TITLE PAGE

ASSESSING THE RELATIONSHIP BETWEEN MONOALLELIC *PRKN* MUTATIONS AND PARKINSON'S RISK

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ABSTRACT

Biallelic *PRKN* (Parkin) mutations cause autosomal recessive Parkinson's (PD); however, the role of monoallelic *PRKN* mutations as a risk factor for PD remains unclear. We investigated the role of single heterozygous *PRKN* mutations in three large independent case-control cohorts totalling 10,858 PD cases and 8,328 controls. Overall, after exclusion of biallelic carriers, single *PRKN* mutations were more common in PD than controls conferring a >1.5-fold increase in risk of PD (P=0.035), with meta-analysis (19,574 PD cases and 468,488 controls) confirming increased risk (OR=1.65, P=3.69E-07). Carriers were shown to have significantly younger ages at onset compared to non-carriers (NeuroX: 56.4 *vs*. 61.4 years; Exome: 38.5 *vs*. 43.1 years). Stratifying by mutation type, we provide preliminary evidence for a more pathogenic risk profile for single *PRKN* copy number variant (CNV) carriers compared to single nucleotide variant carriers. Studies that did not assess biallelic *PRKN* mutations or consist of predominantly early-onset cases may be biasing these estimates, and removal of these resulted in a loss of association (OR=1.23, P=0.614; n=4). Importantly, when we looked for additional CNVs in 30% of PD cases with apparent monoallellic *PRKN* mutations we found that 44% had biallelic mutations suggesting that previous estimates may be influenced by cryptic biallelic mutation status. While this study supports the association of single *PRKN* mutations with PD, it highlights confounding effects therefore caution is needed when interpreting current risk estimates. Together, we demonstrate that comprehensive assessment of biallelic mutation status is essential when elucidating PD risk associated with monoallelic *PRKN* mutations.

INTRODUCTION

Parkinson's (PD) is a multifactorial neurodegenerative disease. Common variation within 78 independent loci increase PD risk (1). Pathogenic mutations in autosomal dominant genes (*LRRK2*, *SNCA* and *VPS35*) as well as biallelic mutations in autosomal recessive (AR) genes (*PRKN*, *DJ-1*, *PINK1* and *FBXO7*) cause Mendelian PD (2). It has been suggested that single heterozygous pathogenic AR mutations can increase the risk of PD, and several lines of evidence have been provided for and against mutations (reviewed in Klein *et al.*, 2007) (3). Previous studies may have been confounded by differences in methods for mutation detection in cases and controls. Biallelic AR mutations in PD genes are rare in PD cases, but single heterozygous mutations in specific AR PD genes are more common and are estimated, depending on the population, to occur in between 0.6% and 3% of unaffected control individuals (4–7). Accurate estimation of any risk associated with single heterozygous AR mutations is therefore essential for the counselling of biallelic carriers, monoallelic carriers and their family members. Furthermore, understanding the risk associated with single AR mutations may provide important insights into disease biology. Here, we investigate whether single carriers of disease-causing *PRKN* mutations are at an increased risk for PD using three large independent case-control cohorts using exome-focused genotype data, whole exome sequencing and resequencing data from the International Parkinson's Disease Genomics Consortium (IPDGC).

RESULTS

We identified a total of 109 monoallelic *PRKN* mutation carriers in 12,251 PD cases and controls (72 PD, 37 controls), carrying 19 different *PRKN* variants known to cause AR PD in the biallelic state, using the NeuroX genotyping platform (8). It is possible that the identified PD cases represent misclassified true biallelic *PRKN* PD cases. To confirm whether PD cases

carry a single pathogenic allele or whether a second variant was missed, we (i) reviewed diagnostic reports if available (n=4), or (ii) assessed available samples using multiplex ligation-dependent probe amplification (MLPA, n=29). Of the 33 available NeuroX samples, representing ~30% of our putative monoallelic individuals (5 controls, 13.5%; 28 PD-Monoallelic, 38.9%), six cases (18% of the available samples, 21% of available PD cases) were found to harbour a second mutation and therefore were removed, leaving a total of 66 PD cases for all subsequent analyses (no controls were found to harbour a second mutation).

After removal of cases with established Mendelian mutations across all known PD genes, 1.0% (66/6,552) of PD cases were found to harbour single heterozygous *PRKN* PD-causing mutations (either heterozygous copy number variants [CNVs] or single nucleotide variants [SNVs], Table 1), compared to 0.6% (37/5,693) of controls. Single heterozygote mutations might increase PD risk (OR=1.55; 95% CI:1.03, 2.33; P=0.035), although ~70% of putative monogenic cases were not assessed for a second mutation. Although speculative, if the remaining apparent monoallelic cases had a similar rate of occult biallelic mutations, then the true underlying monoallelic carrier rate could be estimated to be lower at 0.9%, and there would be no difference between cases and controls (OR=1.39; 95% CI:0.90, 2.16; P=0.117). Using age at onset (AAO) data from 5,710 (87.1%) cases, we found that NeuroX PD cases with single *PRKN* mutations have significantly lower AAOs (Average=56.4 years) than cases without known mutations (Average=61.4 years; Coeff=-5.04; 95% CI:-8.32, -1.71; P=0.003).

