Disease Penetrance of Late-Onset Parkinsonism
A Meta-analysis

Joanne Trinh, BSc; Ilaria Guella, PhD; Matthew James Farrer, PhD

**IMPORTANCE** Mutations in SNCA, LRRK2, VPS35, EIF4G1, and DNAJC13 have been implicated in late-onset familial parkinsonism. However, the estimated disease penetrance of these mutations varies widely.

**OBJECTIVE** To compare penetrance of various mutations reported in published genetic studies to improve the understanding of late-onset parkinsonism.

**DATA SOURCES** Forty-nine previously published studies, including 709 participants, were included for all original and subsequent articles in ISI Web of Science, PubMed electronic databases, and extracted information about number of mutation carriers within families and sporadic cases worldwide for pathogenic mutations in SNCA, LRRK2, VPS35, EIF4G1, and DNAJC13. The end-of-search date was January 31, 2014.

**STUDY SELECTION** Published studies were included if there was information on the ethnicity of the patient or unaffected individual, confirmation of mutation, age of patient or unaffected individual, age at onset, and first motor symptom of patient. Autosomal recessive parkinsonism and genes implicated without significant genetic linkage were excluded from this study.

**DATA EXTRACTION AND SYNTHESIS** The age-associated cumulative incidence was estimated using the Kaplan-Meier method with age at onset as the time variable; asymptomatic carriers were right censored at the age at last contact or age at death.

**MAIN OUTCOMES AND MEASURES** Comparative measures were obtained with log-rank tests, and each penetrance estimate was given separately with 95% confidence intervals.

**RESULTS** All the assessed autosomal dominant Parkinson disease mutations have significantly different age-dependent cumulative incidences ($P < .001$). In particular, penetrance of SNCA duplications was comparable to point mutations (log-rank $P = .97$) and driven by inclusion of SNCA p.A53T (mean age at onset, 45.9 years; 95% CI, 43-49 years). In addition, Israeli Ashkenazi Jewish LRRK2 p.G2019S carriers (mean age at onset, 57.9 years; 95% CI, 54-63 years) were comparable to Tunisian Arab Berbers (mean age at onset, 57.1 years; 95% CI, 45.5-68.7 years) ($P = .58$), whereas Norwegian carriers (mean age at onset, 63 years; 95% CI, 51.4-74.6 years) were significantly different from the other groups ($P < .001$).

**CONCLUSIONS AND RELEVANCE** Parkinson disease pathogenic mutations have an age-dependent penetrance that could be ameliorated or exacerbated by modifier genes or environmental factors in different populations.
Parkinson disease (PD) was originally thought to be due to environmental factors; the heritability of late-onset disease based on twin estimates was negligible, although several families with mendelian forms of parkinsonism have been described. Results of genome-wide association and linkage studies have gradually shifted the emphasis back to genetic factors. Multiple missense and copy number mutations (duplications or triplications) were first described in SNCA. Point mutations were subsequently identified in LRRK2, EIF4G1, VPS35, and DNAJC13 and have been described in late-onset familial parkinsonism.

In autosomal dominant parkinsonism, the disease onset, clinical progression, and pathologic features of mutation carriers can be vastly distinct, albeit consistent with idiopathic PD. SNCA is most robustly associated with PD in every population tested, although a penetrance comparison of point mutations and copy number mutations within families is missing. Only the age-dependent cumulative incidence (penetrance) of LRRK2 mutations has been assessed in detail. The assessment of penetrance specifically for LRRK2 mutations could be due to higher frequency of LRRK2 mutations; p.G2019S alone accounts for up to 18% of Ashkenazi Jewish, approximately 30% to 40% of Tunisian Arab Berber, and approximately 1% of white populations. Penetrance studies are not concordant, most likely because of small sample sizes, unrepresentative case sampling, and/or various statistical analyses. Currently, the 2 main methods used to estimate penetrance for mutations in PD are the Kaplan-Meier method for unrelated individuals and the kin-cohort method within families. The objective of this study was to synthesize data to compare penetrance of various mutations for all published genetic studies to improve the understanding of late-onset parkinsonism. We report a quantitative meta-analysis of pathogenic mutations that lead to late-onset disease and highlight similarities among ethnic groups.

