Association study of DNAJC13, UCHL1, HTRA2, GIGYF2, and EIF4G1 with Parkinson's disease

Prabhjyot Saini, Uladzislau Rudakou, Eric Yu, Jennifer Ruskey, Farnaz
Asayesh, Sandra Laurent, Dan Spiegelman, Stanley Fahn, Cheryl Waters,
Oury Monchi, et al.

HAL Id: hal-03226126

https://hal.umontpellier.fr/hal-03226126

Submitted on 25 Apr 2022

Association study of *DNAJC13, UCHL1, HTRA2, GIGYF2* and *EIF4G1* with Parkinson's disease

Prabhjyot Saini[1,2], **Uladzislau Rudakou**[1,2], **Eric Yu**[1,2], **Jennifer A. Ruskey**[1,2], **Farnaz Asayesh**[1,2], **Sandra B. Laurent**[1,2], **Dan Spiegelman**[1,3], **Stanley Fahn**[4], **Cheryl Waters**[4], **Oury Monchi**[5,6], **Yves Dauvilliers**[7], **Nicolas Dupré**[8,9], **Lior Greenbaum**[10,11,12], **Sharon Hassin-Baer**[10,13], **Alberto J. Espay**[14], **Guy A. Rouleau**[1,2,3], **Roy N. Alcalay**[4,15], **Edward A. Fon**[1,2], **Ronald B. Postuma**[1,3], **Ziv Gan-Or**[1,2,3]

[1]Montreal Neurological Institute, McGill University, Montréal, QC, H3A 1A1, Canada

[2]Department of Human Genetics, McGill University, Montréal, QC, H3A 1A1, Canada

[3]Department of Neurology and neurosurgery, McGill University, Montréal, QC, H3A 0G4, Canada, Canada

[4]Department of Neurology, College of Physicians and Surgeons, Columbia University Medical Center, 710 West 168th Street, New York, NY, 10032-3784 USA

[5]Department of Clinical Neurosciences and Department of Radiology, University of Calgary, 2500 University Drive NW Calgary, Alberta, T2N 1N4, Canada

[6]Cumming School of Medicine, Hotchkiss Brain Institute, Calgary, 3330 Hospital Drive NW Calgary, Alberta, T2N 4N1 Canada

[7]National Reference Center for Narcolepsy, Sleep Unit, Department of Neurology, Gui-de-Chauliac Hospital, CHU Montpellier, University of Montpellier, Inserm U1061, Montpellier, France

[8]Division of Neurosciences, CHU de Québec, Université Laval, 2705 Laurier Boulevard, Quebec City, Quebec G1V 4G2, Canada

[9]Department of Medicine, Faculty of Medicine, Université Laval, 1050 Avenue de la Médecine, Québec, QC G1V 0A6, Canada

[10]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[11]Danek Gertner Institute of Human Genetics, Sheba Medical Center, Tel Hashomer, Israel

[12]Joseph Sagol Neuroscience Center, Sheba Medical Center, Tel Hashomer, Israel

[13]The Movement Disorders Institute, Department of Neurology, Sheba Medical Center, Tel Hashomer, Israel

[14]Gardner Family Center for Parkinson's Disease and Movement Disorders, Department of Neurology, University of Cincinnati, 3113 Bellevue Ave, Cincinnati, OH 45229, USA

[15]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University Medical Center, 710 W 168th St 3, New York, NY 10032, USA

Abstract

Rare mutations in genes originally discovered in multi-generational families have been associated with increased risk of Parkinson's Disease (PD). The involvement of rare variants in *DNAJC13, UCHL1, HTRA2, GIGYF2* and *EIF4G1* loci have been poorly studied or produced conflicting results across cohorts. However, they are still being often referred to as "PD-genes" and used in different models. To further elucidate the role of these five genes in PD, we fully sequenced them using molecular inversion probes in 2,408 PD patients and 3,444 controls from 3 different cohorts. A total of 788 rare variants were identified across the five genes and three cohorts. Burden analyses and optimized sequence Kernel association tests revealed no significant association between any of the genes and PD after correction for multiple comparisons. Our results do not support an association of the five tested genes with PD. Combined with previous studies, it is unlikely that any of these genes plays an important role in PD. Their designation as "*PARK*" genes should be reconsidered.

Keywords

1.0 Introduction

Parkinson's disease (PD) is clinically characterized by progressive movement disability, mainly bradykinesia, tremor and muscle rigidity, often accompanied by other motor and non-motor symptoms (Jankovic, 2008). Common genetic variants of PD have largely been discovered through genome-wide association studies (GWAS), and to date 92 independent risk variants in 80 loci have been identified (Foo et al., 2020; Nalls et al., 2019). Other types of studies, including linkage and next generation sequencing studies in families with multiple affected family members with PD or other forms of parkinsonism led to the

identification of familial PD-associated genes, many of them have received the alias *PARK* (e.g. *PARK1, PARK2*, etc.) (Deng et al., 2018).

Five suggested PD-causing genes identified through family studies and cohorts, *UCHL1* (Lincoln et al., 1999), *GIGYF2* (Lautier et al., 2008), *HTRA2* (Strauss et al., 2005), *EIF4G1* (Chartier-Harlin et al., 2011), and *DNAJC13* (Vilariño-Güell et al., 2013), (also termed *PARK5, PARK11, PARK13, PARK18* and *PARK21*, respectively) have been under scrutiny regarding their association with PD. Their discovery shares several similarities, including the presumed role of loss-of-function, missense mutations and dominant heritability (Nalls et al., 2019). Subsequent studies, in many cases, failed to replicate the association of these genes with PD (Bartonikova et al., 2018; Gagliardi et al., 2018; Kruger et al., 2011; Nichols et al., 2015; Nuytemans et al., 2013; Sun et al., 2014). However, ongoing studies, including those using cellular and animal models, continue to refer to these genes as PD-associated genes, and to invoke their function in PD-related mechanisms (Chen et al., 2018; Tran et al., 2018).

The primary goal of the present study is to use large cohorts of PD patients (n=2,382) and controls (n=3,411) to further examine the potential role of rare variants in these genes in PD.

2.0 Materials & Methods

2.1 Populations

Full sequencing of *UCHL1, HTRA2, GIGYF2, EIF4G1* and *DNAJC13* was performed in 2,408 PD patients and 3,444 controls, all unrelated, from three different cohorts: a) McGill cohort, including 855 patients and 2,441 controls from Quebec, Canada and Montpellier, France, all of European origin, b) Columbia cohort, including 963 patients and 508 controls from New York, Mainly of European or Ashkenazi-Jewish (AJ) ancestry, and c) Sheba cohort, including 590 patients and 495 controls of AJ ancestry collected at Sheba Medical Center, Israel. Demographic details on these cohort can be found in Supplementary Table S1. All subjects were consecutively recruited, and patients were diagnosed by a movement disorders specialist according to the UK Brain Bank Criteria (Hughes et al., 1992) or the MDS criteria (Postuma et al., 2015). All patients and controls signed informed consent at enrollment and the study protocols were approved by the institutional review.

