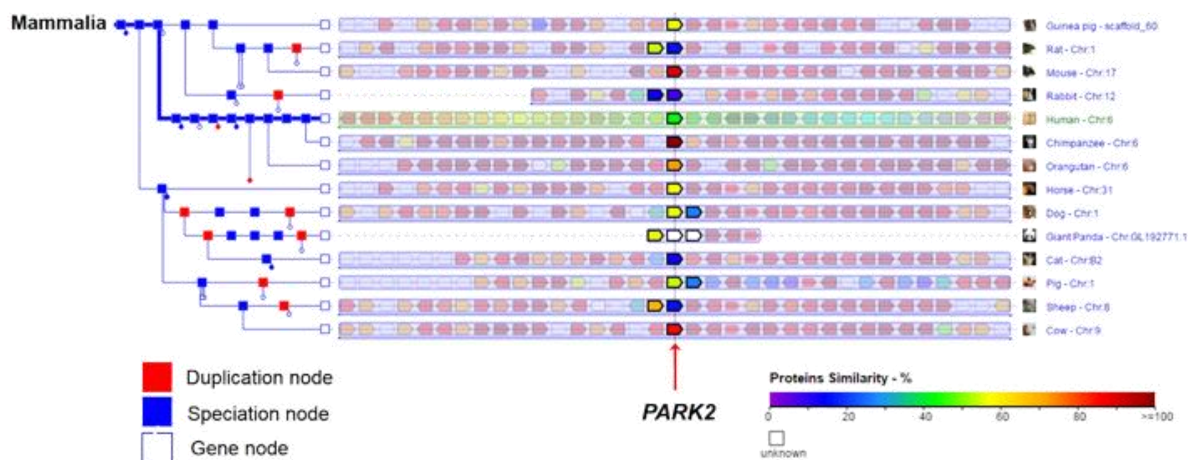

Figure 8 shows the evolutionary PARK2 Gene Tree, constructed using the multiple genome comparison tool PhyloView of Genomicus v.82.01 (http://www.genomicus.biologie.ens.fr/). This tool compares a specific gene with all the genomes that possess a homolog (Louis et al., 2015). Mammalia taxon has been defined as the root of the tree. PARK2 gene is displayed and highlighted in the central part of the figure. The internal nodes of the phylogenetic tree are represented as red boxes for duplication and blue boxes for speciation events. The percentage of similarity of homologous proteins is represented with different colours, as indicated in the legend.

Mutations

Germinal

A wide spectrum of loss-of-function mutations in PARK2 including simple mutations (nonsense, missense and splice site mutations), frameshift indels or in the untraslated regions, as well as Copy Number Variations of the promoter region and single or multiple exons PARK2 mutations, were identified across the entire gene in either homozygous, compound heterozygous or heterozygous state in familial and sporadic patients from different ethnicities. Heterozygous PARK2 variants have also been observed in healthy control individuals, making the assessment of pathogenicity for these variants quite complex. A complete and updated view of all PARK2 currently known mutations is available at the Parkinson Disease Mutation Database (http://www.molgen.vib-ua.be/PDMutDB/), which collects DNA variations screened among more than 800 families and linked to PD.

Somatic

Along with the germinal mutations occuring in Parkinson's Disease, genetic defects have also been observed in solid tumors. Based on the analysis of recent next generation sequencing data, the frequency of PARK2 mutations is relatively high in cervical cancer (5.6 %), lung squamous cell cancer (5.6 %), colorectal cancer (2.4 ~ 5.6 %), gastric cancer (4.6 %), skin cutaneous melanoma (3.5 %), lung adenocarcinoma (2.7 ~ 3.1 %), and endometrioid cancer (2.1%) Most cancer-derived PARK2 mutations are located at conserved regions, and more than 10% of mutations lead to frame shifts or truncations, suggesting that those mutations may disrupt or abolish the function of PARK2 (Xu et al., 2014). A list of the known cancer-derived mutations is available at the COSMIC Database and is summarized in Figure 9.