We next sought to explore the potential increased risk in two independent IPDGC case-control cohorts, using exome sequencing (cases=1,235; controls=473) (8) and resequencing data (cases=3,071; controls=2,162). We identified 28 (23 cases, 5 controls) and 52 (36 cases, 16 controls) carriers of single *PRKN* mutations in the exome (as previously described (8)) and resequencing data respectively. CNVs were not determined in the primary exome or resequencing dataset. In the exome cohort, 1.9% (23/1,231) of cases and 1.1% (5/473) of

controls, and in the resequencing cohort, 1.2% (36/3,071) of cases and 0.7% (16/2,162) of controls harboured single *PRKN* SNVs. Before searching for occult second mutations, a meta-analysis of the three IPDGC (NeuroX, exome sequencing and resequencing) cohorts revealed a significant ~1.5-fold increased risk (OR=1.57; 95% CI:1.15, 2.16; P=0.005; I^2=0.0%, P_{het}=0.960) associated with *PRKN* mutations (Figure 1). AAO data was available on 1,130 PD exome cases (91.8%) and 2,599 resequencing cases (84.6%). Albeit non-significant, exome PD cases carrying single *PRKN* SNVs had lower AAO compared to non-carriers (Average=38.5 years *vs*. 43.1 years; Coeff=-4.34; 95% CI:-8.95, 0.28; P=0.066), with carriers having significantly lower AAO in resequencing cases (Average=52.6 years *vs*. 60.5 years; Coeff=--7.84; 95% CI:-12.59, -3.09; P=0.001). We then used MLPA to search for potentially missed *PRKN* CNVs in mutation carriers. Four of the nine available exome DNA samples (44%, all PD cases) were found to harbour a missed second mutation and were removed from subsequent analyses. Assuming a similar rate of occult biallelic carriage across both datasets, the true rate of monoallelic cases could be estimated to be 1.2% and 0.7% in the exome and resequencing cases as compared with 1.1% and 0.7% of controls, respectively.

We next performed a meta-analysis of available cohorts and studies that reported heterozygous PD-causing mutation rates in cases and controls, from European ancestry cohorts only. Three cohorts (Parkinson's Progression Markers Initiative, PPMI, https://www.ppmi-info.org/; UK Biobank Genotyping and Exome cohorts, https://www.ukbiobank.ac.uk/) and 21 published studies were included in our analyses (5, 6, 17–26, 9, 27, 10–16). Including our cohorts, the meta-analysis revealed a significant 1.65-fold increased PD risk in single *PRKN* mutation carriers (95% CI: 1.36, 2.00; P=3.69E-07; I^2=0.0%, P_{het}=0.594) (Figure 2).

As in our study, occult second mutations are likely biasing these estimates, so we therefore restricted our meta-analysis to 9 studies (9/21, 43%) that searched for a second *PRKN*

mutation (Table 2). Based on these studies, single *PRKN* mutations confer a 2-fold increase in PD risk in carriers (OR=2.00, 95% CI:1.10, 3.62, P=0.023; I^2=1.3%, P_{het}=0.423) (Supplementary Figure 1).

Inclusion of studies that used predominantly early-onset PD (EOPD) cases may additionally be inflating these estimates, we therefore repeated the meta-analysis excluding these EOPD studies (15/21, 71%), which demonstrated a 1.5-fold significant increased risk in carriers (OR=1.50, 95% CI:1.22, 1.84; P=1.05E-04; I^2=0%, P_{het}=0.927) (Supplementary Figure 2).

Restricting our analysis to the four non-EOPD studies that searched for biallelic carriers demonstrated that single *PRKN* mutations were not associated with an increased PD risk in these cohorts (OR=1.23, 95% CI:0.55, 2.75, P=0.614; I^2=0.0%, P_{het}=0.657; Supplementary Figure 3).

The pathogenicity of the common *PRKN* p.R275W variant in AR PD is not as clear cut as other *PRKN* mutations. To test whether the observed SNV association is driven by p.R275W, we repeated the meta-analysis after excluding this variant. Removal of p.R275W resulted in a marginally increased estimate (OR=1.76, 95% CI:1.37, 2.28, P=1.42E-05; I^2=0.0%, P_{het}=0.673; Supplementary Table 1; Supplementary Figure 4). Limiting our analysis to the 8 cohorts which assessed biallelic mutations indicated a >2-fold increased risk (OR=2.41, 95% CI:1.17, 4.96, P=0.017; I^2=0.0%, P_{het}=0.791) (Supplementary Figure 5).