2.2 Genetic analysis

The entire coding regions of the five genes, including 5' and 3' untranslated regions (UTRs) and exon-intron boundaries, were captured using molecular inversion probes (MIPs), followed by sequencing as previously described (Ross et al., 2016). Supplementary Table S2 includes all the MIPs used to capture and sequence *GIGYF2, HTRA2, DNAJC13, UCHL1, EF4G1*, and the full protocol is available upon request. The library was sequenced using Illumina HiSeq 2500/4000 platform at the McGill University and Genome Quebec Innovation Centre. Reads were mapped to the human reference genome (hg19) with Burrows-Wheeler Aligner (Li and Durbin, 2009). Alignment, quality control and variant calling was performed with Genome Analysis Toolkit (GATK, v3.8) (McKenna et al., 2010) and PLINK software v1.9 (Purcell et al., 2007) and ANNOVAR was used for annotation

(Wang, K. et al., 2010). Minor allele frequency from European and Ashkenazi Jewish ancestries were extracted from the public database Genome Aggregation Database (GnomAD) (Lek et al., 2016). The variants were filtered based on a minimum read depth 30X, a genotype quality (GQ) 30, genotyping rate cut-off for individuals was 90%, missingness difference between patients and controls was set at p=0.05 and adjusted by Bonferroni correction, proportion of the reads with alternative alleles 25%, and deviation from Hardy-Weinberg equilibrium was set at p=0.001.

2.3 Statistical Analyses

Burden and optimized Sequence Kernel Association Test (SKAT-O, R package) (Lee et al., 2012) were used to analyze the joint effects of rare variants (minor allele frequency, MAF 0.01). These analyses were performed on five groups of variants: a) all rare variant, b) functional variants, defined as all nonsynonymous, splice-site, frameshift and stop variants, c) loss of function variants, defined as splice-site, frameshift and stop variants, d) nonsynonymous variants and e) variants with Combined Annotation Dependent Depletion (CADD) score of >12.37, which is the threshold for the top 2% of predicted most deleterious variants. We repeated the analysis twice, at coverage of >30X and at coverage of >50X, to ensure high quality and confidence in the variant calls. Bonferroni correction for multiple comparisons took into account the number of groups tested (five), genes (five), number of cohorts (three), number of depth coverage (two) and number of statistical tests (two), which set the threshold for statistical significance on p<0.00083 based on 300 tests. With the merged cohorts, we had 80% power to detect differences, for example, of 1% and 2.7% or 2% and 4% between patients and controls, with p<0.0005. Power was calculated using the online tool at http://powerandsamplesize.com/Calculators/Compare-2-Proportions/2-Sample-Equality.

3.0 Results

3.1 Quality control and variants identified

The average coverage of the five genes range between 237X – 1592X in the different cohorts, and the percentages of read depth of the targeted genes were 93.07% and 88.76% of the bases covered by at least 20X and 50X respectively, and the coverage of each gene was nearly identical in the three cohorts (coverage depth and average coverage for each gene in each cohort are detailed in Supplementary Table S3). We identified a total of 788 rare variants in these five genes. The distribution of rare variants across the coding region and functional domains is available across cohorts and sequencing depth (Supplementary Table S4).

3.2 Association of rare variants and risk of Parkinson's disease

To further investigate whether rare variants in these five genes contribute to PD risk, we conducted a gene-based burden test and found no significant results within cohorts and depths across mutation type (Table 1). SKAT-O test for enrichment of all variant groups across the entire gene region in each cohort and sequencing depth suggested that *DNAJC13* variants were nominally enriched in PD patients in the Sheba cohort (p=0.0426) and were driven by nonsynonymous variants (p=0.0002) (Table 1). However, this association was

driven by higher frequency of nonsynonymous variants in controls (1.9%) than in PD patients (1.1%, Supplementary Table S5), demonstrating that nonsynonymous variants in this gene are not associated with higher risk of PD. In all other four genes there were no statistically significant associations in any of the cohorts tested (Table 1).

4.0   Discussion

Our study, which included full sequencing of *UCHL1, GIGYF2, HTRA2, DNAJC13* and *EIF4G1* in 3 cohorts, identified 788 rare variants (MAF <0.01) that are nonsynonymous, loss-of-function, predicted to be pathogenic by CADD scores, or affect splicing in coding regions of the gene and splice sites. Our results do not support a role for any of these genes in PD.

Of the five genes, *DNAJC13* in the Sheba cohort showed nominal association with controls driven by nonsynonymous variants with higher frequency in controls compared to PD cases. A previously reported variant, p.L1207W (Ross et al., 2016), was detected in all 3 cohorts, but had similar frequencies between cases and controls (Columbia), greater frequency in controls than cases (McGill) or were found exclusively in controls (Sheba, Supplementary Table S6–S8). The original *DNAJC13* association were described in a large-multi-incident family of Dutch-German-Russian-Mennonite ancestry that presented with autosomal dominant PD, where a p.N855S coding variant only partially co-segregated with disease status. Since the original description, several studies have reported other genetic variants in Italian cohorts (p.R903K) (Gagliardi et al., 2018) and Taiwanese cohorts (p.G394V and p.R1382H), yet the pathogenicity of these variants has not been confirmed. In addition, other previously described variants did not segregate by disease (p.R1516H and p.L2170W) (Ross et al., 2016), and in cohorts with sparse number of probands with rare variants in *DNAJC13* (Gagliardi et al., 2018; Lin et al., 2019). No other study was able to confirm the pathogenicity of the *DNAJC13* p.N855S variant. Moreover, in the same Dutch-German-Russian-Mennonite family, another gene, *TMEM230*, has been reported to be associated with PD instead of *DNAJC13.* Similar to *DNAJC13, TMEM230* had imperfect disease segregation within the family (Deng et al., 2016). These inconsistent results, together with the negative results in the current study and previous studies (Foo et al., 2014; Lorenzo-Betancor et al., 2015) call into question a role for *DNAJC13* in PD.

The role of *HTRA2* in PD was initially suggested as two missense variants (p.G399S and p.A141S) were reported to be associated with PD (Strauss et al., 2005). Subsequently, the p.G399S variant co-segregated with PD and essential tremor (ET) in a large Turkish family (Unal Gulsuner et al., 2014), providing further evidence of its potential role in PD. Additional variants were reported in Belgian (p.R404W) (Bogaerts et al., 2008), Chinese (IVS5+29T>A) (Wang, C.Y. et al., 2011), and Taiwanese (p.P143A) PD patients (Lin et al., 2011), yet without evidence for pathogenicity. Evidence for the p.G399S variant remains elusive even after several large-scale studies with PD in various populations worldwide (Kruger et al., 2011; Ross et al., 2008; Simon-Sanchez and Singleton, 2008). Moreover, the p.G399S mutations has been associated with ET, yet in subsequent studies of ET and PD, there was no significant evidence of an association of this variant with PD (He et al., 2017).

Similar to *DNAJC13*, there are insufficient data to conclude that this gene is associated with PD.

Since the first description of the association of *EIF4G1* variants (p.R1205H and p.A502V) with PD (Chartier-Harlin et al., 2011), numerous subsequent studies could not conclude that *EIF4G1* variants caused or associated with PD (Nuytemans et al., 2013; Schulte et al., 2012; Siitonen et al., 2013; Tucci et al., 2012). It is possible that the p.R1205H variant is not highly penetrant, as it was found in the original study (Chartier-Harlin et al., 2011) and in another family where it co-segregated with PD (Nuytemans et al., 2013); however, it was also reported in three controls (Schulte et al., 2012). Ethnic differences could account for the lack of findings as these variants were not found in several Asian ethnicities (Chen et al., 2013; Li et al., 2013; Nishioka et al., 2014; Sudhaman et al., 2013; Zhao et al., 2013). Interestingly, in the present study, the p.R1205H variant was found exclusively in controls in the McGill and Columbia cohorts. Given the multiple negative results and the presence of the p.R1205H in multiple controls, *EIF4G1* is unlikely to play a role in PD.

