PROGRESS IN BIOLOGICAL SCIENCES

Linkage of Parkinson's disease in two very early onset siblings to a locus on chromosome 1

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Abstract

Parkinson's disease (PD) is a prevalent neurodegenerative disease that usually affects individuals over 50 years of age. Age at onset in a small subset of PD cases is considerably lower, and these are considered early onset PD (EOPD) patients. Most PD cases appear sporadic, but approximately 15% are familial, and some of the familial cases exhibit Mendelian inheritance. Genetic analysis of familial cases has led to identification of five major PD causing genes. Mutations in three of these, *PRKN*, *PINK1*, and *DJ-1* are most often observed in EOPD patients belonging to families in which PD is inherited in an autosomal recessive fashion. Here, a PD family with two siblings whose ages of onset were 10 and 14 years was identified. Initially, *PRKN*, *PINK1*, and *DJ-1* were screened, but a putative disease causing mutation was not found. Genome-wide homozygosity mapping using high density microarray chips led to identification of a 6.5 cM linked locus on locus on chromosome 1. *ATP13A2* that encodes a lysosomal type 5 P-type ATPase is positioned within the linked locus. Mutations in *ATP13A2* have previously been reported in a few EOPD patients, and this gene is an appropriate candidate as cause of PD in the pedigree here described.

Keywords: Parkinosn's disease, Early onset parkinson's disease (EOPD), homozygosity mapping, *ATP13A2*.

Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder after Alzheimer's disease and affects approximately two percent of individuals older than 65 years (de Rijk*et al.*, 1995). Resting tremor, bradykinesia, rigidity, and postural instability, are the cardinal signs of PD, and individuals who present with at least two of these features are diagnosed as affected (FAHN, 2003). These symptoms are believed to result from the degeneration of dopamine-containing neurons in the substantia nigra (SN) and the consequent loss of dopamine, a neurotransmitter involved in fine modulation of motor functions (G. Alves, 2008; A.J. Lees, 2009). Lewy bodies, which are eosinopilic inclusion bodies composed of protein aggregates in surviving dopaminergic neurons, are often considered the pathologic hallmark of PD (Spillantini*et al.*, 1997). Both environmental and genetic factors are involved in the etiology of PD. Most cases appear sporadic, but approximately 15% are familial, and some of the familial cases exhibit Mendelian inheritance (Abbas*et al.*, 1999; Bonifati*et al.*, 2004). The average age at onset of symptoms in PD patients is reported as 53 to 60 years in most studies (de Rijk*et al.*, 1995; Kay*et al.*, 2007). Age at onset in approximately 10% of PD cases is considerably lower, and these are considered early onset PD (EOPD) patients (Ghazavi*et al.*, 2010). It appears that average age

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at onset of symptoms in Iranian PD patients is lower than in most other populations (Shojaee*et al.*, 2009). Five major genes for PD have been identified, *SCNA* (*α-synuclein*), *LRRK2* (*Leucine-rich repeat kinase 2*), *PRKN* (*parkin*), *PINK1* (*PTEN-induced putative kinase 1*) and *DJ-1*(Wood-Kaczmar, 2006). The molecular functions of these genes suggest that processes including intracellular transport of lipid and vesicle, proteasom systems, protein aggregation, mitochondrial dysfunction , and oxidative stress are relevant to the etiology of PD. *LRRK2* is of interest because mutations in this gene have been observed in patients affected with clinically typical late onset PD (Haugarvoll, 2008). Mutations in *PRKN*, *PINK1*, and *DJ-1* are most often observed in EOPD patients belonging to families in which PD is inherited in an autosomal recessive fashion (Kitada*et al.*, 1998; Bonifati*et al.*, 2003; Valente*et al.*, 2004). Among the known genes, *PRKN* mutations are the most common cause of EOPD, being observed in 4 to 66% of the patients (Hattori*et al.*, 1998; Kitada*et al.*, 1998; Lucking*et al.*, 2000; Djarmati*et al.*, 2004; Hedrich*et al.*, 2004). The variations in frequencies are due to differences in screening protocols, ethnicity, and age limit set for EOPD. Here, we present genetic analysis of a pair of Iranian siblings affected with very early onset Parkinson's disease.