Mutation Type	Mutant samples
Substitution nonsense	6
Substitution missense	105
Substitution synonymous	52
Insertion inframe	0
Insertion frameshift	2
Deletion inframe	0
Deletion frameshift	4
Complex	1
Other	0

Epigenetics

Promoter hypermethylation is a common epigenetic mechanism to alter the gene expression. PARK2 promoter hypermethylation has been found in acute lymphoblastic leukemia, chronic myeloid leukemia and colorectal cancer (Agirre et al., 2006; Xu et al., 2014). However, the pathogenic role of specific epigenetic changes has not been yet clarified.

Implicated in

Parkinson's Disease

Note

Mutations in PARK2 are responsible of 50% of cases with autosomal recessive juvenile Parkinsonism (AR-JP). They also explain ~15% of the sporadic cases with onset before 45 (Lucking et al., 2000; Bonifati, 2012) and act as susceptibility alleles for late-onset forms of Parkinson disease (2% of cases) (Oliveira et al., 2003).

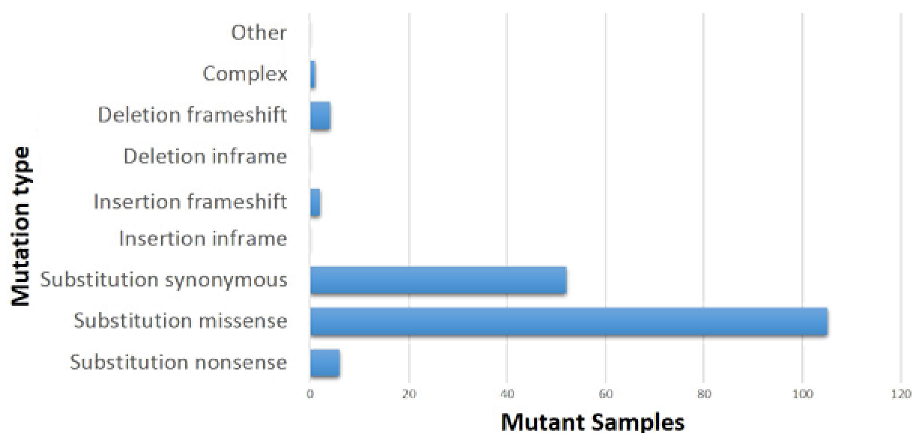

Figure 9 shows the overall distribution of PARK2 somatic mutations in cancer listed in COSMIC Database (http://cancer.sanger.ac.uk/cosmic) (November 2015). The exact number of collected somatic mutations in different cancer types is indicated in Table 3.

Clinical features of PARK2 homozygous mutation carriers are generally indistinguishable from those of idiopathic PD patients with the exception of a clear drop in onset age. Typically PARK2 patients present the classic symptoms of PD (such as bradykinesia, rigidity, and tremor), disease onset before the age of 50 years and a slow disease progression. Although they respond well to levodopa treatment, they are more likely to develop treatment-induced motor complications earlier in the treatment (Nuytemans et al., 2010).

Alzheimer Disease

Lonskaya and colleagues investigated the role of parkin in postmortem brain tissues from 21 patients with Alzheimer Disease (AD) and 15 control subjects. They observed decreased parkin solubility in cortex of patients and parkin co-localization with intraneuronal amyloid-beta depositions (Aβ1-42) in the hippocampus and cortex. Parkin accumulation with intraneuronal Aβ and p-Tau was detected in autophagosomes in AD brains. By using a gene transfer animal model, the authors also demonstrated that the expression of wild type parkin facilitate autophagic clearance and promoted deposition of Aβ1-42 and p-Tau into the lysosome (Lonskaya et al., 2013). Parkin, therefore, may clear autophagic defects via autophagosome degradation.