Methods

Inclusion and Exclusion Criteria

Published studies were included if they had the following information: (1) ethnicity of patient or unaffected individual, (2) confirmation of mutation (not inferred by ascent), (3) age of patient or unaffected individual, (4) patient age at onset, (5) first motor symptom of patient, and (6) nonmotor symptom (cognition) of patient. For each study, we requested information on: (1) ethnicity of patient or unaffected individual, (2) age at onset, age, and/or age at last contact, (3) point mutation, (4) patient age at onset, (5) first motor symptom of patient, and (6) nonmotor symptom (cognition) of patient. We included all studies published in English, and they were not written in English, and (4) about genes for which significant genetic linkage was not reported.

Statistical Analysis

The age-associated cumulative incidence (disease penetrance) was estimated using the Kaplan-Meier method with age at onset as the time variable; asymptomatic carriers were right censored at the age at last contact or age at death (JMP software, version 5; SAS Institute Inc). Statistical comparisons among survival curves were determined with log-rank tests unless otherwise stated.

Results

SNCA copy number mutations and 5 missense mutations (p.A30P, p.E46K, p.H50Q, p.G51D, and p.A53T) were assessed. The cumulative incidences for SNCA triplications, duplications, and point mutations are shown in Figure 1. Penetrance of SNCA triplications had a lower quartile of 31 years or younger, a median of 39 years of age, and an upper quartile of 46 years or older (n = 15); duplications had a lower quartile of 40 years or younger, a median of 48 years of age, and an upper quartile of 61 years or older (n = 41). Point mutations had a lower quartile of 42 years or younger, a median of 49 years, and an upper quartile of 60 or older (n = 59). SNCA triplications were significantly different from duplication and point mutations (P < .01). Penetrance of SNCA duplications and triplications (log-rank P = .97) was driven by inclusion of SNCA p.A53T (mean age at onset, 45.9 years; 95% CI, 43-49 years;
n = 35). Too few carriers were available for meaningful independent analysis of p.A30P (mean age at onset, 59.8 years; 95% CI, 54-76 years; n = 5), p.E46K (mean age at onset, 62.3 years; 95% CI, 49-67 years; n = 8), H50Q (mean age at onset, 64.7 years; 95% CI, 19-40 years; n = 3), and p.G51D (mean age at onset, 32.7 years; 95% CI, 19-40 years; n = 3).

The penetrance of 6 missense LRRK2 mutations (p.N1437H, p.R1441C/G, p.Y1699C, p.G2019S, and p.I2020T) was assessed. All cumulative incidence survival curves for LRRK2 mutations are presented in Figure 2. LRRK2 p.N1437H had a lower quartile of 46 years or younger, a median of 49 years of age, and an upper quartile of 50 years or older (n = 10). LRRK2 p.Y1699C had a lower quartile of 44 years or younger, a median of 50 years of age, and an upper quartile of 56 years or older (n = 16). LRRK2 p.N1437H and LRRK2 Y1699C mutations were most highly penetrant compared with other LRRK2 mutations. The cumulative incidence of LRRK2 p.I2020T had a lower quartile of 51 years or younger, a median of 55 years of age, and an upper quartile of 60 years or older (n = 29). The estimation was similar to LRRK2 p.G2019S, which had a lower quartile of 49 years or younger, a median of 57 years, and an upper quartile of 67 years or older (n = 30). Lastly, the cumulative incidence of LRRK2 p.R1441C and p.R1441G was the least penetrant. LRRK2 p.R1441C had a lower quartile of 65 years or younger, a median of 71 years, and an upper quartile of 77 years or older (n = 27). p.R1441G had a lower quartile of 60 years or younger, a median of 65 years of age, and an upper quartile of 72 years or older (n = 104). The cumulative incidences of LRRK2 p.R1441C and p.R1441G were comparable (P = .31). The comparison of mutations within the kinase domain (p.G2019S and p.I2020T) revealed similar penetrance estimates (P = .23). Mutations within the Ras of complex proteins (Roc) domain (p.N1437H and p.R1441C/G) did not appear to be similar (P < .001). Mutation in the C-terminal of Roc (COR) domain (p.Y1699C) is similar in penetrance to p.N1437H.