Methods

This research was performed in accordance with the Declaration of Helsinki; participants and the guardians of the patients consented to participate after being informed of the nature of the research. One pair of early onset PD diagnosed siblings born to consanguineous parents was identified (Fig. 1). Patient X4014 manifested all four of the cardinal signs of PD and his age at onset was 10 years. His sister manifested three signs and her age at onset was 14 years. The affected children had no other siblings. Mutation screening of *LRRK2,PRKN,DJ-1, and PINK1* was performed as previously described (Shojaee*et al.*, 2009; Ghazavi*et al.*, 2010). Briefly, five exons of *LRRK2* in which mutations have most often been reported and all of the exons of the remaining three genes were amplified by the polymerase chain reaction, and amplicons were sequenced with the same primers using the dideoxynucleotide terminator chemistry and an ABI Prism 3700 instrument (Applied Biosystems, Foster City, CA). The sequences of the primers are presented in Table 1. Sequences were analyzed using Sequencher software (Gene Codes Corporation, Ann Arbor, MI). *LRRK2*, *PRKN*, *DJ-1*, and *PINK1* reference sequences used were, respectively, NC_000012.11, NM_198578.3, NP_940980.3; NC_000006.11, NM_004562.2, NP_004553.2; NC_000001.10, NM_001123377.1, NP_001116849.1; and NC_000001.10,NM_032409.2, NP_115785.1. Finally, linkage analysis was performed on high density microarray chips. The DNA of both siblings and their parents were brought onto Human610 and chips and hybridization was assessed using the iScan reader (Illumina; www.illumina.com). SNPs that had not been genotyped in one or more individual and SNPs that exhibited Mendelian error were removed from the analysis with appropriate options in the Illumina BeadStudio software. Homozygous regions common to both affected individuals and not homozygous in the parents were sought using PLINK v1.02 (Purcell*et al.*, 2007). Threshold criteria for homozygous regions to be pursued were minimum physical length of 1 Mb, presence of at least 50 homozygous adjacent markers and not more than one heterozygous call.

Results

A putative disease causing mutation was not observed in *LRRK2, PRKN, DJ-1, and PINK1* in the DNA of EOPD affected individual X4014 (Fig. 1). C.1138G>C in *PRKN* that causes p.V380L was observed, but this is a very common polymorphism in Iranians (Ghazavi*et al.*, 2010). Homozygosity mapping revealed only one region that was homozygous in both affected siblings, but not homozygous in the parents. The region is located on chromosome 1 and is bordered by rs6660347 at position 12420300 and rs2816040 at position 18889536. The linked locus spans approximately 6.5 cM on chromosome 1.

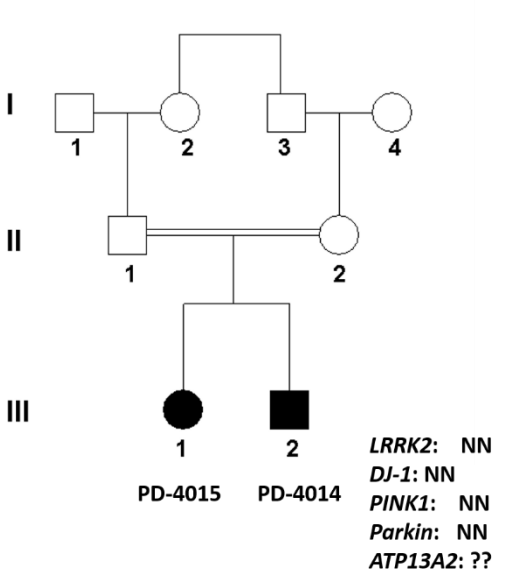


Figure 1. Iranian EOPD pedigree with affected siblings. The genotype of proband X4014 for LRRK2, PRKN, DJ-1, and PINK1 are shown. ATP13A2 has not been screened. N, normal allele.

