Age-specific penetrance of *LRRK2* G2019S in the Michael J. Fox Ashkenazi Jewish *LRRK2* Consortium

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ABSTRACT

Objective: Estimates of the penetrance of *LRRK2* G2019S vary widely (24%–100%), reflective of differences in ascertainment, age, sex, ethnic group, and genetic and environmental modifiers.

Methods: The kin-cohort method was used to predict penetrance in 2,270 relatives of 474 Ashkenazi Jewish (AJ) Parkinson disease (PD) probands in the Michael J. Fox *LRRK2* AJ Consortium in New York and Tel Aviv, Israel. Patients with PD were genotyped for the *LRRK2* G2019S mutation and at least 7 founder *GBA* mutations. *GBA* mutation carriers were excluded. A validated family history interview, including age at onset of PD and current age or age at death for each first-degree relative, was administered. Neurologic examination and *LRRK2* genotype of relatives were included when available.

Results: Risk of PD in relatives predicted to carry an *LRRK2* G2019S mutation was 0.26 (95% confidence interval [CI] 0.18–0.36) to age 80 years, and was almost 3-fold higher than in relatives predicted to be noncarriers (hazard ratio [HR] 2.89, 95% CI 1.73–4.55, $p < 0.001$). The risk among predicted G2019S carrier male relatives (0.22, 95% CI 0.10–0.37) was similar to predicted carrier female relatives (0.29, 95% CI 0.18–0.40; HR male to female: 0.74, 95% CI 0.27–1.63, $p = 0.44$). In contrast, predicted noncarrier male relatives had a higher risk (0.15, 95% CI 0.11–0.20) than predicted noncarrier female relatives (0.07, 95% CI 0.04–0.10; HR male to female: 2.40, 95% CI 1.50–4.15, $p < 0.001$).

Conclusion: Penetrance of *LRRK2* G2019S in AJ is only 26% and lower than reported in other ethnic groups. Further study of the genetic and environmental risk factors that influence G2019S penetrance is warranted. *Neurology*® 2015;85:89–95

GLOSSARY

AJ = Ashkenazi Jewish; **CI** = confidence interval; **FHI** = family history interview; **GBA** = glucocerebrosidase; **HR** = hazard ratio; **PD** = Parkinson disease.

Since 2004, when mutations in *LRRK2* were first identified as a cause of autosomal dominant idiopathic Parkinson disease (PD),¹ *LRRK2* G2019S mutations have been reported in 1% of sporadic and 4% of familial PD.² Select PD populations, e.g., Ashkenazi Jews (AJ) (14.3%–18.8%)^{3–6} and North African Berbers (39.3%),⁷ have much higher frequencies of G2019S mutations. The frequency of *LRRK2* G2019S is estimated at 2% among AJ population controls.⁵ Given the high frequency of mutation carriers among AJ, the prevalence of PD in AJ would be expected to be very high, unless penetrance of *LRRK2* G2019S is incomplete. Penetrance, the probability that an individual with the exposure (in this case G2019S) will develop the outcome, PD, by a certain age, is essential for genetic counseling. Even when confined to *LRRK2* G2019S, penetrance estimates vary widely (24%–100%).⁸ Penetrance estimates may differ based on ethnic group, sex, and the presence of genetic or environmental modifiers of age

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LRRK2 Ashkenazi Jewish Consortium coinvestigators are listed on the *Neurology*® Web site at *Neurology.org*.