GIGYF2 was initially reported in a cohort composed of Italian and French PD patients (Lautier et al., 2008), yet subsequent studies in Portuguese and US cohorts did not find evidence of association with PD (Bras et al., 2009). Numerous additional studies, including in a different Italian cohort and multiple other ethnicities, also failed to identify an association of *GIGYF2* variants with PD (Bartonikova et al., 2018; Bonetti et al., 2009; Di Fonzo et al., 2009; Guo et al., 2009; Huo et al., 2017; Lesage et al., 2010; Li et al., 2010; Meeus et al., 2011; Nichols et al., 2009; Samaranch et al., 2010; Tan et al., 2009; Tan and Schapira, 2010; Tian et al., 2012; Vilarino-Guell et al., 2009; Wang, L. et al., 2010; Wang, L. et al., 2011; Yang et al., 2019; Zhang et al., 2015; Zhang et al., 2009; Zimprich et al., 2009). It is therefore very unlikely that *GIGYF2* is associated with PD.

The association of *UCHL1* was initially reported with the common p.S18Y variant (Lincoln et al., 1999), and while several studies initially supported this association (Maraganore et al., 2004; Ragland et al., 2009) other studies have failed to demonstrate that any *UCHL1* variants are associated with increased risk of PD (Elbaz et al., 2003; Healy et al., 2006; Levecque et al., 2001; Mellick and Silburn, 2000; Momose et al., 2002; Satoh and Kuroda, 2001; Savettieri et al., 2001; Wang et al., 2002; Wintermeyer et al., 2000; Zhang et al., 2000). Since the *UCHL1* p.S18Y is common, it should have been discovered in the large European and Asian GWASs (Foo et al., 2020; Nalls et al., 2019) yet it has not. In the present study, rare variants in *UCHL1* also did not demonstrate any association with PD. Given with the lack of effect of common variants, *UCHL1* is unlikely to be involved in PD.

Our study has several limitations, including the lack of age and sex matching between patients and controls. However, in the Columbia cohort the controls were older than the patients, whereas in the other two cohorts the controls were younger, yet no significant associations were found in any, suggesting that age did not affect the current results. In addition, it is possible that control subjects develop PD in the future, specifically in those cases where variants were found exclusively in controls. Since the risk of PD is about 1-2% in the control population, the effect on the results would likely be minor, even if a few individuals did develop PD. To increase statistical power, we merged the three cohorts for

burden and SKAT-O analyses. No population-adjustments were applied in the merged cohort analysis. However, the stratified analyses demonstrated that differences in sample sizes and disease risk that may occur between populations did not produce spurious associations in the merged cohort. Another limitation of our burden analyses is that since these are rare variant analyses, they do not include adjustments for covariates, since these covariates are likely to have small or no effect. Lastly, despite being a large study, we cannot completely rule out that very rare variants or more common variants with a very small effect on risk could be involved in PD in one or more of five tested genes. The fact that many large studies, including GWASs, genotyping and sequencing studies have so far mostly failed to detect associations, makes this possibility seem unlikely.

Altogether, the present study and the survey of existing literature strongly indicate a lack of association of PD with *UCHL1, HTRA2, GIGYF2, EIF4G1* and *DNAJC13*. The *PARK* aliases that these genes have received may lead to confusion and continue to inspire basic and clinical research as PD models. As the evidence suggests these genes are not associated with PD, we recommend removing the *PARK* designation off these genes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

References

Bartonikova T, Mensikova K, Kolarikova K, Vodicka R, Vrtel R, Otruba P, Kaiserova M, Vastik M, Mikulicova L, Ovecka J, Sachova L, Dvorsky F, Krsa J, Jugas P, Godava M, Bares M, Janout V, Hlustik P, Prochazka M, Kanovsky P, 2018. New endemic familial parkinsonism in south Moravia, Czech Republic and its genetical background. Medicine 97(38), e12313. [PubMed: 30235682]

Bogaerts V, Nuytemans K, Reumers J, Pals P, Engelborghs S, Pickut B, Corsmit E, Peeters K, Schymkowitz J, De Deyn PP, Cras P, Rousseau F, Theuns J, Van Broeckhoven C, 2008. Genetic variability in the mitochondrial serine protease HTRA2 contributes to risk for Parkinson disease. Human mutation 29(6), 832–840. [PubMed: 18401856]

Bonetti M, Ferraris A, Petracca M, Bentivoglio AR, Dallapiccola B, Valente EM, 2009. GIGYF2 variants are not associated with Parkinson's disease in Italy. Movement disorders : official journal of the Movement Disorder Society 24(12), 1867–1868; author reply 1868–1869. [PubMed: 19562763]

Bras J, Simon-Sanchez J, Federoff M, Morgadinho A, Januario C, Ribeiro M, Cunha L, Oliveira C, Singleton AB, 2009. Lack of replication of association between GIGYF2 variants and Parkinson disease. Hum Mol Genet 18(2), 341–346. [PubMed: 18923002]

Chartier-Harlin MC, Dachsel JC, Vilarino-Guell C, Lincoln SJ, Lepretre F, Hulihan MM, Kachergus J, Milnerwood AJ, Tapia L, Song MS, Le Rhun E, Mutez E, Larvor L, Duflot A, Vanbesien-Mailliot C, Kreisler A, Ross OA, Nishioka K, Soto-Ortolaza AI, Cobb SA, Melrose HL, Behrouz B, Keeling BH, Bacon JA, Hentati E, Williams L, Yanagiya A, Sonenberg N, Lockhart PJ, Zubair AC, Uitti RJ, Aasly JO, Krygowska-Wajs A, Opala G, Wszolek ZK, Frigerio R, Maraganore DM, Gosal D, Lynch T, Hutchinson M, Bentivoglio AR, Valente EM, Nichols WC, Pankratz N, Foroud T, Gibson RA, Hentati F, Dickson DW, Destee A, Farrer MJ, 2011. Translation initiator EIF4G1 mutations in familial Parkinson disease. Am J Hum Genet 89(3), 398–406. [PubMed: 21907011]

Chen S, Sanislav O, Annesley SJ, Fisher PR, 2018. Mitochondrial HTRA2 Plays a Positive, Protective Role in Dictyostelium discoideum but Is Cytotoxic When Overexpressed. Genes (Basel) 9(7).

Chen Y, Chen K, Song W, Chen X, Cao B, Huang R, Zhao B, Guo X, Burgunder J, Li J, Shang H-F, 2013. VPS35 Asp620Asn and EIF4G1 Arg1205His mutations are rare in Parkinson disease from Southwest China. Neurobiology of Aging 34(6), 1709.e1707–1709.e1708.

