Published in final edited form as:

Neurobiol Aging. 2019 February ; 74: 236.e1–236.e5. doi:10.1016/j.neurobiolaging.2018.09.022.

No evidence for *DNM3* as genetic modifier of age at onset in idiopathic Parkinson's disease

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Abstract

Parkinson´s disease (PD) is a disorder with highly variable clinical phenotype. The identification of genetic variants modifying age at onset and other traits is of great interest, since it may provide insight into disease mechanisms and potential therapeutic targets. A variant in the *DNM3* gene (rs2421947) has been reported as a genetic modifier of age at onset in *LRRK2-associated* PD. To test the possible effect of genetic variation in *DNM3* on age at onset in idiopathic PD, we examined rs2421947 in a total of 5918 PD patients from seven datasets. We also assessed the potential effect of all common variants in the *DNM3* locus. There was no significant association between rs2421947 and age at onset in any of the individual studies. Meta-analysis of the seven studies was non-significant and the between-study heterogeneity was minimal. No other common variants within the *DNM3* locus affected age at onset. In conclusion, we find no evidence of an association between *DNM3* variants and age at onset in idiopathic PD.

Keywords

Parkinson's disease; age at onset; *DNM3*

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder with a complex etiology. A small proportion of PD patients have a monogenic form of the disease with highly penetrant mutations following an autosomal dominant or recessive inheritance pattern. However, the majority of PD cases are idiopathic, presumably caused by the combined

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Disclosure statement: The authors report no conflicts of interest concerning the research related to the manuscript.

action of multiple genetic variants in interplay with epigenetic, environmental and stochastic factors (Lill, 2016). To date, genome-wide association studies (GWASs) have linked more than 40 risk loci to PD susceptibility (Chang et al., 2017).

In addition to affecting the risk of disease development, genetic variants may also affect the clinical phenotype once the disease has manifested. The clinical heterogeneity of PD is characterized by a marked variation in the pattern and progression of motor-, cognitive- and other non-motor symptoms. Both rare monogenic mutations and common genetic variants have been shown to contribute to the clinical heterogeneity of PD (Pihlstrom et al., 2016; Puschmann, 2013; Winder- Rhodes et al., 2013).

There is a broad range of age at onset in PD, varying between debut in early adulthood to patients reaching the 8th and 9th decade of life before onset of motor symptoms. Several studies have investigated the effect of PD risk loci on onset age. Cumulative genetic risk scores calculated across PD risk loci have been shown to have a small, but consistent, effect on age at onset (Escott-Price et al., 2015; Lill et al., 2015; Nalls et al., 2015; Pihlstrom and Toft, 2015). In addition, risk loci having the greatest effect in PD GWAS meta-analysis *(GBA, SNCA, MAPT* and *TMEM175)* (Nalls et al., 2014) are reported to individually be associated with age at onset (Brockmann et al., 2013; Davis et al., 2016; Lill et al., 2015; Nalls et al., 2015).

Linking common variation to age at onset represents an interesting step toward a better understanding of how genetics affect PD phenotype. In a recent genome-wide study of genetic modifiers of age at onset in leucine-rich repeat kinase 2 (LRRK2) p.G2019S carriers, a *DNM3* haplotype tagged by rs2421947 was identified (Trinh et al., 2016). This *LRRK2* mutation is the most frequent genetic cause of PD in many populations, estimated to have a frequency of 1% in white North American and as high as 39% in North African Arab patients (Healy et al., 2008).

LRRK2 mutations cause an autosomal dominant form of PD often segregating in families, while GWASs provide consistent evidence that common variation at this locus also modulates disease risk. Since *LRRK2* is part of the genetic background for idiopathic PD, variants that modulate age at onset in *LRRK2* parkinsonism may also exert an effect in a much wider group of patients. Herein we report analyses of data from seven studies of PD from Europe and North America to determine associations between the *DNM3* rs2421947 variant and age at onset of idiopathic PD. To study the potential effect of other *DNM3* variants, we also performed a complete assessment of common variation in the gene locus.