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Table 1 Characteristics of probands

	Probands (n = 474)		p Value
	G2019S+ (n = 129)	G2019S– (n = 345)	
Age at interview, y	68.2 (9.7)	67.9 (10.5)	NS
AAO of PD	58.4 (11.0)	61.6 (10.4)	0.003
Males			
Age (n = 279)	68.5 (10.8), n = 64	67.9 (11.0), n = 215	NS
AAO of PD	57.6 (11.9)	61.7 (10.6)	0.009
Females			
Age (n = 195)	68.0 (8.4), n = 65	68.1 (9.7), n = 130	NS
AAO of PD	59.2 (10.1)	61.5 (10.2)	NS

Abbreviations: AAO = age at onset; NS = not significant; PD = Parkinson disease.

at onset. How probands and family members are ascertained and the statistical methodologies used may also help explain this range in estimates; for example,⁸ young-onset and familial cases, both of whom are more likely to harbor genetic mutations, are more likely to be seen at an academic center. Here, we estimate penetrance of *LRRK2* G2019S in a genetically homogenous AJ cohort, using the same validated family history interview (FHI) at 3 academic centers specialized in the care of PD.

METHODS The Michael J. Fox AJ Consortium was formed in 2009. Four-hundred seventy-four AJ PD probands including 415 newly genotyped and 59 previously genotyped participants were recruited at 3 sites: Beth Israel Medical Center (n = 136), Columbia University Medical Center (n = 146), both in New York, and Tel Aviv Medical Center in Tel Aviv, Israel (n = 192).⁶

Standard protocol approvals, registrations, and patient consents. Institutional review boards at each site approved the protocol and each participant signed a written informed consent.

All probands met UK Brain Bank criteria (except that those with family history of PD were not excluded)⁹ and were required to have 2 or more AJ grandparents, with the majority having 4 AJ grandparents. Recruitment of probands was not based on family history of PD. Four hundred seventy-four probands completed a validated FHI on each of their first-degree relatives.¹⁰ Probands and relatives were genotyped for *LRRK2* G2019S and glucocerebrosidase (*GBA*) mutations (8 mutations plus 2 variants in New York, and 7 mutations in Israel).⁶ Probands who carried *GBA* mutations were excluded.⁶

Family history interview. We have used the FHI since 1998 to study familial aggregation of PD and more specifically to study the penetrance of *parkin*,¹¹ *LRRK2* G2019S,⁴ and *GBA*.¹² Most recently, it was used in Gaucher families to ascertain PD.¹³ The FHI assigns a level of certainty of diagnosis of PD to each first-degree relative, based on an algorithm for diagnosis ranging from definite PD to unlikely PD. A “conservative” diagnosis of PD was used in all analyses.¹⁰ We previously established that using a conservative diagnosis of PD derived from the FHI, sensitivity

was 95.5% and specificity 96.2% in relatives, and did not differ among parents, siblings, and offspring.¹⁰

The Michael J. Fox AJ Consortium was designed to perform a detailed examination⁶ and G2019S genotyping on all available first-degree relatives of probands who carried G2019S mutations as well as a subset of noncarrier families, to maintain blinding. FHIs were obtained on 2,270 first-degree relatives from the 474 families. None of the examiners were aware of the genotypes of the relatives. If the relative was examined, information on certainty of diagnosis of PD based on neurologic examination superseded FHI information. Key information derived from the family history for each relative included year of birth, current age or age at death, sex, and age at onset of PD. G2019S genotyping from relatives who were examined was included in penetrance estimates when available.

Statistical analysis. We estimated penetrance to age 80 years using the kin-cohort method.^{14,15} The kin-cohort method uses the *LRRK2* G2019S mutation status in the probands to infer unobserved genotypes in relatives and combines this with PD diagnosis and age at onset of PD, current age, or age at death information derived from the FHI in the relatives to estimate penetrance of *LRRK2* PD in first-degree relatives. We assumed a 2% prevalence⁵ of *LRRK2* G2019S mutation in first-degree relatives who had not been genotyped. We have improved on the traditional kin-cohort methodology¹⁴ in the following ways: (1) when a relative was seen in person, we used the observed *LRRK2* genotype and PD status in the analysis to improve precision of the penetrance estimates,¹⁵ (2) we ensured that the cumulative risk function is cumulative and can only increase, (3) we provided hazard ratios (HRs) as a summary measure to compare *LRRK2* carrier and noncarrier group using the Cox proportional hazards model,¹⁶ and (4) through a bootstrap resampling method, we treated families as independent,¹⁷ and we did not require first-degree family members within a family to have independent age-at-onset distribution. Thus, we accounted for potential residual familial correlation in addition to carrying an *LRRK2* mutation. These modifications improve the accuracy of the penetrance estimates and provide correct inference for their confidence intervals (CIs).