Deng H, Wang P, Jankovic J, 2018. The genetics of Parkinson disease. Ageing Research Reviews 42, 72–85. [PubMed: 29288112]

Deng HX, Shi Y, Yang Y, Ahmeti KB, Miller N, Huang C, Cheng L, Zhai H, Deng S, Nuytemans K, Corbett NJ, Kim MJ, Deng H, Tang B, Yang Z, Xu Y, Chan P, Huang B, Gao XP, Song Z, Liu Z, Fecto F, Siddique N, Foroud T, Jankovic J, Ghetti B, Nicholson DA, Krainc D, Melen O, Vance JM, Pericak-Vance MA, Ma YC, Rajput AH, Siddique T, 2016. Identification of TMEM230 mutations in familial Parkinson's disease. Nat Genet 48(7), 733–739. [PubMed: 27270108]

Di Fonzo A, Fabrizio E, Thomas A, Fincati E, Marconi R, Tinazzi M, Breedveld GJ, Simons EJ, Chien HF, Ferreira JJ, Horstink MW, Abbruzzese G, Borroni B, Cossu G, Dalla Libera A, Fabbrini G, Guidi M, De Mari M, Lopiano L, Martignoni E, Marini P, Onofrj M, Padovani A, Stocchi F, Toni V, Sampaio C, Barbosa ER, Meco G, Oostra BA, Bonifati V, 2009. GIGYF2 mutations are not a frequent cause of familial Parkinson's disease. Parkinsonism Relat Disord 15(9), 703–705. [PubMed: 19482505]

Elbaz A, Levecque C, Clavel J, Vidal JS, Richard F, Correze JR, Delemotte B, Amouyel P, Alperovitch A, Chartier-Harlin MC, Tzourio C, 2003. S18Y polymorphism in the UCH-L1 gene and Parkinson's disease: evidence for an age-dependent relationship. Movement disorders : official journal of the Movement Disorder Society 18(2), 130–137. [PubMed: 12539205]

Foo JN, Chew EGY, Chung SJ, Peng R, Blauwendraat C, Nalls MA, Mok KY, Satake W, Toda T, Chao Y, Tan LCS, Tandiono M, Lian MM, Ng EY, Prakash K-M, Au W-L, Meah W-Y, Mok SQ, Annuar AA, Chan AYY, Chen L, Chen Y, Jeon BS, Jiang L, Lim JL, Lin J-J, Liu C, Mao C, Mok V, Pei Z, Shang H-F, Shi C-H, Song K, Tan AH, Wu Y-R, Xu Y. m., Xu R, Yan Y, Yang J, Zhang B, Koh W-P, Lim S-Y, Khor CC, Liu J, Tan E-K, 2020. Identification of Risk Loci for Parkinson Disease in Asians and Comparison of Risk Between Asians and Europeans: A Genome-Wide Association Study. JAMA Neurology.

Foo JN, Liany H, Tan LC, Au WL, Prakash KM, Liu J, Tan EK, 2014. DNAJ mutations are rare in Chinese Parkinson's disease patients and controls. Neurobiol Aging 35(4), 935.e931–932.

Gagliardi M, Annesi G, Procopio R, Morelli M, Iannello G, Bonapace G, Mancini M, Nicoletti G, Quattrone A, 2018. DNAJC13 mutation screening in patients with Parkinson's disease from South Italy. Parkinsonism Relat Disord 55, 134–137. [PubMed: 29887357]

Guo Y, Jankovic J, Zhu S, Le W, Song Z, Xie W, Liao D, Yang H, Deng H, 2009. GIGYF2 Asn56Ser and Asn457Thr mutations in Parkinson disease patients. Neuroscience letters 454(3), 209–211. [PubMed: 19429085]

He YC, Huang P, Li QQ, Sun Q, Li DH, Wang T, Shen JY, Du JJ, Cui SS, Gao C, Fu R, Chen SD, 2017. Mutation Analysis of HTRA2 Gene in Chinese Familial Essential Tremor and Familial Parkinson's Disease. Parkinson's disease 2017, 3217474.

Healy DG, Abou-Sleiman PM, Casas JP, Ahmadi KR, Lynch T, Gandhi S, Muqit MM, Foltynie T, Barker R, Bhatia KP, Quinn NP, Lees AJ, Gibson JM, Holton JL, Revesz T, Goldstein DB, Wood NW, 2006. UCHL-1 is not a Parkinson's disease susceptibility gene. Annals of neurology 59(4), 627–633. [PubMed: 16450370]

Hughes AJ, Daniel SE, Kilford L, Lees AJ, 1992. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. 55(3), 181–184.

Huo Z, Luo X, Zhan X, Chu Q, Xu Q, Yao J, Pang H, 2017. Genetic analysis of indel markers in three loci associated with Parkinson's disease. PLoS One 12(9), e0184269. [PubMed: 28873462]

Jankovic J, 2008. Parkinson's disease: clinical features and diagnosis. 79(4), 368–376.

Kruger R, Sharma M, Riess O, Gasser T, Van Broeckhoven C, Theuns J, Aasly J, Annesi G, Bentivoglio AR, Brice A, Djarmati A, Elbaz A, Farrer M, Ferrarese C, Gibson JM, Hadjigeorgiou GM, Hattori N, Ioannidis JP, Jasinska-Myga B, Klein C, Lambert JC, Lesage S, Lin JJ, Lynch T, Mellick GD, de Nigris F, Opala G, Prigione A, Quattrone A, Ross OA, Satake W, Silburn PA, Tan EK, Toda T, Tomiyama H, Wirdefeldt K, Wszolek Z, Xiromerisiou G, Maraganore DM, 2011. A large-scale genetic association study to evaluate the contribution of Omi/HtrA2 (PARK13) to Parkinson's disease. Neurobiol Aging 32(3), 548.e549–518.

Lautier C, Goldwurm S, Durr A, Giovannone B, Tsiaras WG, Pezzoli G, Brice A, Smith RJ, 2008. Mutations in the GIGYF2 (TNRC15) gene at the PARK11 locus in familial Parkinson disease. Am J Hum Genet 82(4), 822–833. [PubMed: 18358451]

Lee S, Emond MJ, Bamshad MJ, Barnes KC, Rieder MJ, Nickerson DA, Christiani David C., Wurfel Mark M., Lin X, 2012. Optimal Unified Approach for Rare-Variant Association Testing with Application to Small-Sample Case-Control Whole-Exome Sequencing Studies. The American Journal of Human Genetics 91(2), 224–237. [PubMed: 22863193]

Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, O'Donnell-Luria AH, Ware JS, Hill AJ, Cummings BB, Tukiainen T, Birnbaum DP, Kosmicki JA, Duncan LE, Estrada K, Zhao F, Zou J, Pierce-Hoffman E, Berghout J, Cooper DN, Deflaux N, DePristo M, Do R, Flannick J, Fromer M, Gauthier L, Goldstein J, Gupta N, Howrigan D, Kiezun A, Kurki MI, Moonshine AL, Natarajan P, Orozco L, Peloso GM, Poplin R, Rivas MA, Ruano-Rubio V, Rose SA, Ruderfer DM, Shakir K, Stenson PD, Stevens C, Thomas BP, Tiao G, Tusie-Luna MT, Weisburd B, Won H-H, Yu D, Altshuler DM, Ardissino D, Boehnke M, Danesh J, Donnelly S, Elosua R, Florez JC, Gabriel SB, Getz G, Glatt SJ, Hultman CM, Kathiresan S, Laakso M, McCarroll S, McCarthy MI, McGovern D, McPherson R, Neale BM, Palotie A, Purcell SM, Saleheen D, Scharf JM, Sklar P, Sullivan PF, Tuomilehto J, Tsuang MT, Watkins HC, Wilson JG, Daly MJ, MacArthur DG, Exome Aggregation C, 2016. Analysis of protein-coding genetic variation in 60,706 humans. Nature 536(7616), 285–291. [PubMed: 27535533]

Lesage S, Condroyer C, Lohman E, Troiano A, Tison F, Viallet F, Damier P, Tranchant C, Vidhaillet M, Ouvrard-Hernandez AM, Durr A, Brice A, 2010. Follow-up study of the GIGYF2 gene in French families with Parkinson's disease. Neurobiol Aging 31(6), 1069–1071; discussion 1072-1064. [PubMed: 20004041]

Levecque C, Destee A, Mouroux V, Becquet E, Defebvre L, Amouyel P, Chartier-Harlin MC, 2001. No genetic association of the ubiquitin carboxy-terminal hydrolase-L1 gene S18Y polymorphism with familial Parkinson's disease. Journal of neural transmission (Vienna, Austria : 1996) 108(8–9), 979–984.