Leprosy

Using a positional cloning strategy in 197 Vietnamese leprosy simplex families, Mira et al. found significant associations between leprosy and 17 markers in the 5-prime regulatory region shared by PARK2 and PACRG. They then confirmed these results in 587 Brazilian leprosy cases and 388 unaffected controls. RT-PCR analysis detected wide expression of both PARK2 and PACRG in tissues, and suggested that, in addition to the common bidirectional promoter, gene-specific transcriptional activators may be involved in regulating cell- and tissue-specific gene expression (Mira et al., 2004). In 2013, Alter et al. replicated these findings showing a susceptibility locus in the shared PARK2 and PACRG promoter region in a Vietnamese population.

They also found that two SNPs (rs1333955 and rs2023004) were associated with susceptibility to leprosy in a northern Indian population (Alter et al., 2013).

Gliomas

Veeriah et al. provided evidence that PARK2 acts as a tumour suppressor gene in glioblastoma multiforme. Genetically, they detected PARK2 copy number loss in 53 of 216 glioblastomas and somatic point mutations in 7 glioblastomas specimens (Veeriah et al., 2010). The action of tumour suppressor gene for gliomas has been furthermore described by Yeo et al., who found parkin expression dramatically reduced in glioma cells, while its restoration promoted G(1) phase cell-cycle arrest and mitigated the proliferation rate (Yeo et al., 2012). Authors suggested the analysis of parkin pathway activation as predictive for the survival outcome of patients with glioma. The effects of PARK2 on tumour cell growth were also confirmed by Lin et al., who reported that PARK2 is frequently deleted and underexpressed in human gliomas, and that restoration of PARK2 significantly inhibited glioma cell growth (Lin et al., 2015).

An interesting transcriptional target of parkin is p53. Viotti et al. were able to demonstrate that parkin levels inversely correlate to brain tumour grade and p53 levels in oligodendrogliomas, mixed gliomas and glioblastomas, and established that p53 controls parkin promoter transactivation, mRNA and protein levels (Viotti et al., 2014).