We performed 3 different comparisons. First, we examined cumulative risk of PD to age 80 years in relatives estimated to be carriers of *LRRK2* G2019S compared with relatives estimated to be noncarriers. Known genotypes of 158 relatives (90 G2019S carriers, 68 noncarriers) were included. Second, we examined the penetrance of *LRRK2* G2019S in parents and siblings separately. Third, we compared the cumulative incidence of PD in male relatives estimated to be carriers of G2019S compared with male noncarriers, and female relatives estimated to be G2019S carriers compared with female noncarriers.

RESULTS We established that the sensitivity of the interview was 93.8% and the specificity was 99.8% in our cohort. In the 2 cases in which the family history algorithm based on proband interview yielded “no” and the relatives did have PD, the diagnosis was made by the neurologist for the first time, at the research visit.

Demographic characteristics of probands with and without *LRRK2* G2019S mutations and their relatives are shown in tables 1 and 2. There were 129 G2019S proband mutation carriers and 345 proband noncarriers. The percentage of carriers was similar in

Table 2 Characteristics of first-degree relatives with family history data

	Relatives (n = 2,270)		p Value
	G2019S+ relatives (n = 652)	G2019S- relatives (n = 1,618)	
Age, y	50.1 (1.2)	49.28 (0.6)	NS
AAO of PD (n = 127)	66.3 (2.4), n = 54	65.1 (1.8), n = 73	NS
Males			
Age (n = 1,153)	51.4 (1.5), n = 334	48.0 (0.8), n = 819	0.024
AAO of PD (n = 73)	63.1 (3.8), n = 26	63.2 (3.2), n = 47	NS
Females			
Age (n = 1,117)	48.8 (1.6), n = 318	50.3 (0.9), n = 799	NS
AAO of PD (n = 54)	69.4 (3.2), n = 28	68.6 (2.3), n = 26	NS
Parents			
Age (n = 731)	84.5 (2.3), n = 214	83.4 (1.2), n = 517	NS
AAO of PD (n = 93)	67.2 (2.5), n = 39	67.8 (1.6), n = 54	NS
Siblings			
Age (n = 575)	67.0 (1.5), n = 168	66.0 (0.8), n = 407	NS
AAO of PD (n = 30)	59.2 (4.6), n = 14	63.5 (1.7), n = 16	NS

Abbreviations: AAO = age at onset; NS = not significant; PD = Parkinson disease.

2 New York sites (29% Beth Israel Medical Center, 30% Columbia University Medical Center) and slightly higher in Tel Aviv (41%), but not significantly different from the other 2 sites ($p = 0.875$). Age at onset of PD was not significantly different among men and women overall, or when stratified by *LRRK2* G2019S. The 2,270 relatives included 731 parents, 575 siblings, and 964 children. One hundred twenty-seven relatives (5.6%) had PD based on either examination or FHI. The 127 cases with PD included 73 of 1,618 (4.5%) relatives of probands who did not carry G2019S mutations and 54 of 652 (8.3%) relatives of probands who did carry G2019S mutations. Clinical characteristics of probands^{6,18,19} and relatives^{18,20} in the AJ Consortium with and without G2019S mutations have been previously described. The phenotypic differences between carriers and

noncarriers are subtle, and would not differentially influence diagnosis in PD.