2. Methods

2.1 Study populations

We analyzed individual-level genotypes from seven different datasets. Samples originated from genetic studies of PD from Oslo University Hospital and Mayo Clinic Jacksonville. The remaining five datasets were publicly available and selected due to available individual genotype information in PD patients with a reported age at onset. The following four datasets were accessed from dbGaP: 1) CIDR: Genome Wide Association Study in Familial

Parkinson Disease (Accession number: phs000126.v1.p1), 2) Mayo-Perlegen LEAPS (Linked Efforts to Accelerate Parkinson's Solutions) Collaboration (Accession number: phs000048.v1.p1), 3) National Institute of Neurological Disorders and Stroke (NINDS) Genome-Wide genotyping in Parkinson's Disease (Accession number: phs000089.v3.p2), 4) Genome-Wide Association Study of Parkinson Disease: Genes and Environment performed by The NeuroGenetics Research Consortium (NGRC) (Accession number: phs000196.v2.p1). The last dataset is made available by the Parkinson's Progression Markers Initiative (PPMI, http://www.ppmi-info.org).

All patients have been examined by a neurologist. The Oslo and Mayo Clinic patients were diagnosed according to the revised UKPDSBB criteria. A detailed description of inclusion criteria for the other studies have previously been described (Hamza et al., 2010; Maraganore et al., 2005; Nalls et al., 2016; Pankratz et al., 2009; Simon-Sanchez et al., 2009). Age at onset is either reported as age at symptom onset or age at diagnosis. In the current analysis, PD patients reporting other than Caucasian non-Hispanic ethnicity have been excluded along with LRRK2 p.G2019S carriers that were identified by imputation or had previously been genotyped. A large subset of the Oslo and Mayo Clinic patients was sequenced for genes causing Mendelian forms of PD and mutation carriers were excluded from the analysis. Also, no known carriers of Mendelian PD mutations in the publicly available datasets were included in the analysis. Demographic characteristics are summarized in Table 1. All participants gave written, informed consent. Sample and data collection at each study site was approved by local ethics committees. The study was approved by the Regional Committee for Medical Research Ethics (Oslo, Norway).

2.2 Genotyping and quality control

Mayo Clinic patients were genotyped for rs2421947 using a Taqman assay. A subset of genotypes was validated by Sanger sequencing with complete concordance. For the other studies genome-wide genotypes were available. Oslo samples were genotyped using the Illumina Infinium OmniExpress v.1.1 array. Pre-imputation quality filtering included filtering out variants with genotype rate < 0.95 or Hardy-Weinberg equilibrium $p<10^{-6}$ and removal of individuals with call rate < 0.95, excess heterozygosity > 4 standard deviations (SD) from mean, evidence of cryptic relatedness or sex-check failure. Population outliers were excluded from analysis after inspection of principal component analysis plot (> 2.5 SD from mean). Details of genotyping methods and data quality assessments for the publicly available GWASs and the PPMI study are described in previous publications (Hamza et al., 2010; Maraganore et al., 2005; Nalls et al., 2016; Pankratz et al., 2009; Simon-Sanchez et al., 2009).

Common, pruned, genotyped variants (minor allele frequency > 0.05 and $r^2 < 0.5$) were used to calculate principal components for each of the six genome-wide datasets. For all genome-wide datasets, imputation was performed using the Michigan imputation server (Das et al., 2016) with reference data from the Haplotype Reference Consortium (McCarthy et al., 2016) setting a quality cutoff of $r^2>0.3$ for variants included in the analysis. A set of common, pruned variants from each imputed dataset was merged to assess cryptic

relatedness across studies. Duplicates and related samples were removed. The final sample sets included in analysis after quality control comprise a total of 5918 PD patients (Table 1).