Discussion

Inheritance of PD in the family studied appeared autosomal recessive as multiple affected individuals were born to unaffected consanguineous parents. Although *LRRK2* mutations are most often observed in patients affected with clinically typical late onset, it has become evident that the gene is associated with a broad spectrum of clinical and phenotypic features (Hedrich*et al.*, 2006; Saunders-Pullman*et al.*, 2006; Haugarvoll, 2008; K.*et al.*, 2008). For this reason and because mutations in *LRRK2* have been found in a larger fraction of PD patients than any of the other known PD causing genes, some mutation prone exons of this gene were screened in the proband of our family. *PRKN*, *DJ-1*, and *PINK1*are more reasonable candidate genes because they most often cause EOPD, which is the phenotype that manifests in our siblings. However, putative disease associated mutations in these genes were not observed.

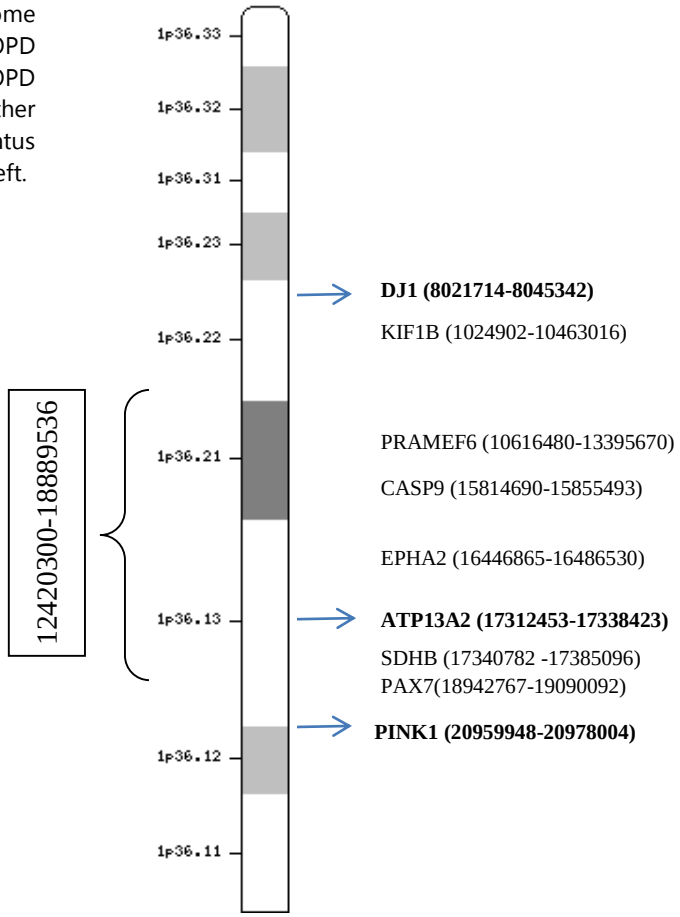
Homozygosity mapping identified a linked locus on chromosome 1 that overlaps the position of the cluster of known genes that cause EOPD (Fig. 2). *DJ1* and *PINK1* are located, respectively, at nucleotide 8021714-8045342 and 20959948-20978004.The homozygous region in the PD family which spans positions 12541683-18917464 is quiteclose to these genes, but in fact does includes neither *DJ1* nor *PINK1*.This observation suggests that mutations in deep intronic sequences not screened and copy number variations of these genes are unlikely to be cause of disease in the pedigree. Interestingly, in addition to the *PRKN*, *DJ1* and *PINK1*, mutations in *ATP13A2* have recently been reported to be cause of EOPD in a few patients (Santoro*et al.*; Di Fonzo*et al.*, 2007). *ATP13A2* encodes a lysosomal type 5 P-type ATPase named ATPase type 13A2 isoform 2. Prior to being considered a PD causing gene, *ATP13A2* had been identified as the causative gene of a rare autosomal recessive, L-dopa-responsive, pallido-pyramidal disease called Kufor-Rakeb syndrome (KRS). KRS patients often also exhibit some of the clinical presentations of PD (Najim al-Din*et al.*, 1994; Ramirez*et al.*, 2006). *ATP13A2* is located at positions 17312453-17338423, close to *PINK1*, *DJ-1* on chromosome 1(Fig. 2) (Ramirez*et al.*, 2006). Notably, *ATP13A2* is indeed a reasonable candidate PD causing gene. The program STRING (http://string-db.org/) which is a text mining based software that clusters together proteins involved in common pathways, associates the ATPase coded by *ATP13A2* with protein products of *DJ-1*, *FBX07*, *LRRK2*, *Parkin*, *PINK1*, *UCHL1*, and *SNCA*, all of which are PD associated genes (Fig. 3). The homozygous region in our EOPD affected individuals is inclusive of *ATP13A2*. The gene which contains 29 exons will be screened in the patients under study. It is hoped that the findings will further contribute to our understandings of the pathogenesis of PD.