Penetrance of *LRRK2* G2019S. Penetrance estimates (cumulative risks of PD to age 80 years) are shown in table 3. Penetrance of PD in relatives predicted to have a G2019S mutation was 0.26 (95% CI 0.02–0.36) to age 80, and was almost 3-fold higher than relatives predicted to be noncarriers (HR 2.89, 95% CI 1.73–4.55, $p < 0.001$) (figure 1). When male and female relatives were examined separately (figure 2, A and B), the penetrance to age 80 among predicted mutation carrier male relatives (0.22, 95% CI 0.10–0.37) (figure 2A) was not statistically different from predicted carrier female relatives (0.29, 95% CI 0.18–0.40 [figure 2B]; HR male to female: 0.74, 95% CI 0.27–1.63, $p = 0.44$). In contrast, the risk of PD to age 80 among predicted noncarrier male relatives (0.15, 95% CI 0.11–0.20) was higher than for predicted noncarrier female relatives (0.07, 95% CI 0.04–0.10; HR male to female: 2.40, 95% CI 1.50–4.15, $p < 0.001$). While the penetrance among male and female G2019S carriers was similar, the risk of PD for women relatives predicted to carry a G2019S mutation compared with noncarrier women relatives was 5-fold (HR 5.03, 95% CI 2.57–9.94, $p < 0.001$) (figure 2B) while for men the risk of PD was not significantly elevated among male relatives predicted to carry an *LRRK2* G2019S (HR 1.55, 95% CI 0.53–3.33, $p = 0.43$) compared with noncarrier men (figure 2A). The large sex difference in HRs is attributable to the sex difference of PD distribution in noncarriers. Risk was elevated both among mutation carrier parents (HR 2.94, 95% CI 1.57–5.01, $p < 0.001$) (figure e-1A on the *Neurology*[®] Web site at Neurology.org) and siblings (HR 3.39, 95% CI 1.36–7.95, $p = 0.009$) (figure e-1B).

There were 12 multiplex families having more than one first-degree relative with PD. We accounted

Table 3 Cumulative risk of PD to age 80 years in first-degree relatives

Relatives	Cumulative risk in relatives to age 80 y		HR (95% CI) in G2019S carriers compared with noncarriers	Total relatives PD (n); noncarrier PD (n); G2019S PD (n)
	Noncarriers	G2019S carriers		
Total (n = 2,270), noncarrier (1,618), G2019S (652)	0.10 (0.07–0.13)	0.26 (0.02–0.36)	2.89 (1.73–4.55); $p < 0.001$	Total relatives PD (127); noncarrier PD (73); G2019S PD (54)
Male relatives (n = 1,153), noncarrier (819), G2019S (334)	0.15 (0.11–0.20)	0.22 (0.10–0.37)	1.55 (0.53–3.33); $p < 0.426$	Total relatives PD (73); noncarrier PD (47); G2019S PD (26)
Female relatives (n = 1,117), noncarrier (799), G2019S (318)	0.07 (0.04–0.10)	0.29 (0.18–0.40)	5.03 (3.57–9.94); $p < 0.001$	Total relatives PD (54); noncarrier PD (26); G2019S PD (28)
Parents (n = 731), noncarrier (517), G2019S (214)	0.11 (0.08–0.14)	0.28 (0.18–0.39)	2.94 (1.57–5.01); $p < 0.001$	Total relatives PD (93); noncarrier PD (54); G2019S PD (39)
Siblings (n = 575), noncarrier (407), G2019S (168)	0.09 (0.05–0.14)	0.26 (0.13–0.42)	3.39 (1.36–7.95); $p = 0.009$	Total relatives PD (30); noncarrier PD (16); G2019S PD (14)

Abbreviations: CI = confidence interval; HR = hazard ratio; PD = Parkinson disease.