Li H, Durbin R, 2009. Fast and accurate short read alignment with Burrows-Wheeler transform. Bioinformatics 25(14), 1754–1760. [PubMed: 19451168]

Li K, Tang BS, Guo JF, Lou MX, Lv ZY, Liu ZH, Tian Y, Song CY, Xia K, Yan XX, 2013. Analysis of EIF4G1 in ethnic Chinese. BMC neurology 13, 38. [PubMed: 23617574]

Li L, Funayama M, Tomiyama H, Li Y, Yoshino H, Sasaki R, Kokubo Y, Kuzuhara S, Mizuno Y, Hattori N, 2010. No evidence for pathogenic role of GIGYF2 mutation in Parkinson disease in Japanese patients. Neuroscience letters 479(3), 245–248. [PubMed: 20641165]

Lin CH, Chen ML, Chen GS, Tai CH, Wu RM, 2011. Novel variant Pro143Ala in HTRA2 contributes to Parkinson's disease by inducing hyperphosphorylation of HTRA2 protein in mitochondria. Human genetics 130(6), 817–827. [PubMed: 21701785]

Lin CH, Chen PL, Tai CH, Lin HI, Chen CS, Chen ML, Wu RM, 2019. A clinical and genetic study of early-onset and familial parkinsonism in taiwan: An integrated approach combining gene dosage analysis and next-generation sequencing. Movement disorders : official journal of the Movement Disorder Society 34(4), 506–515. [PubMed: 30788857]

Lincoln S, Vaughan J, Wood N, Baker M, Adamson J, Gwinn-Hardy K, Lynch T, Hardy J, Farrer M, 1999. Low frequency of pathogenic mutations in the ubiquitin carboxyterminal hydrolase gene in familial Parkinson's disease. Neuroreport 10(2).

Lorenzo-Betancor O, Ogaki K, Soto-Ortolaza AI, Labbe C, Walton RL, Strongosky AJ, van Gerpen JA, Uitti RJ, McLean PJ, Springer W, Siuda J, Opala G, Krygowska-Wajs A, Barcikowska M, Czyzewski K, McCarthy A, Lynch T, Puschmann A, Rektorova I, Sanotsky Y, Vilarino-Guell C, Farrer MJ, Ferman TJ, Boeve BF, Petersen RC, Parisi JE, Graff-Radford NR, Dickson DW, Wszolek ZK, Ross OA, 2015. DNAJC13 p.Asn855Ser mutation screening in Parkinson's disease and pathologically confirmed Lewy body disease patients. European journal of neurology 22(9), 1323–1325. [PubMed: 26278106]

Maraganore DM, Lesnick TG, Elbaz A, Chartier-Harlin MC, Gasser T, Kruger R, Hattori N, Mellick GD, Quattrone A, Satoh J, Toda T, Wang J, loannidis JP, de Andrade M, Rocca WA, 2004. UCHL1 is a Parkinson's disease susceptibility gene. Annals of neurology 55(4), 512–521. [PubMed: 15048890]

McKenna A, Hanna M, Banks E, Sivachenko A, Cibulskis K, Kernytsky A, Garimella K, Altshuler D, Gabriel S, Daly M, DePristo MA, 2010. The Genome Analysis Toolkit: A MapReduce framework for analyzing next-generation DNA sequencing data. 20(9), 1297–1303.

Meeus B, Nuytemans K, Crosiers D, Engelborghs S, Pals P, Pickut B, Peeters K, Mattheijssens M, Corsmit E, Cras P, De Deyn PP, Theuns J, Van Broeckhoven C, 2011. GIGYF2 has no major role in Parkinson genetic etiology in a Belgian population. Neurobiol Aging 32(2), 308–312. [PubMed: 19321232]

Mellick GD, Silburn PA, 2000. The ubiquitin carboxy-terminal hydrolase-L1 gene S18Y polymorphism does not confer protection against idiopathic Parkinson's disease. Neuroscience letters 293(2), 127–130. [PubMed: 11027850]

Momose Y, Murata M, Kobayashi K, Tachikawa M, Nakabayashi Y, Kanazawa I, Toda T, 2002. Association studies of multiple candidate genes for Parkinson's disease using single nucleotide polymorphisms. 51(1), 133–136.

Nalls MA, Blauwendraat C, Vallerga CL, Heilbron K, Bandres-Ciga S, Chang D, Tan M, Kia DA, Noyce AJ, Xue A, Bras J, Young E, von Coelln R, Simón-Sánchez J, Schulte C, Sharma M, Krohn L, Pihlstrøm L, Siitonen A, Iwaki H, Leonard H, Faghri F, Gibbs JR, Hernandez DG, Scholz SW, Botía JA, Martinez M, Corvol J-C, Lesage S, Jankovic J, Shulman LM, Sutherland M, Tienari P, Majamaa K, Toft M, Andreassen OA, Bangale T, Brice A, Yang J, Gan-Or Z, Gasser T, Heutink P, Shulman JM, Wood NW, Hinds DA, Hardy JA, Morris HR, Gratten J, Visscher PM, Graham RR, Singleton AB, Adarmes-Gómez AD, Aguilar M, Aitkulova A, Akhmetzhanov V, Alcalay RN, Alvarez I, Alvarez V, Bandres-Ciga S, Barrero FJ, Bergareche Yarza JA, Bernal-Bernal I, Billingsley K, Blauwendraat C, Blazquez M, Bonilla-Toribio M, Botía JA, Boungiorno MT, Bras J, Brice A, Brockmann K, Bubb V, Buiza-Rueda D, Cámara A, Carrillo F, Carrión-Claro M, Cerdan D, Chelban V, Clarimón J, Clarke C, Compta Y, Cookson MR, Corvol J-C, Craig DW, Danjou F, Diez-Fairen M, Dols-Icardo O, Duarte J, Duran R, Escamilla-Sevilla F, Escott-Price V, Ezquerra M, Faghri F, Feliz C, Fernández M, Fernández-Santiago R, Finkbeiner S, Foltynie T, Gan-Or Z, García C, García-Ruiz P, Gasser T, Gibbs JR, Gómez Heredia MJ, Gómez-Garre P, González MM, Gonzalez-Aramburu I, Guelfi S, Guerreiro R, Hardy J, Hassin-Baer S, Hernandez DG, Heutink P, Hoenicka J, Holmans P, Houlden H, Infante J, Iwaki H, Jesús S, Jimenez-Escrig A, Kaishybayeva