Highly significant differences were observed when LRRK2 p.G2019S mutation carriers were stratified by population. Penetration estimates of LRRK2 p.G2019S for this stratification are shown in Figure 3. In particular, Israeli Ashkenazi Jews (mean age at onset, 57.9 years; 95% CI, 54-63 years; n = 61) were comparable to Tunisian Arab Berbers (mean age at onset, 57.1 years; 95% CI, 45.5-68.7 years; n = 220) (P = .58), whereas Norwegian carriers (mean age at onset, 63 years; 95% CI, 51.4-74.6 years; n = 84) were significantly different from both groups (P < .001) (Figure 3).

The cumulative incidence of VPS35, EIF4G1, and DNAJC13 mutations is shown in Figure 4. VPS35 p.D620N had a lower quartile of 45 years or younger, a median of 49 years of age, and an upper quartile of 59 years or older (n = 61). EIF4G1 p.R1205H had a lower quartile of 56 years or younger, a median of 62 years of age, and an upper quartile of 69.5 years or older (n = 20). DNAJC13 p.N855S had a lower quartile of 61 years or younger, a median of 68 years of age, and an upper quartile of 76 years or older (n = 18) (Figure 4).

The age-dependent cumulative incidence was significantly different across mutations (P < .001). Overall, SNCA triplications (n = 15) were highly penetrant, and LRRK2 p.G2019S in Norway (n = 84) had reduced penetration.

Discussion

This study summarizes and systematically compares the age-dependent cumulative incidence of all mutations that lead to late-onset Parkinsonism. Fifteen rare pathogenic mutations in 5 genes (SNCA, LRRK2, VPS35, EIF4G1, and DNAJC13) were assessed. All mutation carriers were combined, whether from the literature or contributed by corresponding authors, providing the most accurate penetrance estimates to date. Nevertheless, the study has many limitations, including cultural and environmental differences among populations, access to healthcare, and ascertainment bias. Various diagnostic criteria and the movement disorders neurologic expertise at different centers have to be considered (eTable 1 in the Supplement). Moreover, age at onset is retrospective, subjective, and dependent on a variety of symptoms and signs, although well correlated with age at diagnosis.16

All comparisons used the same statistical measure to estimate cumulative incidence and simplified comparisons among mutations. The Kaplan-Meier method is a reverse survival curve analysis, ideally suited for sporadic patients and unrelated probands, that censors for asymptomatic carriers.
In contrast, the kin-cohort method excludes probands, using only relatives with inferred genotypes to specifically avoid inflating penetrance estimates. However, a disadvantage is that the phenotypic and genotypic information of the relatives may be inaccurate. Although analyses have been adapted to compensate for a variety of study designs, the Kaplan-Meier and kin-cohort methods are the major methods used in penetrance estimates of PD. Bias from the inclusion of probands and family members has been assessed using a variety of statistical methods, and sensitivity analyses for LRRK2 p.R1441G and p.G2019S have comparable results. This study was limited by published data, the relatedness of the study participants, and the total number of carriers and families with each gene. With these caveats acknowledged, the CIs are provided for genetic counseling (eFigures 1-14 in the Supplement).

Penetrance estimates for monogenic Parkinsonism vary by gene, mutation, and ethnicity. SNCA triplications are more penetrant than duplications for which genomic dosage has been directly correlated with messenger RNA and protein expression. Clinically, SNCA triplication carriers have an earlier onset, faster progression, and more fulminant disease compared with duplication carriers, findings that more closely resemble late-onset idiopathic PD. Seldom do SNCA triplications or duplication carriers have dementia as a first symptom; typically, cognitive decline is noted several years after the onset of Parkinsonism. Nevertheless, many have a current clinical diagnosis of dementia with Lewy bodies, with diffuse Lewy body disease on autopsy. Overall, SNCA point mutations and SNCA duplications are similar in penetrance. Although most nonsense carriers have SNCA p.A53T and have been described with young-onset Parkinsonism with an aggressive course and most duplication carriers are described as having dementia with Lewy bodies, they are comparable. The frequency of SNCA multiplications and point mutations is extremely rare (up to 1% in different populations); thus, meaningful comparisons of clinical features is problematic, although a global study of SNCA multiplication and missense carriers has recently been initiated (The Parkinson Progression Markers Initiative by The Michael J Fox Foundation for Parkinson Research).