Figure 1 Age-specific cumulative risk of *LRRK2* G2019S Parkinson disease in first-degree relatives

Estimated age-specific risk of PD in *LRRK2* G2019S carriers (solid red line) and noncarriers (solid black line) and their confidence intervals (dashed lines). Estimation obtained from 2,266 first-degree relatives of 473 probands using kin-cohort methods¹⁵ under a Cox proportional hazards model. The hazard ratio of *LRRK2* G2019S mutation was estimated to be 2.89.

for the influence of potential residual correlation among PD cases on the inference (i.e., computing CIs) by bootstrap based on independent families. Age-specific penetrance estimates by decade (age 30 to age 80) for (1) G2019S carriers vs noncarriers (table e-1A), (2) men only (table e-1B) and women only (table e-1C), (3) parents (table e-1D), and (4) siblings (table e-1E) are included in a supplementary table. We performed a sensitivity analysis by changing the population mutation frequency of *LRRK2* to 0% and the penetrance estimates did not differ.

DISCUSSION We have determined that penetrance of PD to age 80 years for *LRRK2* G2019S is 0.26 (95% CI 0.18–0.36), in the largest, systematically studied AJ cohort genotyped for *LRRK2* G2019S and *GBA*. We have also shown a similar penetrance in male and female carriers, while predicted noncarrier relatives demonstrate the typical male-to-female ratio of PD. The similar penetrance may explain the finding by several groups of approximately equal number of men and women among *LRRK2* G2019S PD cases.^{4–6,21} These findings have important implications for genetic counseling. Only 25% of first-degree relatives of AJ PD cases in New York who were unaware of their *LRRK2* G2019S mutation status indicated that they would be interested in knowing their genetic test results if penetrance were 25%,²² similar to the penetrance we have estimated. The number of relatives who

expressed interest in genetic testing increased when presented with hypothetical scenarios depicting higher penetrance.²² Therefore, it is essential that health professionals and AJ individuals at risk of PD are educated about these risk estimates, to facilitate informed decisions about genetic testing.

Estimates of penetrance of *LRRK2* G2019S across several populations have been reviewed.²³ We reported a lifetime penetrance of 24% up to age 80 years (95% CI 13.5%–43.7%) in 2,975 carrier and noncarrier relatives of 459 cases with PD and 2,044 relatives of 310 control probands using the kin-cohort method,^{14,24} which was similar in AJ and non-AJ cases.⁴ In contrast,² a risk of 28% at age 59 years, 51% at 69 years, and 74% at 79 years for the G2019S mutation in 1,045 mutation carriers from 133 families from 24 populations worldwide has been reported. Recently, the Tunisian population, which is known to have a high rate of consanguinity, was studied. Penetrance was estimated at 80% by age 70 years and women were affected a median of 5 years earlier than men.²⁵ Age at diagnosis did not predict progression in this cohort. The methodology used in this very large cohort included primarily PD cases (350 cases with idiopathic PD, 220 affected *LRRK2* carriers, and 12 unaffected *LRRK2* carriers). Sampling mainly PD-affected individuals may have led to an overestimation of *LRRK2* penetrance since essentially almost all individuals in the Tunisian sample developed PD at a certain age before recruitment by their study ascertainment scheme.²⁵ The authors further compared the Tunisian with a Norwegian cohort and found lower penetrance in Norway despite similar incidence of disease.²⁶ Systematic assessment of penetrance estimates in the *LRRK2* consortium using a common assessment battery and inclusion of both proband and relative characteristics may provide further refinement to these estimates. There is no published study using the identical FHI in distinct ethnic groups at multiple sites. To compare penetrance estimates among several ethnic groups, in a separately funded project, we are administering the FHI to non-AJ G2019S PD probands who are participating in the Michael J. Fox *LRRK2* Consortium including 5 sites in Europe and 2 in the United States, which will facilitate comparison to the current study.