G, Kaiyrzhanov R, Karimova A, Kia DA, Kinghorn KJ, Koks S, Krohn L, Kulisevsky J, Labrador-Espinosa MA, Leonard HL, Lesage S, Lewis P, Lopez-Sendon JL, Lovering R, Lubbe S, Lungu C, Macias D, Majamaa K, Manzoni C, Marín J, Marinus J, Marti MJ, Martinez M, Martínez Torres I, Martínez-Castrillo JC, Mata M, Mencacci NE, Méndez-del-Barrio C, Middlehurst B, Mínguez A, Mir P, Mok KY, Morris HR, Muñoz E, Nalls MA, Narendra D, Noyce AJ, Ojo OO, Okubadejo NU, Pagola AG, Pastor P, Perez Errazquin F, Periñán-Tocino T, Pihlstrom L, Plun-Favreau H, Quinn J, R'Bibo L, Reed X, Rezola EM, Rizig M, Rizzu P, Robak L, Rodriguez AS, Rouleau GA, Ruiz-Martínez J, Ruz C, Ryten M, Sadykova D, Scholz SW, Schreglmann S, Schulte C, Sharma M, Shashkin C, Shulman JM, Sierra M, Siitonen A, Simón-Sánchez J, Singleton AB, Suarez-Sanmartin E, Taba P, Tabernero C, Tan MX, Tartari JP, Tejera-Parrado C, Toft M, Tolosa E, Trabzuni D, Valldeoriola F, van Hilten JJ, Van Keuren-Jensen K, Vargas-González L, Vela L, Vives F, Williams N, Wood NW, Zharkinbekova N, Zharmukhanov Z, Zholdybayeva E, Zimprich A, Ylikotila P, Shulman LM, von Coelln R, Reich S, Savitt J, Agee M, Alipanahi B, Auton A, Bell RK, Bryc K, Elson SL, Fontanillas P, Furlotte NA, Huber KE, Hicks B, Jewett EM, Jiang Y, Kleinman A, Lin K-H, Litterman NK, McCreight JC, McIntyre MH, McManus KF, Mountain JL, Noblin ES, Northover CAM, Pitts SJ, Poznik GD, Sathirapongsasuti JF, Shelton JF, Shringarpure S, Tian C, Tung J, Vacic V, Wang X, Wilson CH, Anderson T, Bentley S, Dalrymple-Alford J, Fowdar J, Gratten J, Halliday G, Henders AK, Hickie I, Kassam I, Kennedy M, Kwok J, Lewis S, Mellick G, Montgomery G, Pearson J, Pitcher T, Sidorenko J, Silburn PA, Vallerga CL, Visscher PM, Wallace L, Wray NR, Xue A, Yang J, Zhang F, 2019. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. The Lancet Neurology 18(12), 1091–1102. [PubMed: 31701892]

Nichols N, Bras JM, Hernandez DG, Jansen IE, Lesage S, Lubbe S, Singleton AB, 2015. EIF4G1 mutations do not cause Parkinson's disease. Neurobiology of Aging 36(8), 2444.e2441–2444.e2444. [PubMed: 26022768]

Nichols WC, Kissell DK, Pankratz N, Pauciulo MW, Elsaesser VE, Clark KA, Halter CA, Rudolph A, Wojcieszek J, Pfeiffer RF, Foroud T, 2009. Variation in GIGYF2 is not associated with Parkinson disease. Neurology 72(22), 1886–1892. [PubMed: 19279319]

Nishioka K, Funayama M, Vilarino-Guell C, Ogaki K, Li Y, Sasaki R, Kokubo Y, Kuzuhara S, Kachergus JM, Cobb SA, Takahashi H, Mizuno Y, Farrer MJ, Ross OA, Hattori N, 2014. EIF4G1 gene mutations are not a common cause of Parkinson's disease in the Japanese population. Parkinsonism Relat Disord 20(6), 659–661. [PubMed: 24704100]

Nuytemans K, Bademci G, Inchausti V, Dressen A, Kinnamon DD, Mehta A, Wang L, Zuchner S, Beecham GW, Martin ER, Scott WK, Vance JM, 2013. Whole exome sequencing of rare variants in EIF4G1 and VPS35 in Parkinson disease. Neurology 80(11), 982–989. [PubMed: 23408866]

Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G, 2015. MDS clinical diagnostic criteria for Parkinson's disease. 30(12), 1591–1601.

Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, Maller J, Sklar P, de Bakker PIW, Daly MJ, Sham PC, 2007. PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses. The American Journal of Human Genetics 81(3), 559–575. [PubMed: 17701901]

Ragland M, Hutter C, Zabetian C, Edwards K, 2009. Association between the ubiquitin carboxyl-terminal esterase L1 gene (UCHL1) S18Y variant and Parkinson's Disease: a HuGE review and meta-analysis. American journal of epidemiology 170(11), 1344–1357. [PubMed: 19864305]

Ross JP, Dupre N, Dauvilliers Y, Strong S, Ambalavanan A, Spiegelman D, Dionne-Laporte A, Pourcher E, Langlois M, Boivin M, Leblond CS, Dion PA, Rouleau GA, Gan-Or Z, 2016. Analysis of DNAJC13 mutations in French-Canadian/French cohort of Parkinson's disease. Neurobiol Aging 45, 212.e213–212.e217.

Ross OA, Soto AI, Vilarino-Guell C, Heckman MG, Diehl NN, Hulihan MM, Aasly JO, Sando S, Gibson JM, Lynch T, Krygowska-Wajs A, Opala G, Barcikowska M, Czyzewski K, Uitti RJ, Wszolek ZK, Farrer MJ, 2008. Genetic variation of Omi/HtrA2 and Parkinson's disease. Parkinsonism Relat Disord 14(7), 539–543. [PubMed: 18790661]

Samaranch L, Lorenzo E, Pastor MA, Riverol M, Luquin MR, Rodriguez-Oroz MC, Obeso JA, Pastor P, 2010. Analysis of the GIGYF2 gene in familial and sporadic Parkinson disease in the Spanish population. European journal of neurology 17(2), 321–325. [PubMed: 19845746]

Satoh J, Kuroda Y, 2001. A polymorphic variation of serine to tyrosine at codon 18 in the ubiquitin C-terminal hydrolase-L1 gene is associated with a reduced risk of sporadic Parkinson's disease in a Japanese population. Journal of the neurological sciences 189(1–2), 113–117. [PubMed: 11535241]

Savettieri G, De Marco EV, Civitelli D, Salemi G, Nicoletti G, Annesi G, Ciro Candiano IC, Quattrone A, 2001. Lack of association between ubiquitin carboxy-terminal hydrolase L1 gene polymorphism and PD. Neurology 57(3), 560–561. [PubMed: 11502942]

Schulte EC, Mollenhauer B, Zimprich A, Bereznai B, Lichtner P, Haubenberger D, Pirker W, Brucke T, Molnar MJ, Peters A, Gieger C, Trenkwalder C, Winkelmann J, 2012. Variants in eukaryotic translation initiation factor 4G1 in sporadic Parkinson's disease. Neurogenetics 13(3), 281–285. [PubMed: 22707335]

Siitonen A, Majounie E, Federoff M, Ding J, Majamaa K, Singleton AB, 2013. Mutations in EIF4G1 are not a common cause of Parkinson's disease. European journal of neurology 20(4), e59. [PubMed: 23490116]

Simon-Sanchez J, Singleton AB, 2008. Sequencing analysis of OMI/HTRA2 shows previously reported pathogenic mutations in neurologically normal controls. Hum Mol Genet 17(13), 1988–1993. [PubMed: 18364387]

Strauss KM, Martins LM, Plun-Favreau H, Marx FP, Kautzmann S, Berg D, Gasser T, Wszolek Z, Muller T, Bornemann A, Wolburg H, Downward J, Riess O, Schulz JB, Kruger R, 2005. Loss of function mutations in the gene encoding Omi/HtrA2 in Parkinson's disease. Hum Mol Genet 14(15), 2099–2111. [PubMed: 15961413]

Sudhaman S, Behari M, Govindappa ST, Muthane UB, Juyal RC, Thelma BK, 2013. VPS35 and EIF4G1 mutations are rare in Parkinson's disease among Indians. Neurobiol Aging 34(10), 2442.e2441–2443.