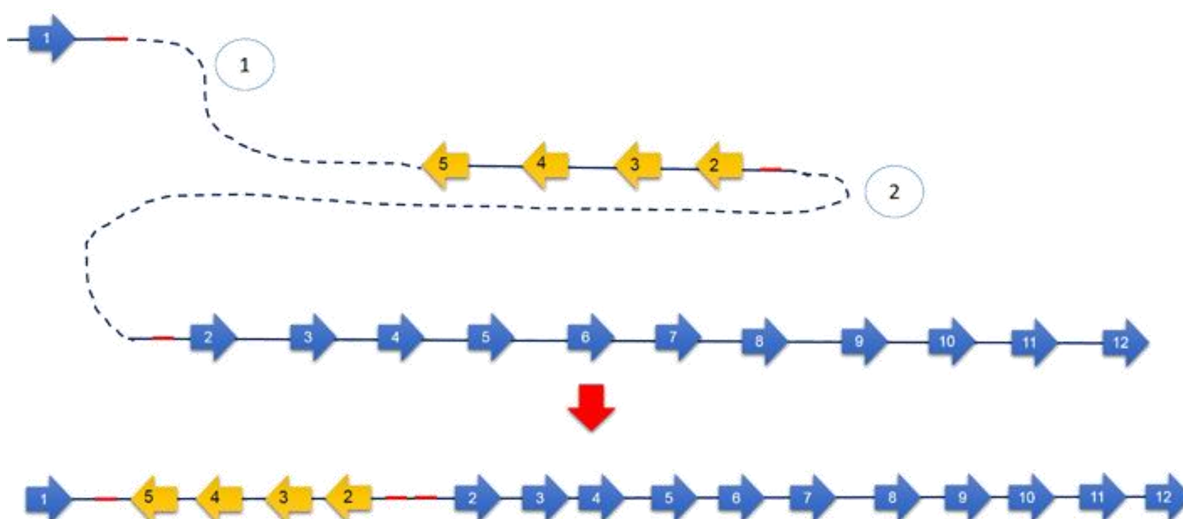

Figure 10 (adapted from Ambroziak et al., 2015) shows the hypothesized mechanism of the Ex2-5 duplication observed in a patient with early-onset PD. The authors suggest the FoSTeS/MMBIR (fork stalling and template switching/micro-homology-mediated break-induced replication) mechanism as responsible of the rearrangement. Upon replicating, the first exon of the PARK2 gene replication fork stalled and one strand invaded either the sister molecule or the homologue chromosome in inverted orientation (1), resulting in inverted duplication. Subsequently, the original forks were restored, but primed upstream of the point where it first stalled (2), leading to the triplication of the red-highlighted region (Ambroziak et al., 2015).

Colon cancer

Microarray analysis revealed copy number loss in 24 of 98 colon cancers and different PARK2 somatic point mutations in 2 colon cancer cells lines (Veeriah et al., 2010). Additionally, in 100 primary colorectal carcinomas, Poulogiannis et al. demonstrated by array comparative genomic hybridization that 33% show PARK2 copy number loss (Poulogiannis et al., 2010). The PARK2 deletions are mostly focal, heterozygous, and show maximum incidence in exons 3 and 4. Deficiency in expression of PARK2 is significantly associated also with adenomatous polyposis coli (APC) deficiency in human colorectal cancer. Moreover, in the same study, interbreeding of Park2 heterozygous knockout mice with Apc(Min) mice resulted in a dramatic acceleration of intestinal adenoma development and increased polyp multiplicity.

Lung adenocarcinoma

Somatic homozygous deletions of exon 2 of the PARK2 gene were found in 2 lung adenocarcinoma cell lines, Calu-3 and H-1573, suggesting that the loss of this locus and the resulting changes in its expression are involved in the development of the tumour (Cesari et al., 2003). Additional germline and somatic deletions were also reported by Iwakawa et al. in five patients with lung adenocarcinoma and in 31/267 lung adenocarcinoma, indicating that somatic PARK2 mutations occur rarely in lung adenocarcinoma development, but germline mutations could contribute to tumour progression (Iwakawa et al., 2012). Very recently, Xiong et al. reported the PARK2 germline mutation c.823C>T (p.Arg275Trp) in a family with eight cases of lung cancer (Xiong et al., 2015).

Ovarian Cancer

Two different groups identified both PARK2 genetic alterations and downregulated expression in ovarian cancer. Cesari et al. detected two PARK2 truncating deletions in 3 of 20 ovarian tumour samples, supporting the hypothesis that hemizygous or homozygous deletions are responsible for the abnormal expression of PARK2 in tumour biopsies and tumour cell lines. They suggest that PARK2 may act as a tumour suppressor gene and may contribute to the initiation and/or progression of ovarian cancer (Cesari et al., 2003). Denison et al. found four cell lines and four primary tumours as heterozygous for the duplication or deletion of a Parkin exon. The analysis of Parkin protein expression revealed that most of the ovarian cancer cell lines and primary tumours had diminished or absent Parkin expression (Denison et al., 2003).

Other malignancies

Alterations or molecular defects involving the coding region of the gene (single nucleotide mutations, copy numbers, gene breakage), epigenetic mechanisms, the mRNA up or down regulation, the protein level and the abnormal splicing of PARK2 have been linked to a wide range of other human malignancies (i.e. acute lymphoblastic leukemia, chronic myeloid leukemia, clear cell renal cell carcinoma, hepatocellular carcinoma, head and neck squamous cell carcinoma, gastric cancer, pancreatic adenocarcinoma, breast cancer, bladder urothelial cancer, thyroid cancer, adenoid cystic carcinoma) (Xu et al., 2014).