The contribution of biallelic *PRKN* CNVs to AR PD is well established; however, that of heterozygous CNV carriers remains unclear. We identified monoallelic *PRKN* CNVs in 0.17% (11/6,552) of non-Mendelian PD cases compared to 0.07% (4/5,693) controls (Table 1) using the NeuroX data only. None of these CNV carriers overlapped with NeuroX SNV carriers. There was a >2.5-fold increase in PD risk for *PRKN* CNV heterozygote carriers compared to controls (OR=2.53; 95% CI:0.80, 7.99; P=0.113) but this was not statistically significant.

It has been suggested that monoallelic *PRKN* CNVs might confer a higher risk that is associated with a more pathogenic profile compared to other AR mutations (28). To assess this, we compared differences in risk between CNV and SNVs carriers in the NeuroX cohort. A total of 55 *PRKN* SNV carriers were seen in non-Mendelian PD cases (55/6,552; 0.8%) compared to 33 controls (33/5,693; 0.6%) (OR=1.43; 95% CI:0.92, 2.21; P=0.108) (Table 1). To test whether *PRKN* CNVs confer a more "pathogenic" risk profile compared to SNVs we performed AAO analysis in the NeuroX data only. Carriers of heterozygous *PRKN* CNVs had a mean AAO of 58.4 years, compared to non-carriers (61.4 years) (Coeff=-3.11; 95% CI:-11.15, 4.93; P=0.449).

To further investigate the potential different risk profiles, we performed separate meta-analyses of published *PRKN* mutation data for SNVs and CNVs. Meta-analyses, including the current data, revealed significant independent increased PD risks for SNVs (OR=1.56, 95% CI:1.22, 2.00, P=4.46E-04; I^2=0%, P_{het}=0.968) and CNVs (OR=1.85, 95% CI:1.38, 2.50, P=4.55E-05; I^2=0.0%, P_{het}=0.640) (Figure 3; Supplementary Table 2). Restricting our meta-analysis to studies that searched for second hits suggested that PD risk was larger in carriers of single *PRKN* CNVs (OR=3.11, 95% CI:1.23, 7.89, P=0.016; I^2=0.0%, P_{het}=0.879) compared to those harbouring heterozygous SNVs (OR=1.59, 95% CI:0.79, 3.20, P=0.191; I^2=0.0%, P_{het}=0.785).

DISCUSSION

The role of rare biallelic mutations in *PRKN* in AR PD (MIM#600116) is well established. Here, using data from a large PD case-control cohort, we identified a total of 109 carriers of single heterozygous *PRKN* mutations. After exclusion of PD cases with known mutations, we demonstrated that carriers of single mutations were at a small but significantly increased risk of PD (OR=1.55; 95% CI:1.03, 2.33; P=0.035). This was confirmed by a meta-analysis with

two additional IPDGC cohorts (cases=10,954; controls=8,328) which demonstrated a significant >1.5-fold increased risk (P=0.005). Carriers also had significantly lower AAOs than non-carriers (56.4 years *vs*. 61.4 years; P=0.003). Similar findings were seen in the exome and resequencing data for increased risk (Exome, OR=2.20; Resequencing, OR=1.59) and younger AAOs compared to non-carriers (Exome, 38.5 years *vs*. 43.1 years; Resequencing, 52.6 years *vs*. 60.5 years). A meta-analysis of 19,574 PD cases and 468,488 controls from 27 cohorts further confirmed that heterozygous *PRKN* mutations confer an increased PD risk (OR=1.65; P=3.69E-07). However, several confounding factors are likely biasing these estimates in favour of increased risk and are explored below. Large-scale studies in systematically recruited cohorts that have comprehensively interrogated biallelic *PRKN* mutations are therefore needed to accurately determine the risk associated with single mutations.

The relatively common p.R275W (c.823C>T, rs34424986) variant, the most frequent PD-associated variant in *PRKN*, has not been reported in the homozygous state and has only been reported in compound heterozygotes with another mutation in multiple AR PD families (MIM#602544), and has been classified as likely pathogenic. p.R275W reduces protein stability by disrupting binding to phosphorylated ubiquitin and results in reduced Parkin levels (29) supporting the pathogenicity of p.R275W. We examined whether the increased PD risk associated with single *PRKN* variants was driven by this variant. The observation that the OR increases after removal suggests that p.R275W may have reduced effect on enzyme activity compared to other mutations, and that, due to its more common frequency, its presence may be diluting the true effect of heterozygous *PRKN* mutations in PD biology.

Our analysis provides some support for a more “pathogenic” risk profile associated with *PRKN* CNVs as compared with SNVs (CNVs, OR=2.53; SNVs, OR=1.43) in the NeuroX data. Both mutation types appear to be associated with lower AAOs; however, the small

number of observed CNVs prevents any definitive conclusions from being drawn. While the meta-analysis results here support the increased risk for *PRKN* CNV carriers (OR=1.85), albeit marginally higher than *PRKN* SNVs (OR=1.56), the increased risk associated with *PRKN* CNVs should be interpreted with care. Small sample sizes, low CNV frequency and failure to investigate/report CNVs may have resulted in an underestimated effect size seen in the meta-analysis. Failure to conclusively look for second *PRKN* hits may also be a potential confounder when trying to estimate the risk associated with single *PRKN* mutations. Additional work in larger cohorts where both *PRKN* SNVs and CNVs are routinely assessed is therefore needed to gain more accurate insight into the different risk profiles associated with different mutation types.