Sun S, Zhao Y, Jin G, Kang H, 2014. Lack of association between UCHL1 S18Y gene polymorphism and Parkinson's disease in the Asian population: a meta-analysis. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 35(12), 1867–1876.

Tan EK, Lin CH, Tai CH, Tan LC, Chen ML, Li R, Lim HQ, Pavanni R, Yuen Y, Prakash KM, Zhao Y, Wu RM, 2009. Non-synonymous GIGYF2 variants in Parkinson's disease from two Asian populations. Human genetics 126(3), 425–430. [PubMed: 19449032]

Tan EK, Schapira AH, 2010. Summary of GIGYF2 studies in Parkinson's disease: the burden of proof. European journal of neurology 17(2), 175–176. [PubMed: 19906271]

Tian JY, Guo JF, Wang L, Sun QY, Yao LY, Luo LZ, Shi CH, Hu YC, Yan XX, Tang BS, 2012. Mutation analysis of LRRK2, SCNA, UCHL1, HtrA2 and GIGYF2 genes in Chinese patients with autosomal dorminant Parkinson's disease. Neuroscience letters 516(2), 207–211. [PubMed: 22503729]

Tran HH, Dang SNA, Nguyen TT, Huynh AM, Dao LM, Kamei K, Yamaguchi M, Dang TTP, 2018. Drosophila Ubiquitin C-Terminal Hydrolase Knockdown Model of Parkinson's Disease. Scientific reports 8(1), 4468. [PubMed: 29535397]

Tucci A, Charlesworth G, Sheerin UM, Plagnol V, Wood NW, Hardy J, 2012. Study of the genetic variability in a Parkinson's Disease gene: EIF4G1. Neuroscience letters 518(1), 19–22. [PubMed: 22561553]

Unal Gulsuner H, Gulsuner S, Mercan FN, Onat OE, Walsh T, Shahin H, Lee MK, Dogu O, Kansu T, Topaloglu H, Elibol B, Akbostanci C, King MC, Ozcelik T, Tekinay AB, 2014. Mitochondrial serine protease HTRA2 p.G399S in a kindred with essential tremor and Parkinson disease. Proceedings of the National Academy of Sciences of the United States of America 111(51), 18285–18290. [PubMed: 25422467]

Vilariño-Güell C, Rajput A, Milnerwood AJ, Shah B, Szu-Tu C, Trinh J, Yu I, Encarnacion M, Munsie LN, Tapia L, Gustavsson EK, Chou P, Tatarnikov I, Evans DM, Pishotta FT, Volta M, Beccano-Kelly D, Thompson C, Lin MK, Sherman HE, Han HJ, Guenther BL, Wasserman WW, Bernard V, Ross CJ, Appel-Cresswell S, Stoessl AJ, Robinson CA, Dickson DW, Ross OA, Wszolek ZK, Aasly JO, Wu R-M, Hentati F, Gibson RA, McPherson PS, Girard M, Rajput M, Rajput AH, Farrer MJ, 2013. DNAJC13 mutations in Parkinson disease. Human Molecular Genetics 23(7), 1794–1801. [PubMed: 24218364]

Vilarino-Guell C, Ross OA, Soto AI, Farrer MJ, Haugarvoll K, Aasly JO, Uitti RJ, Wszolek ZK, 2009. Reported mutations in GIGYF2 are not a common cause of Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 24(4), 619–620. [PubMed: 19133664]

Wang CY, Xu Q, Weng L, Zhang Q, Zhang HN, Guo JF, Tan LM, Tang JG, Yan XX, Tang BS, 2011. Genetic variations of Omi/HTRA2 in Chinese patients with Parkinson's disease. Brain research 1385, 293–297. [PubMed: 21338583]

Wang J, Zhao CY, Si YM, Liu ZL, Chen B, Yu L, 2002. ACT and UCH-L1 polymorphisms in Parkinson's disease and age of onset. Movement disorders : official journal of the Movement Disorder Society 17(4), 767–771. [PubMed: 12210873]

Wang K, Li M, Hakonarson H, 2010. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. Nucleic Acids Research 38(16), e164–e164. [PubMed: 20601685]

Wang L, Guo JF, Zhang WW, Xu Q, Zuo X, Shi CH, Luo LZ, Liu J, Hu L, Hu YC, She L, Jiang H, Yan XX, Xia K, Pan Q, Tang BS, 2010. Novel GIGYF2 gene variants in patients with Parkinson's disease in Chinese population. Neuroscience letters 473(2), 131–135. [PubMed: 20178831]

Wang L, Guo JF, Zhang WW, Xu Q, Zuo X, Shi CH, Luo LZ, Liu J, Hu L, Hu YC, Yan XX, Tang BS, 2011. Follow-up study of variants of the GIGYF2 gene in Chinese patients with Parkinson's disease. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 18(12), 1699–1701. [PubMed: 22115759]

Wintermeyer P, Kruger R, Kuhn W, Muller T, Woitalla D, Berg D, Becker G, Leroy E, Polymeropoulos M, Berger K, Przuntek H, Schols L, Epplen JT, Riess O, 2000. Mutation analysis and association studies of the UCHL1 gene in German Parkinson's disease patients. Neuroreport 11(10), 2079–2082. [PubMed: 10923647]

Yang N, Zhao Y, Liu Z, Zhang R, He Y, Zhou Y, Xu Q, Sun Q, Yan X, Guo J, Tang B, 2019. Systematically analyzing rare variants of autosomal-dominant genes for sporadic Parkinson's disease in a Chinese cohort. Neurobiology of Aging 76, 215.e211–215.e217.

Zhang J, Hattori N, Leroy E, Morris HR, Kubo S, Kobayashi T, Wood NW, Polymeropoulos MH, Mizuno Y, 2000. Association between a polymorphism of ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) gene and sporadic Parkinson's disease. Parkinsonism Relat Disord 6(4), 195–197. [PubMed: 10900392]

Zhang Y, Sun QY, Yu RH, Guo JF, Tang BS, Yan XX, 2015. The contribution of GIGYF2 to Parkinson's disease: a meta-analysis. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 36(11), 2073–2079.