Table 1. Primers used for ampificationof exons of LRRK2, PRKN, DJ-1, and PINK1.

Exon	Forward primers	Reverse primers
	LRRK2	
31	5'-AAAGCAAATATCAACAGGAATGTG-3'	5'-GACTAAATAAAACAGCTGCCTCAC-3'
34	5'-GATCAAAGCTCAAAGTGTGATCTC-3'	5'-TACATGTCAGTAGGAGGTTTACACTAG-3'
35	5'-AATATTTCATGCATCTACATCTGAG-3'	5'-CTAATTCTTCAGCTGCCTTCC-3'
41	5'-ACTTTAAGGGACAAAGTGAGCAC-3'	5'-AAGAAAGGGAGGTAAGATTCCAC-3'
48	5'-CAAGGTAGCCAATCTGTTTGTG-3'	5'-TCTATTCAGAGGCAGAAAGGAAG-3'
	PRKN	
1	5'-GATGTTTGGCAGCTCCTAGGTG-3'	5'-TTGGCCCCGTCATTGACAGTTG-3'
2	5'-AAATCTCGTGGGTAACTAACTCTG-3'	5'-CTTCCAATCTTTCCTGCTTGCTG-3'
3	5'-CAGTGTTGTTTGTCTACCGTGTG-3'	5'-TCCTTGTAGTGAATTAGAGACTCC-3'
4	5'-TGCTGAGTAAGTCACAGGGCTG-3'	5'-AGAGCAGAAAGAAATCCAGAAGAC-3'
5	5'-GCACATCCCTTGAAAGGGTCAC-3'	5'-CTGGCTCTCCTTTTCTCACCTC-3'
6	5'-TTGTTGACCACTTTGGCACAAGG-3'	5'-AAATAAAGCAGACACTCCCCAGG-3'
7	5'-TCTATGTAGTTCATTGAGTGCCTC-3'	5'-CAACACAATTCCTTCATTCCCCAG-3'
8	5'-TTTCTAAAGAGGTGCGGTTGGAG-3'	5'-AGTGTCCTCACACATATCTCCAG-3'
9	5'-CACACTTATATGTCTTGCCAGTTG-3'	5'-TGTAAGTTCAAAGATGTCTAAGTCC-3'
10	5'-GGAAGGAAATGTGACCCATCATC-3'	5'-AGGGAAAAGCTATTTTGGACATGC-3'
11	5'-CATACGCCACATGCCAGGGAG-3'	5'-ATAAATGCTAACTGTGTGCCTCAC-3'
12a*	5'-TCTCTGCCCTTGTATTGCTTGTG-3'	5'-GTGCTCTGGTATTTGTGTCATCC-3'
12b*	5'-CCATGAAAAACAGCAGAG-3'	5'-GTACATTAACTTGATTTCTTCCCTG-3'
12c*	5'-GCAATAGTCAAAAACATTTGTTTATCC-3'	5'-ATGTCAACATAAGGAATATTCTAGTG-3'
12d*	5'-TATACCCCTTTGGCACACCCTC-3'	5'-CCTCAGATGGTTGGAAGAAATGG-3'
	DJ-1	
1	5'-GGGCTGTCCAGCTAGAAACTC-3'	5'-TGGAAATCCCCTCACTGAAGTC-3'
2	5'-TACTACACCTTTTAGCACCCTC-3'	5'-CAAGCGTTAAATGTGAGCAGTG-3'
3	5'-GAGGATCATTTGAGCCCAGGAG-3'	5'-TCCTCACCCTCTTAATCTGTCG-3'
4	5'-ACCATTCCGTCATGTGGATACAC-3'	5'-GAGAACTGCTTGAACCCAGGG-3'
5	5'-ATGTGGAAGAGTGCGTTTCTC-3'	5'-ATGACACCAACTTCATGCCAC-3'
6	5'-TGTTGTTAGAGAAGGGGTCTGTG-3'	5'-CAGAAGTTCAAGACCAGCATGC-3'
7	5'-GGGCTTCTAAGAGCTTGGAGTG-3'	5'-GGAGACTTGCTATGTTGCCCAG-3'
	PINK1	
1	5'-TGATGTTCACATTCAGGACCTG-3'	5'-AGCAGCCGATCAGTAATGGTG-3'
2	5'-TGATCCCAGTGAAGCAACAGAG-3'	5'-CTCTTGCACTCAAGTGATCCTC-3'
3	5'-GTCATCTTATCTCGAAGGTCAG-3'	5'-CAGTCAATCATGCAACACTGTG-3'
4	5'-TTCTCCACCTGTGTTCTGCCAC-3'	5'-TGTTAGGGTTAGGCCGTTCCTC-3'
5	5'-TGCTTGAACCTGGAAGGTGGAG-3'	5'-TGCTAACCTCTTGTGTGCGGAG-3'
6	5'-CATTTCCGTGTTCGCACAGCAG-3'	5'-AACTCTGTCCCAAGGAACCCAG-3'
7	5'-GTCCACTGAATGCAGGAGACTC-3'	5'-TATGCTGTGGTGGCTAGTGCTC-3'
8	5'-GAGTGAAGGGCATCAGTAGGG-3'	5'-TGCTGTGGGTGATGACTGACTG-3'