Breakpoints

PARK2 belongs to the family of extremely large human genes and is located within FRA6E, one of the most unstable common fragile sites (CFSs) of the human genome. CFSs are intrinsically difficult to replicate, and are known to play a major role in carcinogenesis. Some factors have been considered to contribute to instabilities, including late-replicating genomic regions, high AT content, flexible DNA sequences or regions enriched in repetitive elements. The exact size of the region of instability of FRA6E is not yet clear; however, it has been suggested that it may span even 9 Mb at 6q25.1-6q26 and that the main fragility core is localised on the telomeric end, within the PARK2 gene sequence. The most common molecular mechanisms which seem predominantly involved in the rearrangement processes of this genomic region are non-homologous end joining (NHEJ) and fork stalling and template switching (FoSTeS)/micro-homology mediated break-induced replication (MMBIR) (Figure 10) (Ambroziak et al., 2015).

References

Agirre X, Román-Gómez J, Vázquez I, Jiménez-Velasco A, Garate L, Montiel-Duarte C, Artieda P, Cordeu L, Lahortiga I, Calasanz MJ, Heiniger A, Torres A, Minna JD, Prósper F. Abnormal methylation of the common PARK2 and PACRG promoter is associated with downregulation of gene expression in acute lymphoblastic leukemia and chronic myeloid leukemia. Int J Cancer. 2006 Apr 15;118(8):1945-53

Alter A, Fava VM, Huong NT, Singh M, Orlova M, Van Thuc N, Katoch K, Thai VH, Ba NN, Abel L, Mehra N, Alcaïs A, Schurr E. Linkage disequilibrium pattern and age-at-diagnosis are critical for replicating genetic associations across ethnic groups in leprosy. Hum Genet. 2013 Jan;132(1):107-16

Ambroziak W, Koziorowski D, Duszyc K, Górka-Skoczylas P, Potulska-Chromik A, Sławek J, Hoffman-Zacharska D. Genomic instability in the PARK2 locus is associated with Parkinson's disease. J Appl Genet. 2015 Nov;56(4):451-461

Bonifati V. Autosomal recessive parkinsonism. Parkinsonism Relat Disord. 2012 Jan;18 Suppl 1:S4-6

Cesari R, Martin ES, Calin GA, Pentimalli F, Bichi R, McAdams H, Trapasso F, Drusco A, Shimizu M, Masciullo V, D'Andrilli G, Scambia G, Picchio MC, Alder H, Godwin AK, Croce CM. Parkin, a gene implicated in autosomal recessive juvenile parkinsonism, is a candidate tumor suppressor gene on chromosome 6q25-q27 Proc Natl Acad Sci U S A 2003 May 13;100(10):5956-61

Chan NC, Salazar AM, Pham AH, Sweredoski MJ, Kolawa NJ, Graham RL, Hess S, Chan DC. Broad activation of the ubiquitin-proteasome system by Parkin is critical for mitophagy Hum Mol Genet 2011 May 1;20(9):1726-37

Chung KK, Zhang Y, Lim KL, Tanaka Y, Huang H, Gao J, Ross CA, Dawson VL, Dawson TM. Parkin ubiquitinates the alpha-synuclein-interacting protein, synphilin-1: implications for Lewy-body formation in Parkinson disease Nat Med 2001 Oct;7(10):1144-50

Cookson MR. Parkinsonism due to mutations in PINK1, parkin, and DJ-1 and oxidative stress and mitochondrial pathways Cold Spring Harb Perspect Med 2012 Sep 1;2(9):a009415

D'Agata V, Grimaldi M, Pascale A, Cavallaro S. Regional and cellular expression of the parkin gene in the rat cerebral cortex Eur J Neurosci 2000 Oct;12(10):3583-8

D'Amico AG, Maugeri G, Magro G, Salvatorelli L, Drago F, D'Agata V. Expression pattern of parkin isoforms in lung adenocarcinomas Tumour Biol 2015 Jul;36(7):5133-41