2.3 Statistical analyzes

First we tested all seven studies individually for association between the *DNM3* rs2421947 variant and age at onset under an additive linear regression model. In an alternative binary analysis, age at onset was dichotomized by the median onset calculated across all seven datasets (61 years of age) and logistic regression was used to test for association with the *DNM3* rs2421947 variant within each dataset. In both regression analyses, sex and the first five principal components were used as covariates in the genome-wide datasets, while sex was the single covariate in analysis of the Mayo Clinic study. Association analyses were performed in PLINK (https://www.cog-genomics.org/plink/1.9/) (Chang et al., 2015). Inverse-variance, fixed-effects meta-analysis of the seven studies was conducted using GWAMA (Magi and Morris, 2010). Between-study heterogeneity was assessed using Cochran's Q test and Higgins's I statistic. Due to the increased burden of recessive disease-causing mutations in early-onset PD (Puschmann, 2013), we repeated the linear regression analysis excluding all patients with an age at onset < 40 years of age.

Next, common variation within *DNM3* as well as 100kb upstream and downstream of the gene was analyzed by linear regression in the six genome-wide datasets. Variants with a minor allele frequency below 0.01 in each dataset were excluded from analysis. Association analysis, both within the individual datasets and meta-analysis were performed as described for *DNM3* rs2421947. To estimate the degree of multiple testing, we generated a combined, pruned dataset using a cutoff of LD > r^2=0.5, leaving 226 independent variants. Adjusting for 226 independent tests by Bonferroni correction, a p-value < 0.0002 was considered significant. Power calculations were performed with the function pwr.f2.test in the R package pwr (version 1.2–1; https://cran.r-project.org/web/packages/pwr/index.html).

3. Results

We found no significant association between rs2421947 and age at onset in any of the individual studies, both when analyzed as a quantitative trait and in the alternative binary analysis. The frequency of the alternative allele G of rs2421947 was similar in all the seven studies, varying between 54% and 56%. Meta-analysis of the seven studies analyzed as a quantitative trait was non-significant (p = 0.55) and the between-study heterogeneity was minimal (I^2= 0%, p=0.77). Results from linear regression analysis of the individual studies and meta-analysis are shown in Figure 1. We obtained similar results when we excluded patients with an age at onset < 40 years from the analysis. Meta-analysis of age at onset as a binary trait was also nonsignificant (OR=1.03, 95% CI=0.96 – 1.11, p=0.44) and between-study heterogeneity was minimal (I^2=0%, p=0.85).

Next, we analyzed all common variants within the *DNM3* gene and the flanking genomic region. Variants covered in at least four out of the six analyzed genome-wide datasets were included in the meta-analysis, constituting 1932 variants. None of the meta-analyzed variants had a significant association with age at onset when corrected for multiple testing. Results from the extended *DNM3* analysis are provided in Supplementary Table 1. Tests for

statistical heterogeneity indicated that heterogeneity was low (I^2< 50%) for the vast majority (97%) of the meta-analyzed variants. Studies of the combined impact of PD risk loci on age at onset report a phenotypic variance explained by the calculated genetic risk score of 0.6% and 0.7%, with the signal mostly being driven by two individually age at onset-associated variants (Lill et al., 2015; Nalls et al., 2015). Assuming a variance explained of ~ 0.5% for the tested variant, we have a power of over 99% for the primary analysis of rs2421947 (N=5918) and a power of 89.5% to achieve a p-value of 0.0002 (N=4931) in the extended *DNM3* analysis.

The effect of rs2421947 on age at onset was also assessed in the LRRK2 p.G2019S carriers (N=39) that had been excluded from the aforementioned analyses, although this test was limited by a small sample size. Association with age at onset analyzed as a quantitative trait, with sex and dataset as covariables, was nonsignificant for rs2421947, with the trend for direction of effect reversed relative to the original report by Trinh et al. (Trinh et al., 2016) (Effect allele=G, Beta=1.79, 95% CI=−3.31–6.89, p=0.50). Trinh et al. report a correlation between rs2421947 genotype and *DNM3* mRNA levels in striatal brain tissue (Trinh et al., 2016). We explored the Genotype-Tissue Expression (GTEx) Portal (version 7; https://www.gtexportal.org/home/) and found that significant expression quantitative trait loci (eQTLs) for *DNM3* are reported in cerebellar hemisphere and cerebellum, but not in any of the other brain regions examined by the GTEx project. Interestingly, rs2421947 and variants in high LD $\left(r^2 \geq 0.6\right)$ are not reported as significant eQTLs for *DNM3* in any brain tissue.