*Exon 12 of PRKN amplified and sequenced in multiple reactions because of long length.

Figure 2. Schematic drawing of region of chromosome 1 that includes linked region and cluster of EOPD causing genes. The relative positions of known EOPD genes DJ1, PINK1, and ATP13A2 as well as a few other genes are shown. The region linked to disease status identified by homozygosity mapping is shown at left.



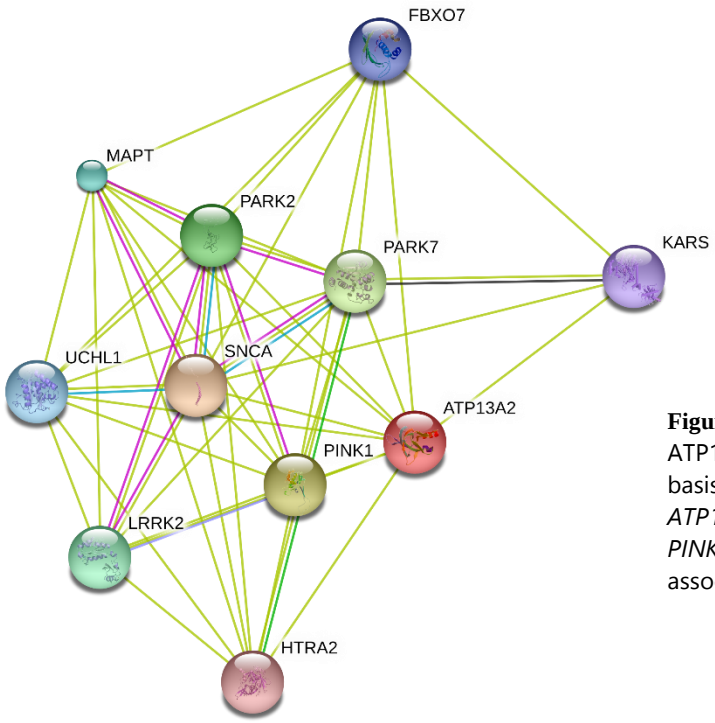


Figure 3. STRING clustering of proteins associated with ATP13A2. The program clusters together proteins on basis of physical or functional interactions. It clusters *ATP13A2* together with *DJ-1*, *FBX07*, *LRRK2*, *Parkin*, *PINK1*, *UCHL1*, and *SNCA*, all of which are PD associated genes.