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

Gong Y, Zack TI, Morris LG, Lin K, Hukkelhoven E, Raheja R, Tan IL, Turcan S, Veeriah S, Meng S, Viale A, Schumacher SE, Palmedo P, Beroukhim R, Chan TA. Pan-cancer genetic analysis identifies PARK2 as a master regulator of G1/S cyclins Nat Genet 2014 Jun;46(6):588-94

Gu WJ, Abbas N, Lagunes MZ, Parent A, Pradier L, Bohme GA, Agid Y, Hirsch EC, Raisman-Vozari R, Brice A. Cloning of rat parkin cDNA and distribution of parkin in rat brain J Neurochem 2000 Apr;74(4):1773-6

Henn IH, Bouman L, Schlehe JS, Schlierf A, Schramm JE, Wegener E, Nakaso K, Culmsee C, Berninger B, Krappmann D, Tatzelt J, Winklhofer KF. Parkin mediates neuroprotection through activation of IkappaB kinase/nuclear factor-kappaB signaling J Neurosci 2007 Feb 21;27(8):1868-78

Horowitz JM, Myers J, Stachowiak MK, Torres G. Identification and distribution of Parkin in rat brain Neuroreport 1999 Nov 8;10(16):3393-7

Huynh DP, Dy M, Nguyen D, Kiehl TR, Pulst SM. Differential expression and tissue distribution of parkin isoforms during mouse development Brain Res Dev Brain Res 2001 Oct 24;130(2):173-81

Ikeuchi K, Marusawa H, Fujiwara M, Matsumoto Y, Endo Y, Watanabe T, Iwai A, Sakai Y, Takahashi R, Chiba T. Attenuation of proteolysis-mediated cyclin E regulation by alternatively spliced Parkin in human colorectal cancers Int J Cancer 2009 Nov 1;125(9):2029-35

Imai Y, Soda M, Hatakeyama S, Akagi T, Hashikawa T, Nakayama KI, Takahashi R. CHIP is associated with Parkin, a gene responsible for familial Parkinson's disease, and enhances its ubiquitin ligase activity Mol Cell 2002 Jul;10(1):55-67

Iwakawa R, Okayama H, Kohno T, Sato-Otsubo A, Ogawa S, Yokota J. Contribution of germline mutations to PARK2 gene inactivation in lung adenocarcinoma Genes Chromosomes Cancer 2012 May;51(5):462-72

Jin SM, Youle RJ. PINK1- and Parkin-mediated mitophagy at a glance J Cell Sci 2012 Feb 15;125(Pt 4):795-9

Kasap M, Akpinar G, Sazci A, Idrisoglu HA, Vahabolu H. Evidence for the presence of full-length PARK2 mRNA and Parkin protein in human blood Neurosci Lett 2009 Sep 4;460(3):196-200

Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M, Mizuno Y, Shimizu N. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism Nature 1998 Apr 9;392(6676):605-8

Lücking CB, Dürr A, Bonifati V, Vaughan J, De Michele G, Gasser T, Harhangi BS, Meco G, Denèfle P, Wood NW, Agid Y, Brice A; French Parkinson's Disease Genetics Study Group; European Consortium on Genetic

Susceptibility in Parkinson's Disease. Association between early-onset Parkinson's disease and mutations in the parkin gene N Engl J Med 2000 May 25;342(21):1560-7

La Cognata V, Iemmolo R, D'Agata V, Scuderi S, Drago F, Zappia M, Cavallaro S. Increasing the Coding Potential of Genomes Through Alternative Splicing: The Case of PARK2 Gene Curr Genomics 2014 Jun;15(3):203-16

LaVoie MJ, Ostaszewski BL, Weihofen A, Schlossmacher MG, Selkoe DJ. Dopamine covalently modifies and functionally inactivates parkin Nat Med 2005 Nov;11(11):1214-21