4. Discussion

In this study, we found no evidence for a modifying effect of rs2421947 or other common *DNM3* variants on age at onset in idiopathic PD. A *DNM3* haplotype tagged by rs2421947 was identified by Trinh et al. as a modifier of age at onset in LRRK2 p.G2019S carriers. They reported that the median age at onset of *DNM3* GG homozygotes was 12.5 years younger than that of CC homozygotes. This is a large difference in onset age compared to the effect of other variants associated with age at onset in PD, and could be meaningful in the clinical setting. As shown by the 95% confidence interval of our primary analysis, it is highly unlikely that we did not detect an effect altering the onset of PD more than a few months per G allele.

We performed a meta-analysis including a total of 5918 PD patients, and the high number of analyzed individuals is a strength of our study. However, by including cases from different study sites with variations in study design, heterogeneity may be introduced in meta-analysis of the genetic data. We assessed this and found low heterogeneity. We accounted for population substructure within the individual studies by including five eigenvectors in the regression model. The meta-analyzed studies use mostly self-reported symptom onset. Age at onset is subjective and may be prone to recall bias. Nevertheless, the reliability of self- and family-reported age at onset compared to medical records is high and all three methods have been regarded as valid (Reider et al., 2003).

A recent study of LRRK2 p.G2019S carriers in the Spanish population did not find and association between *DNM3* rs2421947 and age at onset of PD (Fernandez- Santiago et al.,

2018). Linkage patterns vary among populations, and the possibility that disease relevant variation could be tagged by different genetic markers in Europeans/North Americans as compared to the Arab-Berber population studied by Trinh et al. prompted us to extend our analysis to all imputed common variants across the *DNM3* locus. The genomic region flanking the *DNM3* gene is included in our analysis to cover potential regulatory variants, although this increases the multiple testing burden. On the other hand, regulatory variants affecting *DNM3* expression may reside in an even more distal part of the genome not covered in our analysis. eQTL data could be used to identify potential regulatory variants and reduce the number of tests to adjust for. However, the currently available databases are incomplete since eQTLs in addition to depending on tissue and cell-type, also may vary between different physiological conditions (Albert and Kruglyak, 2015).

Despite recent efforts to elucidate the genetic architecture behind age at onset and other clinical characteristics of PD, the vast majority of genetic variation affecting PD phenotypes remains unexplained. Many studies have limited their analysis to known risk loci of PD, while attempts at identifying novel genetic modifiers of age at onset have proven challenging. Genetic modifiers of age at onset may be limited to sub-groups of patients carrying specific mutations or susceptibility variants. Variations in the *MAPT* gene have been found to be associated with age at onset in PD patients carrying a *LRRK2* mutation (Gan-Or et al., 2012; Golub et al., 2009). A recent GWAS of age at onset analyzed PD patients with and without a family history of the disease separately. No significant association was found in those without a family history of PD, while two signals were detected in individuals reporting to have a first or second-degree relative with PD. Both these signals mapped to gene regions that are not known to affect PD risk (Hill-Burns et al., 2016).

Discovering genetic modifiers of phenotype in PD is important, since it may provide insight into disease mechanisms and help in identifying potential therapeutic targets. *DNM3* has previously not been identified by GWASs of disease risk or onset age (Chang et al., 2017; Hill-Burns et al., 2016; Latourelle et al., 2009; Nalls et al., 2014). We found no association between common *DNM3* variants and age at onset in idiopathic PD, but the possible contribution of rare variants within this genetic locus cannot be excluded. Variability within the *DNM3* locus may be a specific modifier of *LRRK2* parkinsonism, although this has yet to be replicated in independent studies. *DNM3* encodes the protein dynamin-3 which is highly expressed in neurons (Raimondi et al., 2011). The LRRK2 protein has been shown to interact with dynamin-3 and other members of the dynamin GTPase superfamily that regulate membrane dynamics important for endocytosis and mitochondrial morphology (Stafa et al., 2014). Trinh et al. report a correlation between rs2421947 genotype and *DNM3* mRNA levels in striatal tissue, but such an association is not observed in the GTEx Portal. There are several methodological differences between these analyses and additional evidence is needed before conclusions regarding rs2421947 as an eQTL for *DNM3* in the brain can be drawn.