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References

1. A.J. Lees JH, T. Revesz (2009) Parkinson's disease. *Lancet* 373, 2055–2066
2. Abbas N, Lucking CB, Ricard S, Durr A, Bonifati V, De Michele G, Bouley S, Vaughan JR, Gasser T, Marconi R, Broussolle E, Brefel-Courbon C, Harhangi BS, Oostra BA, Fabrizio E, Bohme GA, Pradier L, Wood NW, Filla A, Meco G, Denefle P, Agid Y & Brice A (1999) A wide variety of mutations in the parkin gene are responsible for autosomal recessive parkinsonism in Europe. French Parkinson's Disease Genetics Study Group and the European Consortium on Genetic Susceptibility in Parkinson's Disease. *Hum Mol Genet* 8, 567-574
3. Bonifati V, Ostra BA & Heutink P (2004) Linking DJ-1 to neurodegeneration offers novel insights for understanding the pathogenesis of Parkinson's disease. *J Mol Med (Berl)* 82, 163-174
4. Bonifati V, Rizzu P, van Baren MJ, Schaap O, Breedveld GJ, Krieger E, Dekker MC, Squitieri F, Ibanez P, Joosse M, van Dongen JW, Vanacore N, van Swieten JC, Brice A, Meco G, van Duijn CM, Oostra BA & Heutink P (2003) Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. *Science* 299, 256-259
5. de Rijk MC, Breteler MM, Graveland GA, Ott A, Grobbee DE, van der Meche FG & Hofman A (1995) Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. *Neurology* 45, 2143-2146
6. Di Fonzo A, Chien HF, Socal M, Giraudo S, Tassorelli C, Iliceto G, Fabbrini G, Marconi R, Fincati E, Abbruzzese G, Marini P, Squitieri F, Horstink MW, Montagna P, Libera AD, Stocchi F, Goldwurm S, Ferreira JJ, Meco G, Martignoni E, Lopiano L, Jardim LB, Oostra BA, Barbosa ER & Bonifati V (2007) ATP13A2 missense mutations in juvenile parkinsonism and young onset Parkinson disease. *Neurology* 68, 1557-1562
7. Djarmati A, Hedrich K, Svetel M, Schafer N, Juric V, Vukosavic S, Hering R, Riess O, Romac S, Klein C & Kostic V (2004) Detection of Parkin (PARK2) and DJ1 (PARK7) mutations in early-onset Parkinson disease: Parkin mutation frequency depends on ethnic origin of patients. *Hum Mutat* 23, 525
8. FAHN S (2003) Description of Parkinson's Disease as a Clinical Syndrome. *Ann. N.Y. Acad. Sci* 991, 1-14
9. G. Alves EBF, K.F. Pedersen, M.D. Gjerstad, J.P. Larsen (2008) Epidemiology of Parkinson's disease. *J. Neurol* 255, 18–32
10. Ghazavi F, Fazlali Z, Banihosseini SS, Hosseini SR, Kazemi MH, Shojaee S, Parsa K, Sadeghi H, Sina F, Rohani M, Shahidi GA, Ghaemi N, Ronaghi M & Elahi E (2010) PRKN, DJ-1, and PINK1 screening identifies novel splice site mutation in PRKN and two novel DJ-1 mutations. *Mov Disord* 26, 80-89
11. Hattori N, Kitada T, Matsumine H, Asakawa S, Yamamura Y, Yoshino H, Kobayashi T, Yokochi M, Wang M, Yoritaka A, Kondo T, Kuzuhara S, Nakamura S, Shimizu N & Mizuno Y (1998) Molecular genetic analysis of a novel Parkin gene in Japanese families with autosomal recessive juvenile parkinsonism: evidence for variable homozygous deletions in the Parkin gene in affected individuals. *Ann Neurol* 44, 935-941
12. Haugarvoll k (2008) Lrrk2 R1441C parkinsonism is clinically similar to sporadic Parkinson disease. *Neurology*70:1456–1460
13. Hedrich K, Eskelson C, Wilmot B, Marder K, Harris J, Garrels J, Meija-Santana H, Vieregge P, Jacobs H, Bressman SB, Lang AE, Kann M, Abbruzzese G, Martinelli P, Schwinger E, Ozelius LJ, Pramstaller PP, Klein C & Kramer P (2004) Distribution, type, and origin of Parkin mutations: review and case studies. *Mov Disord* 19, 1146-1157
14. Hedrich K, Winkler S, Hagenah J, Kabakci K, Kasten M, Schwinger E, Volkmann J, Pramstaller PP, Kostic V, Vieregge P & Klein C (2006)