Lin DC, Xu L, Chen Y, Yan H, Hazawa M, Doan N, Said JW, Ding LW, Liu LZ, Yang H, Yu S, Kahn M, Yin D, Koeffler HP. Genomic and Functional Analysis of the E3 Ligase PARK2 in Glioma Cancer Res 2015 May 1;75(9):1815-27

Lonskaya I, Shekoyan AR, Hebron ML, Desforges N, Algarzae NK, Moussa CE. Diminished parkin solubility and co-localization with intraneuronal amyloid- are associated with autophagic defects in Alzheimer's disease J Alzheimers Dis 2013;33(1):231-47

Louis A, Nguyen NT, Muffato M, Roest Crollius H. Genomicus update 2015: KaryoView and MatrixView provide a genome-wide perspective to multispecies comparative genomics Nucleic Acids Res 2015 Jan;43(Database issue):D682-9

Maugeri G, D'Amico AG, Magro G, Salvatorelli L, Barbagallo GM, Saccone S, Drago F, Cavallaro S, D'Agata V. Expression profile of parkin isoforms in human gliomas Int J Oncol 2015 Oct;47(4):1282-92

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

Narendra D, Tanaka A, Suen DF, Youle RJ. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy J Cell Biol 2008 Dec 1;183(5):795-803

Nuytemans K, Theuns J, Cruts M, Van Broeckhoven C. Genetic etiology of Parkinson disease associated with mutations in the SNCA, PARK2, PINK1, PARK7, and LRRK2 genes: a mutation update Hum Mutat 2010 Jul;31(7):763-80

Oliveira SA, Scott WK, Martin ER, Nance MA, Watts RL, Hubble JP, Koller WC, Pahwa R, Stern MB, Hiner BC, Ondo WG, Allen FH Jr, Scott BL, Goetz CG, Small GW, Mastaglia F, Stajich JM, Zhang F, Booze MW, Winn MP, Middleton LT, Haines JL, Pericak-Vance MA, Vance JM. Parkin mutations and susceptibility alleles in late-onset Parkinson's disease Ann Neurol 2003 May;53(5):624-9

Pawlyk AC, Giasson BI, Sampathu DM, Perez FA, Lim KL, Dawson VL, Dawson TM, Palmiter RD, Trojanowski JQ, Lee VM. Novel monoclonal antibodies demonstrate biochemical variation of brain parkin with age J Biol Chem 2003 Nov 28;278(48):48120-8

Poulogiannis G, McIntyre RE, Dimitriadi M, Apps JR, Wilson CH, Ichimura K, Luo F, Cantley LC, Wyllie AH, Adams DJ, Arends MJ. PARK2 deletions occur frequently in sporadic colorectal cancer and accelerate adenoma development in Apc mutant mice Proc Natl Acad Sci U S A 2010 Aug 24;107(34):15145-50

Ren Y, Zhao J, Feng J. Parkin binds to alpha/beta tubulin and increases their ubiquitination and degradation J Neurosci 2003 Apr 15;23(8):3316-24

Rosen KM, Veereshwarayya V, Moussa CE, Fu Q, Goldberg MS, Schlossmacher MG, Shen J, Querfurth HW. Parkin protects against mitochondrial toxins and beta-amyloid accumulation in skeletal muscle cells J Biol Chem 2006 May 5;281(18):12809-16

Schlossmacher MG, Frosch MP, Gai WP, Medina M, Sharma N, Forno L, Ochiishi T, Shimura H, Sharon R, Hattori N, Langston JW, Mizuno Y, Hyman BT, Selkoe DJ, Kosik KS. Parkin localizes to the Lewy bodies of Parkinson disease and dementia with Lewy bodies Am J Pathol 2002 May;160(5):1655-67

Scuderi S, La Cognata V, Drago F, Cavallaro S, D'Agata V. Alternative splicing generates different parkin protein isoforms: evidences in human, rat, and mouse brain Biomed Res Int 2014;2014:690796