This large study builds on previous work looking at single *PRKN* mutations in PD aetiology. While several failed to identify single known pathogenic *PRKN* mutations in controls thereby supporting increased disease risk, others have found equal frequencies in both cases and controls providing evidence against increased risk (4, 7, 13, 17, 18, 30–32). These estimates have, however, been based on relatively small sample sets which have made it difficult to conclusively determine if single mutations confer any risk. The inclusion of non-ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) variants represents a potential confounder in that we may be overestimating the frequency of disease relevant single *PRKN* mutations. Limiting our analyses to ClinVar variants only did not result in considerably different risk estimates across all comparisons (All studies, OR=1.70, P=2.65E-07; Biallelic studies, OR=1.99, P=0.036; non-EOPD studies, OR=1.55, P=5.6E-05). Another confounder relates to the fact that we observed a significant rate of occult second pathogenic mutations in putative monoallelic cases in our NeuroX cohort. The detected rate of occult biallelic carrier status was high in our two datasets (6/28, 21% and 4/9, 44%), approaching one half of PD cases with apparent monoallelic status. Additionally, several studies included in the analyses here

have not searched for potentially hidden biallelic mutations in all cases and controls or have only interrogated a subset of *PRKN* mutations. Inclusion of these PD cases in our analysis is likely to appreciably influence our estimate. However, restricting the meta-analyses to 9 cohorts that searched for biallelic *PRKN* mutations in all cases and controls demonstrated that single mutations confer a 2-fold increase in risk in carriers. A further confounding factor is the use of EOPD cases (<50 years) in such studies which may be additionally inflating risk estimates as *PRKN* mutations are more likely to occur in PD cases of younger onset. This was observed in the IPDGC cohorts, with a higher estimate in the exome cohort compared to the NeuroX and resequencing cohorts. The additional removal of predominantly EOPD studies resulted in the loss of the original association (OR=1.23; P=0.614) but this was based on a few small studies (n=4). This suggests that current estimates of the effect of single mutations in modulating PD risk may not be accurate, but also stresses the importance of comprehensively searching for biallelic mutations in systematically recruited cohorts. It remains possible that there are further "occult" coding variants of unknown significance or non-coding mutations affecting the promotor or splicing that have not yet been identified.

There are some limitations to our study. NeuroX biallelic and monoallelic cases will have been missed as not all possible PD-causing variants are represented on the chip with only 16.8% of studied pathogenic variants present (33) (Supplementary Table 3). The same applies to the detection of biallelic carriers in the UK Biobank genotyping cohort. Identifying *PRKN* CNVs from NeuroX SNP genotype data using PennCNV may have missed smaller deletions/duplications. The false positive rate of PennCNV as a method for CNV detection was estimated to be 9.0-17.7%, with false positive CNVs predominantly small in size and occurring regardless of genotyping chip used (34). Our CNV detection false-positive rate in the NeuroX cohort is 6.9%. However, the fact that (i) the NeuroX variants are not evenly distributed across the *PRKN* locus (accounts for four misclassified samples), and (ii) we were

looking for CNVs as small as a single exon, may have resulted in our approach missing or inaccurately calling CNVs in our large cohort comprising predominantly late-onset PD cases. There are limitations in defining CNVs from IPDGC and UK Biobank exome data, so CNVs were only investigated using MLPA in identified PD-Monoallelic exome cases. As the exome cohort predominantly consists of EOPD cases, it is likely that additional *PRKN* CNVs carriers were undetected. We therefore sought to validate the monoallelic status of available carriers by accessing diagnostic reports or directly assessing CNVs using MLPA and discovered a high rate of undetected second hits in both our datasets. Previous studies which have not systematically searched for second hits may have therefore erroneously determined the monoallelic carrier rate meaning that the estimates derived from our in-house cohorts and other published meta-analyses may not be accurate. It is therefore very important that any proposed increased risk associated with single *PRKN* mutations be considered with caution as, based on findings presented here, a substantial part of the reported excess on monoallelic carriers may relate to occult biallelic status.

Across autosomal recessive diseases there is a great deal of interest in the potential role of single heterozygous mutations as risk factors for disease. Heterozygous *PINK1* mutations in PD (35) and *MUTYH* mutations in colorectal cancer (36) do not confer an increased risk of PD or cancer respectively. However, single autosomal recessive mutations may increase the risk of related, but separate conditions from the prototypic recessive disease. Single *CFTR* mutation carriers are more susceptible to cystic fibrosis related conditions (37) and monoallelic *ATM* mutation carriers have higher risks for cancers and ischemic heart disease – especially breast cancer in female carriers. This current study highlights the importance of ensuring that all potential confounders are taken into consideration when assessing single mutations as any unaccounted for biases would generate inaccurate risk estimates and have significant repercussions on counselling of patients and their family members.