Recurrent LRRK2 (Park8) mutations in early-onset Parkinson's disease. *Mov Disord* 21, 1506-1510

15. K. H, R. R & JM. K (2008) Lrrk2 R1441C parkinsonism is clinically similar to sporadic Parkinson disease. *Neurology*70:1456–1460
16. Kay DM, Moran D, Moses L, Poorkaj P, Zabetian CP, Nutt J, Factor SA, Yu CE, Montimurro JS, Keefe RG, Schellenberg GD & Payami H (2007) Heterozygous parkin point mutations are as common in control subjects as in Parkinson's patients. *Ann Neurol* 61, 47-54
17. Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M, Mizuno Y & Shimizu N (1998) Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature* 392, 605-608
18. Lucking CB, Durr A, Bonifati V, Vaughan J, De Michele G, Gasser T, Harhangi BS, Meco G, Denefle P, Wood NW, Agid Y & Brice A (2000) Association between early-onset Parkinson's disease and mutations in the parkin gene. *N Engl J Med* 342, 1560-1567
19. Najim al-Din AS, Wriekat A, Mubaidin A, Dasouki M & Hiari M (1994) Pallido-pyramidal degeneration, supranuclear upgaze paresis and dementia: Kufor-Rakeb syndrome. *Acta Neurol Scand* 89, 347-352
20. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA & Bender D, Maller, J., Sklar, P., de Bakker, P.I., Daly, M.J. and Sham,P.C. (2007) PLINK: a tool set for wholegenome association and population-based linkage analyses. *Am. J. Hum. Genet* 81, 559–575
21. Ramirez A, Heimbach A, Grundemann J, Stiller B, Hampshire D, Cid LP, Goebel I, Mubaidin AF, Wriekat AL, Roeper J, Al-Din A, Hillmer AM, Karsak M, Liss B, Woods CG, Behrens MI & Kubisch C (2006) Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. *Nat Genet* 38, 1184-1191
22. Santoro L, Breedveld GJ, Manganelli F, Iodice R, Pisciotta C, Nolano M, Punzo F, Quarantelli M, Pappata S, Di Fonzo A, Oostra BA & Bonifati V Novel ATP13A2 (PARK9) homozygous mutation in a family with marked phenotype variability. *Neurogenetics* 12, 33-39
23. Saunders-Pullman R, Lipton RB, Senthil G, Katz M, Costan-Toth C, Derby C, Bressman S, Verghese J & Ozelius LJ (2006) Increased frequency of the LRRK2 G2019S mutation in an elderly Ashkenazi Jewish population is not associated with dementia. *Neurosci Lett* 402, 92-96
24. Shojaee S, Sina F, Farboodi N, Fazlali Z, Ghazavi F, Ghorashi SA, Parsa K, Sadeghi H, Shahidi GA, Ronaghi M & Elahi E (2009) A clinic-based screening of mutations in exons 31, 34, 35, 41, and 48 of LRRK2 in Iranian Parkinson's disease patients. *Mov Disord* 24, 1023-1027
25. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R & Goedert M (1997) Alpha-synuclein in Lewy bodies. *Nature* 388, 839-840
26. Valente EM, Abou-Sleiman PM, Caputo V, Muqit MM, Harvey K, Gispert S, Ali Z, Del Turco D, Bentivoglio AR, Healy DG, Albanese A, Nussbaum R, Gonzalez-Maldonado R, Deller T, Salvi S, Cortelli P, Gilks WP, Latchman DS, Harvey RJ, Dallapiccola B, Auburger G & Wood NW (2004) Hereditary early-onset Parkinson's disease caused by mutations in PINK*Science* 304, 1158-1160
27. Wood-Kaczmar A, Gandhi, S.,Wood, N. W. (2006) Understanding the molecular causes of Parkinson's disease. *Trends Mol Med* 12, 521-528.