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

Shimura H, Schlossmacher MG, Hattori N, Frosch MP, Trockenbacher A, Schneider R, Mizuno Y, Kosik KS, Selkoe DJ. Ubiquitination of a new form of alpha-synuclein by parkin from human brain: implications for Parkinson's disease Science 2001 Jul 13;293(5528):263-9

Staropoli JF, McDermott C, Martinat C, Schulman B, Demireva E, Abeliovich A. Parkin is a component of an SCF-like ubiquitin ligase complex and protects postmitotic neurons from kainate excitotoxicity Neuron 2003 Mar 6;37(5):735-49

Stichel CC, Augustin M, Kühn K, Zhu XR, Engels P, Ullmer C, Lübbert H. Parkin expression in the adult mouse brain Eur J Neurosci 2000 Dec;12(12):4181-94

Sun X, Liu J, Crary JF, Malagelada C, Sulzer D, Greene LA, Levy OA. ATF4 protects against neuronal death in cellular Parkinson's disease models by maintaining levels of parkin J Neurosci 2013 Feb 6;33(6):2398-407

Tay SP, Yeo CW, Chai C, Chua PJ, Tan HM, Ang AX, Yip DL, Sung JX, Tan PH, Bay BH, Wong SH, Tang C, Tan JM, Lim KL. Parkin enhances the expression of cyclin-dependent kinase 6 and negatively regulates the proliferation of breast cancer cells J Biol Chem 2010 Sep 17;285(38):29231-8

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

Viotti J, Duplan E, Caillava C, Condat J, Goiran T, Giordano C, Marie Y, Idbaih A, Delattre JY, Honnorat J, Checler F, Alves da Costa C. Glioma tumor grade correlates with parkin depletion in mutant p53-linked tumors and results from loss of function of p53 transcriptional activity Oncogene 2014 Apr 3;33(14):1764-75

West AB, Lockhart PJ, O'Farell C, Farrer MJ. Identification of a novel gene linked to parkin via a bi-directional promoter J Mol Biol 2003 Feb 7;326(1):11-9

Xiong D, Wang Y, Kupert E, Simpson C, Pinney SM, Gaba CR, Mandal D, Schwartz AG, Yang P, de Andrade M, Pikielny C, Byun J, Li Y, Stambolian D, Spitz MR, Liu Y, Amos CI, Bailey-Wilson JE, Anderson M, You M. A recurrent mutation in PARK2 is associated with familial lung cancer Am J Hum Genet 2015 Feb 5;96(2):301-8

Xu L, Lin DC, Yin D, Koeffler HP. An emerging role of PARK2 in cancer J Mol Med (Berl) 2014 Jan;92(1):31-42

Yamamoto A, Friedlein A, Imai Y, Takahashi R, Kahle PJ, Haass C. Parkin phosphorylation and modulation of its E3 ubiquitin ligase activity J Biol Chem 2005 Feb 4;280(5):3390-9

Yeo CW, Ng FS, Chai C, Tan JM, Koh GR, Chong YK, Koh LW, Foong CS, Sandanaraj E, Holbrook JD, Ang BT, Takahashi R, Tang C, Lim KL. Parkin pathway activation mitigates glioma cell proliferation and predicts patient

survival Cancer Res 2012 May 15;72(10):2543-53

Yoshii SR, Kishi C, Ishihara N, Mizushima N. Parkin mediates proteasome-dependent protein degradation and rupture of the outer mitochondrial membrane J Biol Chem 2011 Jun 3;286(22):19630-40

Zhang Y, Gao J, Chung KK, Huang H, Dawson VL, Dawson TM. Parkin functions as an E2-dependent ubiquitin- protein ligase and promotes the degradation of the synaptic vesicle-associated protein, CDCrel-1 Proc Natl Acad Sci U S A 2000 Nov 21;97(24):13354-9

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