In conclusion, while much of the data demonstrates that harbouring a single heterozygous *PRKN* mutation increases PD risk and that single *PRKN* CNVs may be more pathogenic than *PRKN* SNVs, there may be confounding factors. This is supported by our finding of no increased risk associated with single *PRKN* mutations upon restricting our analysis to studies that assessed biallelic mutations in cases and controls, and studies that did not include predominantly EOPD cases. Before the risk associated with single heterozygous mutations can be accurately defined, we highlight the importance of assessing 'second hits' in all cases and controls where both SNVs and CNVs are systematically interrogated in large-scale cohorts that have been systematically recruited.

MATERIALS AND METHODS

High-quality genotype data from the NeuroX chip on 6,558 PD cases and 5,693 controls was assessed as part of the IPDGC (dbGaP Study Accession number: phs000918.v1.p1) (see Supplementary Table 4 for full list of *PRKN* variants captured). Sample collection and variant genotyping have been described elsewhere (33). IPDGC exome sequencing data from 1,235 PD cases and 473 controls were used as a replication cohort (EGA Study Accession numbers: EGAS00001002103, EGAS00001002110, EGAS00001002113, EGAS00001002156; dbGaP Study Accession number: phs001103.v1.p1), and is described elsewhere (8). Additional replication cohorts used include: IPDGC resequencing cohort (cases=3,071, controls=2,162), UK Biobank Genotyping (cases=1,428, controls=312,098; downloaded April 2018, under application number 33601) and UK Biobank exome sequencing (cases=114, controls=38,263; downloaded May 2019) cohorts and the PPMI Exome sequencing *de novo* cohort (cases=385, controls=179). The IPDGC resequencing cohort (PD: 54.8% male, average AAO=63.8 years; controls: 44.8% male, average age at recruitment =60.4 years) targeted sequencing genetic data covering PD-associated genes (including *ATP13A2, FBXO7, GBA, LRRK2, MAPT,*

PARK7 (DJ-1), PINK1, PLA2G6, PRKN, SNCA, and VPS35) (35, 38). Duplicate samples were removed, where possible, from all analyses. Samples with missing call rates >5% were excluded during quality control. Variants (excluding synonymous) from known Mendelian PD-causing genes were extracted. Pathogenic mutations were identified as previously described (8). Rare *PRKN* (NM_013988 and NM_004562) CNVs were identified in the NeuroX cohort using PennCNV (34). CNVs spanning a minimum of ten variants were selected and visually confirmed. Monoallelic PD cases were defined as those carrying a single heterozygous pathogenic *PRKN* allele as defined according to OMIM (http://omim.org/), the Movement Disorder Society Genetic mutation database (https://www.mdsgene.org/) or the Parkinson Disease Mutation Database (http://www.molgen.vib-ua.be/PDMutDB/) (Supplementary Table 4). Where available, samples were investigated by (i) accessing sample diagnostic records, or (ii) using MLPA (SALSA P051 v.D1 probe mix [MRC-Holland, The Netherlands]) to confirm their monoallelic status. Without phasing information, any two PD-causing hits identified in an individual are assumed to be in trans.

To assess whether PD risk might be associated with (i) all monoallelic variants, (ii) CNVs alone or (iii) SNVs alone, as indicated by case-control differences, we used logistic regression correcting for gender and principal components (C1-4). Linear regression was used to investigate the impact of single AR mutations on AAO.

A literature review was undertaken (on 01/10/2019) to identify published data on heterozygous *PRKN* mutations, using search terms including combinations of the following terms: Parkinson's disease, PD, *Parkin, PARK2* and heterozygous. Additional studies were identified by manual search of references cited in published articles. Should any of the studies include previously published data, the most recent data was selected where possible. Meta-analysis was conducted using standard methods modelling fixed effects, using

Cochran's Q-statistic to test for heterogeneity (P_{het}) (39) and the I^2 statistic (40) to quantify the proportion of the total variation caused by heterogeneity relating to possible differences in sample recruitment and assessment between studies. Meta-analyses were performed for CNVs and SNVs separately to investigate potential different risk profiles for each mutation type.