Zhang Y, Zheng L, Zhang T, Wang Y, Xiao Q, Fei QZ, Cui PJ, Cao L, Chen SD, 2009. GIGYF2 Asn56Ser mutation is rare in Chinese Parkinson's disease patients. Neuroscience letters 463(3), 172–175. [PubMed: 19638301]

Zhao Y, Ho P, Prakash KM, Foo JN, Liu JJ, Au WL, Tan LC, Tan EK, 2013. Analysis of EIF4G1 in Parkinson's disease among Asians. Neurobiol Aging 34(4), 1311.e1315–1316.

Zimprich A, Schulte C, Reinthaler E, Haubenberger D, Balzar J, Lichtner P, El Tawil S, Edris S, Foki T, Pirker W, Katzenschlager R, Daniel G, Brucke T, Auff E, Gasser T, 2009. PARK11 gene (GIGYF2) variants Asn56Ser and Asn457Thr are not pathogenic for Parkinson's disease. Parkinsonism Relat Disord 15(7), 532–534. [PubMed: 19250854]

Table 1:

SKAT-O and burden analysis results for each gene, across cohort and coverage depth for mutation type

Depth of coverage	Gene	Number of Variants Tested	All rare		Number of Variants Tested	Rare CADD		Number of Variants Tested	Rare functional		Number of Variants Tested	Rare nonsynonymous		Number of Variants Tested	Rare loss-of-function	
			SKAT-O	SKAT Burden		SKAT-O	SKAT Burden		SKAT-O	SKAT Burden		SKAT-O	SKAT Burden		SKAT-O	SKAT Burden
30x								McGill								
	DNAJC13	143	0.727	0.494	37	0.905	1	47	0.845	0.647	44	0.899	0.800	NV	NV	NV
	EIF4G1	56	0.733	0.818	16	0.637	0.986	38	0.566	0.836	23	0.872	0.690	8	0.315	1
	GIGYF2	164	0.254	0.236	19	0.237	0.477	48	0.104	0.075	24	0.320	0.659	9	0.885	0.854
	HTRA2	13	0.592	0.341	3	0.798	0.798	7	0.292	0.513	2	0.223	0.223	1	0.611	0.611
	UCHL1	26	0.827	1	2	0.729	0.341	12	0.502	1	4	0.480	0.313	NV	NV	NV
								Columbia								
	DNAJC13	97	0.709	0.493	28	0.344	0.206	32	0.500	0.317	31	0.594	0.393	NV	NV	NV
	EIF4G1	47	0.511	0.341	13	0.983	0.862	26	0.384	0.239	17	0.634	0.429	5	0.406	0.759
	GIGYF2	118	0.783	0.576	11	0.638	0.555	36	0.793	0.640	15	0.889	0.758	6	0.555	0.584
	HTRA2	10	0.276	0.323	2	0.344	0.774	6	0.835	0.835	2	0.344	0.774	NV	NV	NV
	UCHL1	19	0.751	0.715	3	0.928	0.771	9	0.891	0.741	3	0.781	0.547	NV	NV	NV
								Sheba								
	DNAJC13	60	0.042	0.569	21	0.002	0.264	24	0.001	0.152	23	0.001	0.117	NV	NV	NV
	EIF4G1	34	0.703	0.489	14	0.544	0.678	18	0.617	0.583	13	0.635	0.688	2	0.103	0.103
	GIGYF2	88	0.278	0.203	8	0.837	0.709	35	0.198	0.232	8	0.654	0.473	14	0.165	0.159
	HTRA2	7	0.066	0.080	3	0.046	0.046	6	0.264	0.138	3	0.046	0.046	NV	NV	NV
	UCHL1	6	0.479	0.344	1	0.845	0.845	5	0.574	0.335	2	0.918	0.795	NV	NV	NV
								Merged								
	DNAJC13	219	0.003	0.644	64	0.039	0.076	79	0.006	0.007	75	0.011	0.015	NV	NV	NV
	EIF4G1	104	0.669	0.850	31	0.035	0.172	62	0.365	0.239	42	0.238	0.712	7	0.208	0.150
	GIGYF2	284	0.246	0.787	32	0.634	0.449	94	0.322	0.418	38	0.682	0.840	24	0.310	0.302
	HTRA2	24	0.917	0.953	7	0.869	0.579	18	0.728	0.975	6	0.844	0.844	1	0.700	0.700
	UCHL1	39	0.406	0.817	5	0.429	0.376	18	0.601	1	6	0.181	0.280	NV	NV	NV
50x								McGill								

Depth of coverage	Gene	Number of Variants Tested	All rare		Number of Variants Tested	Rare CADD		Number of Variants Tested	Rare functional		Number of Variants Tested	Rare nonsynonymous		Number of Variants Tested	Rare loss-of-function	
			SKAT-O	SKAT Burden		SKAT-O	SKAT Burden		SKAT-O	SKAT Burden		SKAT-O	SKAT Burden		SKAT-O	SKAT Burden
	DNAJC13	82	0.602	0.544	23	0.399	1	28	0.410	0.833	25	0.416	0.860	NV	NV	NV
	EIF4G1	13	0.438	1	2	0.864	0.864	11	0.299	1	3	0.945	0.834	5	0.241	0.870
	GIGYF2	103	0.331	0.351	15	0.129	1	37	0.093	0.136	20	0.163	0.800	3	0.845	0.845
	HTRA2	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV
	UCHL1	17	0.435	0.288	2	0.715	0.715	4	0.282	0.193	4	0.282	0.193	NV	NV	NV
Columbia																
	DNAJC13	66	0.619	0.411	19	0.359	0.218	22	0.386	0.236	21	0.502	0.322	NV	NV	NV
	EIF4G1	7	0.568	0.590	NV	NV	NV	3	0.329	0.989	NV	NV	NV	1	0.331	0.331
	GIGYF2	70	0.370	0.228	9	0.453	0.264	25	0.308	0.181	11	0.618	0.434	2	0.202	0.135
	HTRA2	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV
	UCHL1	14	0.525	0.694	3	0.468	0.378	3	0.695	0.922	3	0.695	0.922	NV	NV	NV
Sheba																
	DNAJC13	38	0.043	0.151	14	2×10^{-4}	0.132	15	5×10^{-4}	0.139	14	2×10^{-4}	0.132	NV	NV	NV
	EIF4G1	2	0.615	0.369	1	0.754	0.754	1	0.754	0.754	1	0.754	0.754	NV	NV	NV
	GIGYF2	40	0.626	0.416	5	0.607	0.444	19	0.510	0.335	7	0.780	0.608	NV	NV	NV
	HTRA2	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV
	UCHL1	4	0.546	0.395	1	0.847	0.847	2	0.917	0.792	2	0.917	0.792	NV	NV	NV
Merged																
	DNAJC13	146	0.018	0.561	42	0.154	0.128	52	0.078	0.053	48	0.099	0.072	NV	NV	NV
	EIF4G1	20	0.540	0.653	3	0.931	0.758	14	0.453	0.580	4	0.970	0.831	5	0.383	0.755
	GIGYF2	164	0.033	0.276	26	0.614	0.432	64	0.886	0.701	33	0.779	0.593	5	0.735	0.584
	HTRA2	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV	NV
	UCHL1	26	0.009	0.412	4	0.067	0.087	6	0.015	0.512	6	0.015	0.512	NV	NV	NV

Abbreviations: SKAT: Sequence Kernel Association Test; SKAT-O: Optimized Sequence Kernel Association Test; CADD: Combined Annotation Dependent Depletion; NV: No Variant