There is a large body of evidence supporting the increased prevalence of idiopathic PD in men compared with women by a factor of nearly 2 to 1.²⁷ While differential environmental (occupational and behavioral) exposures have been cited as a risk of PD in men,²⁸ in women, hormonal influences, including both the timing and levels of endogenous estrogen (menarche, hysterectomy with or without oophorectomy) or exogenous estrogen or other sex steroids, have been considered. Most studies have

Figure 2 Age-specific cumulative risk of *LRRK2* G2019S PD in male and female first-degree relatives

(A) Estimated age-specific risk of Parkinson disease (PD) in male *LRRK2* G2019S carriers (solid red line) and male noncarriers (solid black line) and their confidence intervals (dashed lines). Estimation obtained from 1,151 first-degree male relatives of 448 probands using kin-cohort methods¹⁵ under a Cox proportional hazards model. The hazard ratio of *LRRK2* G2019S mutation was estimated to be 1.55. (B) Estimated age-specific risk of PD in female *LRRK2* G2019S carriers (solid red line) and female noncarriers (solid black line) and their confidence intervals (dashed lines). Estimation obtained from 1,115 first-degree female relatives of 436 probands using kin-cohort methods¹⁵ under a Cox proportional hazards model. The hazard ratio of *LRRK2* G2019S mutation was estimated to be 5.03.

been retrospective and rarely have both accurate exposure data and diagnostic information on PD.²⁹ As a result, there is no consensus on the effect of hormonal influences on risk of PD. Whether differences in sex distribution in idiopathic PD are attributable to specific genetic factors, different developmental trajectories influenced by sex, or differential exposure to environmental risk factors remains unknown. Both

individual variability and population heterogeneity may exist.²⁸

Studies in AJ,^{4–6} Italian,²¹ and Tunisian²⁵ *LRRK2* PD populations have shown a similar frequency in men and women. In an Italian study, women were more likely to report a family history of PD, but this was true for both *LRRK2* and non-*LRRK2* G2019S mutation carriers.²¹ In a study of Jewish patients with PD,³⁰ women were more likely to report a family history in a first-degree relative (32.9% compared with 17.2%) and were twice as likely to have a parent with PD, even after adjustment for *LRRK2* G2019S. The authors therefore postulated that it is only a relative genetic load in women that is increased, with the overall greater prevalence of PD in men because of an excess of environmental exposure in men superimposed on a similar genetic load. Our data, showing an increased penetrance in noncarrier male relatives, support this hypothesis. In non-*LRRK2* carriers, either men are more likely to have an environmental or behavioral exposure that increases their risk or women have a protective factor.

In Tunisia, age at onset of *LRRK2* PD was 5 years earlier in women compared with men,²⁵ but this has not been demonstrated in other studies.²¹ Cross-sectional studies do not demonstrate any phenotypic differences between male and female carriers to explain a difference in disease progression.

Autosomal dominant inheritance of mutations in *LRRK2* ensures that men and women are equally likely to inherit a mutation. Among *LRRK2* carriers, we postulate that the genetic contribution is the major cause of PD in both sexes, explaining the similar prevalence of PD in men and women. Sex differences in other genes associated with PD have been examined in a small study of *LRRK2*, *parkin*, *ATP13A2*, and *PINK1* mutations (n = 27) in the context of nonmotor signs and found that 48% were men.³¹ However, in a larger study of *GBA* and *parkin* that included heterozygote carriers,³² the sex distribution was similar to idiopathic PD.

Strengths of this study include the systematic data collection using a validated FHI in a homogenous population genotyped for *LRRK2* G2019S, and excluding PD cases with *GBA* mutations. The kin-cohort method that we used improved efficiency by including PD diagnosis by examination and genotype when available. Methodologic improvements to make the penetrance estimates more accurate and the CIs more precise were used. Weaknesses of the study include the fact that not all first-degree relatives were examined (32.5% deceased), and that the only population studied was AJ, making it difficult to compare with other PD populations. Patient recruitment was clinic-based, and while patients were not recruited based on family history, the estimates cannot extend

to populations. There are currently no statistical methods that incorporate covariates of probands or relatives, including demographic or clinical characteristics, genetic attributes, and environmental exposures, into models of penetrance. Development of these methods is under way.