Further insight into disease mechanisms may be gained by examining complex genetic interactions. A novel epistatic interaction between two genetic variants was reported by a recent study incorporating genetic, molecular and clinical data into models to predict motor

progression in PD (Latourelle et al., 2017). Larger patient cohorts with comprehensive characterization of disease phenotype will benefit future studies of how genetics affect clinical heterogeneity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors thank all study participants, investigators and funding partners for their contribution to the data analyzed in the current publication. The funding organizations had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Victoria Berge-Seidl and Mathias Toft are funded by a grant from the South-Eastern Norway Regional Health Authority. Mathias Toft is also supported by the Research Council of Norway. Lasse Pihlstrøm is supported by the Norwegian Health Association. Mayo Clinic is a Morris K. Udall Parkinson's Disease Research Center of Excellence (NINDS P50 #NS072187 to OR and ZKW), Zbigniew K. Wszolek is also funded by Mayo Clinic Center for Individualized Medicine, Mayo Clinic Neuroscience Focused Research Team (Cecilia and Dan Carmichael Family Foundation, and the James C. and Sarah K. Kennedy Fund for Neurodegenerative Disease Research at Mayo Clinic in Florida), the gift from Carl Edward Bolch, Jr., and Susan Bass Bolch, The Sol Goldman Charitable Trust, and Donald G. and Jodi P. Heeringa. Owen Ross is supported by NINDS R01 NS078086, Department of Defense award W81XWH-16-PRMRP-IIRA, Michael J. Fox Foundation. The analyses presented in the current publication are based on the use of study data downloaded from the dbGaP web site, under dbGaP accession phs000126.v1.p1, phs000048.v1.p1, phs000089.v3.p2 and phs000196.v2.p1. Data was also obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org. PPMI - a public-private partnership - is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners including AbbVie, Avid Radiopharmaceuticals, Biogen, BioLegend, Bristol-Myers Squibb, GE Healthcare, Genentech, GlaxoSmithKline, Lilly, Lundbeck, Merck, Meso Scale Discovery, Pfizer, Piramal, Roche, Sanofi Genzyme, Servier, Takeda, Teva and UCB.

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Highlights

No association between rs2421947 and age at onset in idiopathic Parkinson's disease

Common genetic variation in the *DNM3* locus has no modifying effect on age at onset

Genetic modifier of *LRRK2*-parkinsonism is not transferable to idiopathic disease