LRRK2 mutations confer the highest population-attributable risk to PD, but the function of the encoded protein still remains unclear. Most pathogenic mutations are within 3 contiguous domains: kinase, Roc, and COR. Penetration of mutations within the kinase domain (LRRK2 p.G2019S and p.I2020T) is similar and significantly higher than Roc domain mutations (p.R1441C and p.R1441G). LRRK2 p.R1441C and p.R1441G mutations have similar penetrance estimates (P = .31). However, we observe increased penetrance of LRRK2 p.N1437H, which could be hampered by the rarity of this mutation (n = 10). The COR domain mutations are highly penetrant but could also be attributable to a smaller sample size (n = 7).

SNCA mutations (triplications, duplications, and point mutations) had a larger effect, with an earlier onset (mean age at onset, 38.5-49.5 years) compared with LRRK2 mutations (mean age at onset, 46.8-68.8 years) (eFigure 15 in the Supplement). SNCA mutation carriers have a more aggressive phenotype, whereas LRRK2 carriers have a more benign clinical course compared with idiopathic PD. In LRRK2 Parkinsonism, there is less rapid eye movement sleep behavior disorder and gastrointestinal dysfunction, which are 2 main clinical features affected by Braak staging. SNCA mutation carriers primarily have Lewy body–like inclusions of α-synuclein aggregates. In contrast, LRRK2 carriers (p.N1437H, p.R1441C/G/H, p.G2019S, or p.I2020T) have pleiomorphic pathologic features, including α-synuclein, 4-repeat tau, or TDP-43 proteinopathies on a background of neuronal loss and gliosis. Perhaps LRRK2 carriers with 4-repeat tau or TDP-43 proteinopathies have more mild features than synucleinopathies, and burden and type of end-stage disease therefore probably reflect the clinical course.

This study highlights the role of ethnicity as a major contributor of penetrance. Stratification of LRRK2 p.G2019S Parkinsonism by ethnicity was possible because of the large sample size. Israeli Ashkenazi Jews have a significantly higher penetrance compared with Norwegian LRRK2 p.G2019S mutation carriers and are comparable in penetrance to Tunisian Arab Berbers. In New York, the disease in Ashkenazi Jewish carriers is less penetrant (24% penetrance at 80 years of age); these differences may reflect a sample of 7 carriers, the exclusion of family members, and environmental factors. In contrast, similarities in age at onset between Israeli Jew and Tunisian Arab Berber carriers may reflect similar genetic and environmental backgrounds. Nevertheless, ethnic differences are an important consideration in genetic counseling.

Mutations in SNCA, LRRK2, VPS35, EIF4G1, and DNAJC13 have been directly implicated in familial Parkinsonism. These proteins are centrally involved in synaptic transmission, early endosomal sorting or recycling, and lysosomal autophagy. Indeed, LRRK2, VPS35, and DNAJC13 directly immunoprecipitate with members of the Wiskott-Aldrich syndrome protein and scar homolog complex, which regulates actin remodeling and membrane trafficking in these processes. Whether this network is similarly perturbed in idiopathic PD has yet to be established. Differences in the penetrance estimates may reflect the type of substitution, its location, and its functional consequence. Mutations may affect interactions with binding partners and downstream signaling pathways, thus influn-
Age is considered the greatest risk factor for PD, and genetic susceptibility is only one influence. The penetrance of mutations in late-onset parkinsonism is also dependent on ethnicity and potentially environmental factors. Thus, heterogeneity among mutation carriers may be an important consideration when identifying modifiers of disease. Prospective, longitudinal evaluation of carriers and further meta-analyses will be required for more precise penetrance estimates and provide the opportunity to inform therapeutic trials.

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