This study demonstrates reduced penetrance of the *LRRK2* G2019S mutation in AJ, highlighting the need to identify other genetic or environmental factors contributing to the pathogenesis of *LRRK2* G2019S-mediated disease. If penetrance is actually lower in AJ than in other ethnic groups, there may be specific genetic or environmental factors in AJ that delay onset of PD.

AUTHOR CONTRIBUTIONS

Karen Marder: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision, obtaining funding. Yuanjia Wang: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Roy Alcalay: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data. Helen Mejia-Santana: study concept or design, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Ming-Xin Tang: analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Annie Lee: analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, statistical analysis. Deborah Raymond: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients, acquisition of data, study supervision. Anat Mirelman: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Rachel Saunders-Pullman: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and will give final approval, acquisition of data, obtaining funding. Lorraine Clark: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis, study supervision, obtaining funding. Laurie Ozelius: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data. Avi Orr-Urtreger: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, contribution of vital reagents/tools/patients, acquisition of data, obtaining funding. Nir Giladi: study concept or design, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision, obtaining funding. Susan Bressman: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision, obtaining funding.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

K. Marder receives research support from the NIH: NS036630 (principal investigator [PI]), 1UL1 RR024156-01 (director PCIR), PO412196-G (coinvestigator [COI]), and PO412196-G (COI). She received compensation for participating on the steering committee for U01NS052592 and from the Parkinson's Disease Foundation, Huntington's Disease Society of America, the Parkinson Study Group, CHDI, and the Michael J. Fox Foundation. Y. Wang receives research support from the NIH

(NS073671 [PI], NS082062 [PI]) and the Michael J. Fox Foundation. R. Alcalay receives research support from the NIH (K02NS080915), the Parkinson's Disease Foundation, the Smart Foundation, and the Michael J. Fox Foundation. H. Mejia-Santana and M. Tang report no disclosures relevant to the manuscript. A. Lee receives research support from the NIH TL1 Personalized Medicine Training Program. D. Raymond and A. Mirelman report no disclosures relevant to the manuscript. R. Saunders-Pullman serves on the scientific advisory board of the Dystonia Medical Research Foundation. She receives research support from the NIH (K02 NS073836), the Michael J. Fox Foundation for Parkinson's Research, the Bachmann-Strauss Dystonia & Parkinson Foundation, and the Marclad Foundation. L. Clark receives research support from the NIH (NINDS R01 NS060113 [PI], NINDS R01 NS073872 [CO-PI], NIA 5P50AG008702 [Project 3, PI], and NINDS NS36630 [COI] and 2P50NS038370-11 [COI]), the Parkinson's Disease Foundation (PI) and the Michael J. Fox Foundation (COI). L. Ozelius receives salary support from NIH (NS037409, NS075881, DC011805). She is a current member of the scientific advisory boards of the National Spasmodic Dysphonia Association, the Benign Essential Blepharospasm Research Foundation, and Tourette Syndrome Association, Inc. Dr. Ozelius receives royalty payments from Athena Diagnostics related to patents. A. Orr-Urtreger receives research support from the Kahn Foundation, Chief Scientist of the Israeli Ministry of Health, and the Michael J. Fox Foundation for Parkinson's Research. N. Giladi reports no disclosures relevant to the manuscript. S. Bressman serves on the advisory boards of the Michael J. Fox Foundation, the Dystonia Medical Research Foundation, the Bachmann-Strauss Dystonia & Parkinson Foundation, and the board of We Move. She has consulted for Bristol-Myers Squibb. She has received research support from the Michael J. Fox Foundation, NIH, and Dystonia Medical Research Foundation. Go to Neurology.org for full disclosures.

Received November 1, 2014. Accepted in final form March 12, 2015.

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