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CONFLICT OF INTEREST STATEMENT

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LEGENDS TO FIGURES

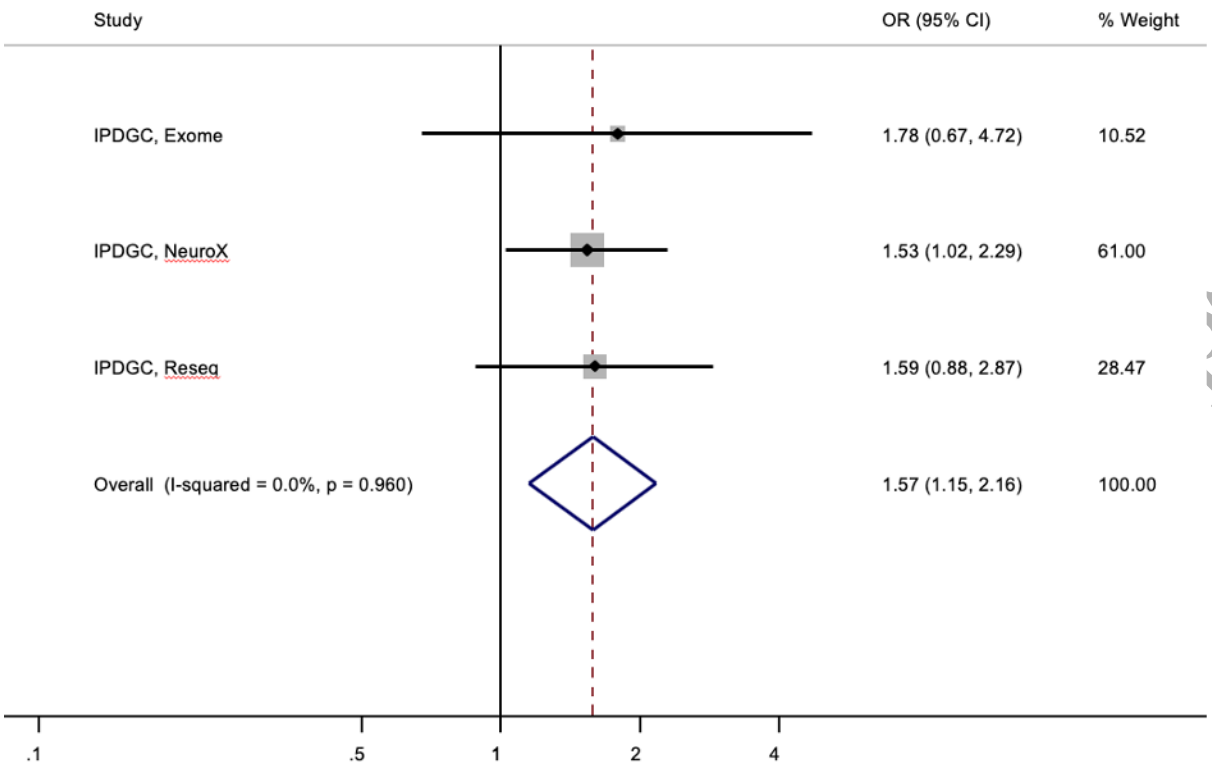

Figure 1: Forest plot of the odds ratio (OR) of the Parkinson's risk associated with heterozygous *PRKN* mutations in three independent International Parkinson's disease Genomics Consortium (IPDGC) cohorts.