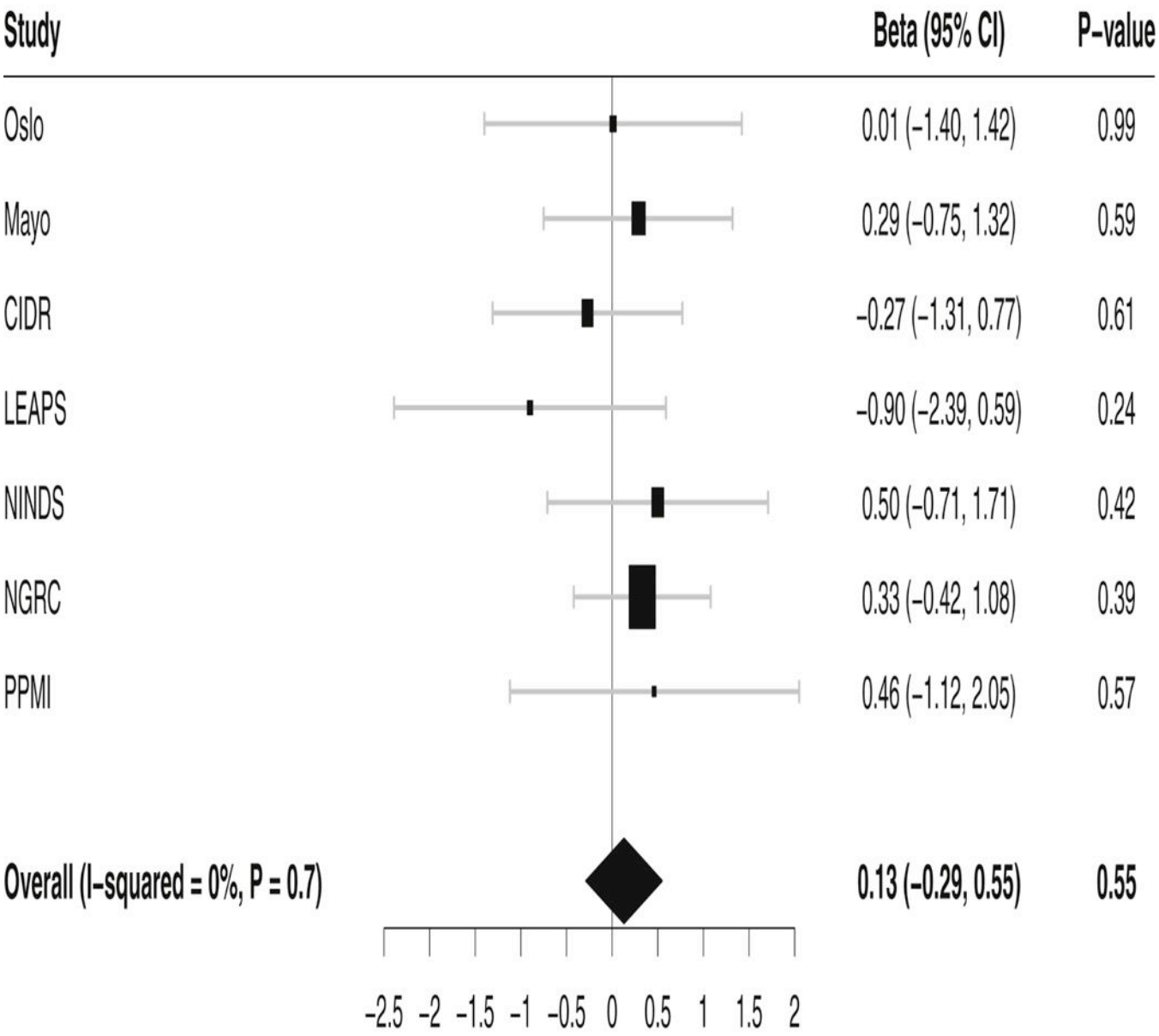

Figure 1. Study-specific and meta-analysis results for the *DNM3* variant rs2421947

Forest plot showing the effect of rs2421947 on age at onset in idiopathic Parkinson's disease in individual studies and meta-analysis. The effect size of the G allele is given as a beta estimate with a 95% confidence interval (CI). The size of the squares indicates the size of the datasets. CIDR, Center for Inherited Disease Research; LEAPS, Linked Efforts to Accelerate Parkinson's Solutions; NINDS, National Institute of Neurological Disorders and Stroke; NGRC, NeuroGenetics Research Consortium; PPMI, Parkinson's Progression Markers Initiative.

Table 1.

Demographic characteristics of study samples

Study	Population	PD patients	% Male	Age at onset ± SD	Genotyping method
Oslo	Norway	472	64	55.9 ± 11.2	Illumina Infinium OmniExpress v.1.1.
Mayo	USA	987	64	65.5 ± 11.8	Taqman assay
CIDR	North America, Europe and Australia	823	59	62.0 ± 10.7	Illumina HumanCNV370 BeadChip
LEAPS	USA	439	62	60.9 ± 11.1	Perlegen DNA chip (85k SNP markers)
NINDS	USA	912	60	58.4 ± 13.2	Illumina HumanHap550 BeadChip
NGRC	USA	1971	68	58.4 ± 11.9	Illumina HumanOmni1_Quad
PPMI	USA and Europe	314	68	59.7 ± 9.8	Illumina NeuroX

CIDR, Center for Inherited Disease Research; LEAPS, Linked Efforts to Accelerate Parkinson's Solutions; NINDS, National Institute of Neurological Disorders and Stroke; NGRC, NeuroGenetics Research Consortium; PPMI, Parkinson's Progression Markers Initiative; PD, Parkinson's disease; SD, Standard Deviation.