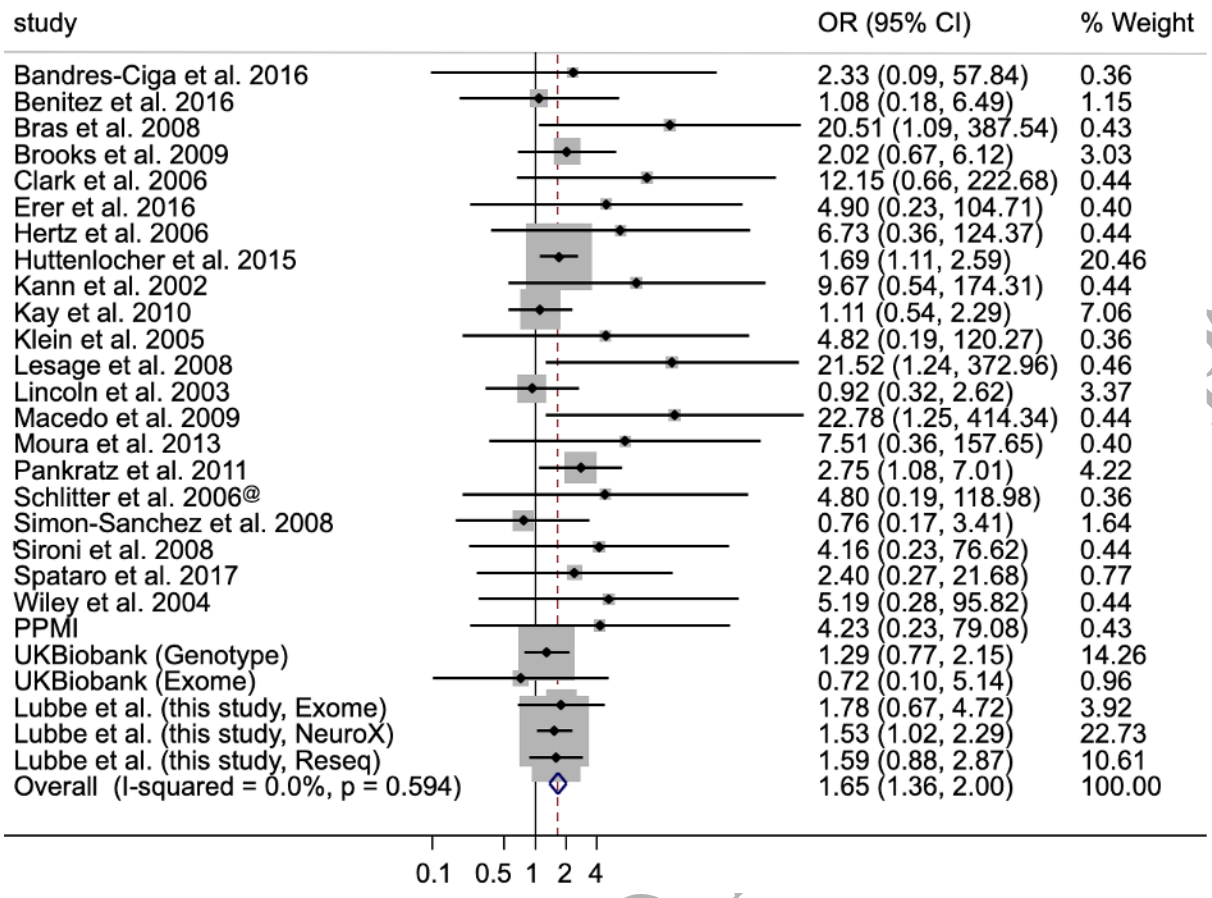

Figure 2: Forest plot of the odds ratio (OR) of the Parkinson's risk associated with heterozygous *PRKN* mutations.

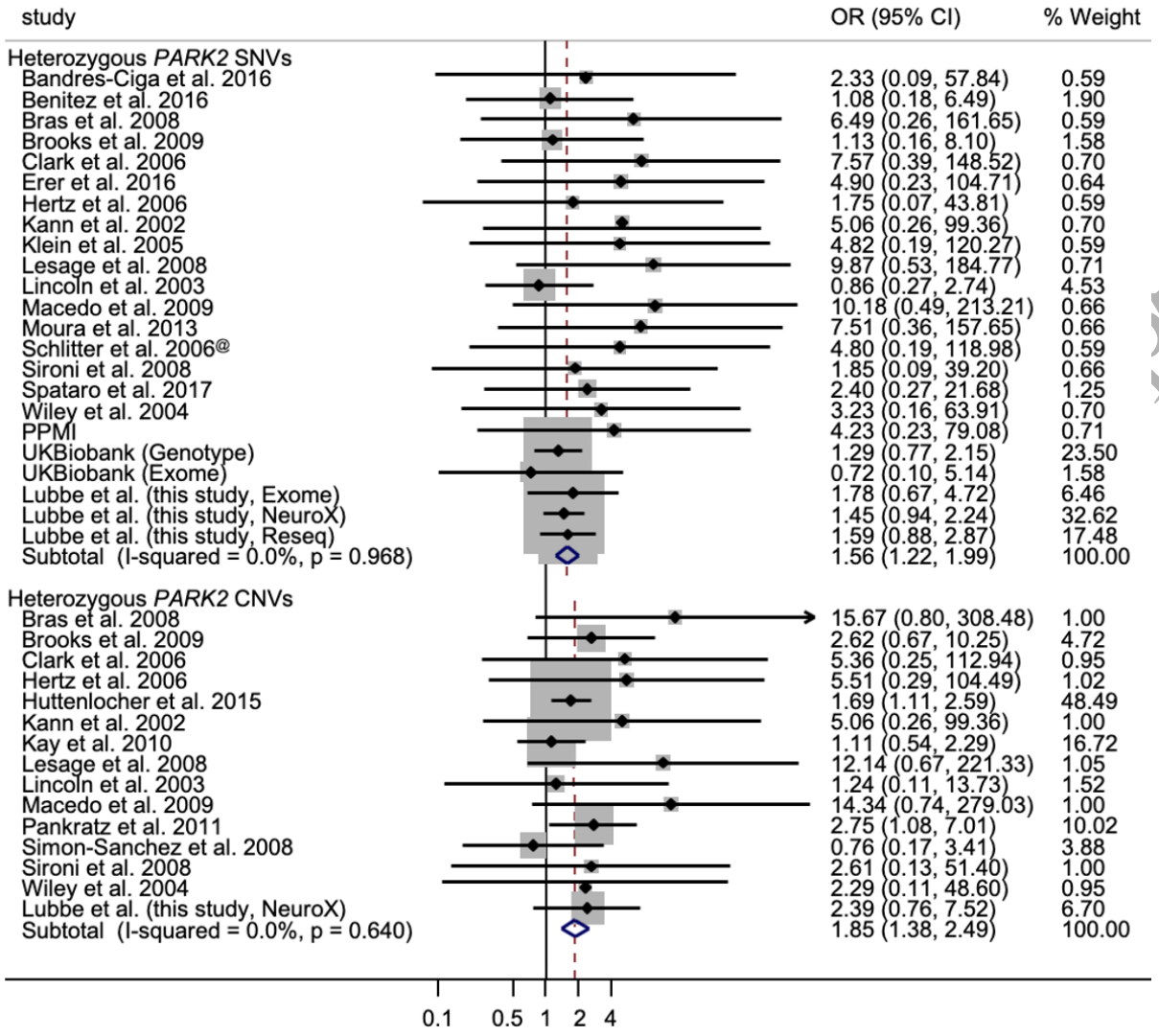

Figure 3: Forest plot of the odds ratio (OR) of the Parkinson's risk associated with heterozygous *PRKN* single nucleotide variant (SNV) and copy number variant (CNV) carriers.

TABLES

Table 1: NeuroX Parkinson's risk profiles associated with single heterozygous *PRKN* mutations.

Type	N (Freq)		OR (95% CI)	P_{log}	AAO	Coeff (95% CI)	P_{reg}
	Controls	PD			(with data)		
All							

With	37 (0.6%)	66 (1.0%)	1.55 (1.03, 2.32)	0.035	56.4 (86.4%)	-5.04 (-8.34, -1.75)	0.003
Without	5,656	6,486			61.4 (87.2%)		
CNV							
With	4 (0.1%)	11 (0.2%)	2.53 (0.80, 7.99)	0.113	58.4 (90.0%)	-3.11 (-11.15, 4.93)	0.449
Without	5,689	6,541			61.4 (87.2%)		
SNV							
With	33 (0.6%)	55 (0.8%)	1.43 (0.92, 2.21)	0.108	56.0 (85.5%)	-5.41 (-9.02, -1.81)	0.003
Without	5,660	6,497			61.4 (87.2%)		

Key: AAO, age at onset; CI, confidence interval; CNV, copy number variant; Coeff, linear regression coefficient correcting for gender and principal components 1-4; Freq, frequency; N, number of samples; OR, odds ratio correcting for gender and principal components 1-4; *PRKN*, *Parkin* (NM_013988 and NM_004562); PD, Parkinson's cases; SNV, single nucleotide variant.

Table 2: Meta-analyses of heterozygous *PRKN* mutation carriers in studies that investigated and excluded PD patients with biallelic *PRKN* mutations.

Study	PD		Controls		OR (95% CI)
	Carrier	Non-carrier	Carrier	Non-carrier	
Benitez et al. 2016	3	466	2	335	1.08 (0.18-6.49)
Brooks et al. 2009	9	241	5	271	2.02 (0.67-6.12)
Clark et al. 2006	5	95	0	105	12.15 (0.66-222.68)
Hertz et al. 2006	5	82	0	50	6.73 (0.37-124.37)
Klein et al. 2005	1	62	0	100	4.82 (0.19-120.27)
Lesage et al. 2008	9	150	0	170	21.35 (1.24-372.96)
Lincoln et al. 2003	9	304	6	186	0.92 (0.32-2.62)
Spataro et al. 2017	4	240	1	144	2.40 (0.27-21.68)
Wiley et al. 2004	5	96	0	45	5.19 (0.28-95.82)
Pooled	**50**	**1,736**	**9**	**1,406**	**2.00 (1.10-3.62)**

Key: Carrier, number of samples harbouring mutation, CI, confidence intervals; OR, odds ratio; *PRKN*, *Parkin* (NM_013988 and NM_004562); PD, Parkinson's cases.

ABBREVIATIONS

%	Percent
AAO	Age at onset
AR	Autosomal recessive
c.	coding DNA reference sequence
C1-4	Principal component 1 to 4
CI	Confidence interval
CNV	Copy number variant
Coeff	β-Coefficient
dbGaP	Database of Genotypes and Phenotypes
DNA	Deoxyribonucleic acid
EGA	European Genome-phenome Archive
EOPD	Early-onset Parkinson's
FBXO7	F-box protein 7
Freq	Frequency
I^2	Proportion of total variation caused by heterogeneity
IPDGC	International Parkinson's Disease Genomics Consortium
LRRK2	Leucine-rich repeat kinase 2
MLPA	Multiplex ligation-dependent probe amplification
MRC-Holland	Microbiology Research Centre Holland
N	Number
NM_*	Messenger RNA sequence identifier
OMIM	Online Mendelian Inheritance in Man
OR	Odds ratio

P	P-value
p.	protein reference sequence
PARK7	Parkinsonism associated deglycase or *DJ-1*
PD	Parkinson's
PD-Monoallelic	Parkinson's cases harbouring a single heterozygous *PARK2* mutation
P_{het}	Cochran's Q-statistic test for heterogeneity P-value
PINK1	PTEN-Induced putative kinase 1
P_{log}	Logistic regression P-value
PPMI	Parkinson's Progression Markers Initiative
P_{reg}	Linear regression P-value
PRKN	Parkin
Reseq	Resequencing
SNCA	α-Synuclein
SNV	Single nucleotide variant
VPS35	Vacuolar protein sorting 35, yeast, homolog of
vs.	Versus