Published in final edited form as:

Mov Disord. 2018 July ; 33(6): 966–973. doi:10.1002/mds.27342.

Application of the Movement Disorder Society Prodromal Criteria in healthy *G2019S-LRRK2* carriers

Anat Mirelman, PhD^{1,2}, Rachel Saunders-Pullman, MD, MS, MPH^{4,5}, Roy N Alcalay, MD, MSc⁶, Shiran Shustak, BSc¹, Avner Thaler, MD, PhD^{1,2}, Tanya Gurevich, MD^{1,2}, Deborah Raymond, MS⁴, Helen Mejia-Santana, MS⁶, Martha Orbe Reilly, MD⁶, Laurie Ozelius, PhD⁵, Lorraine Clark, PhD^{6,7}, Mali Gana-Weisz, PhD³, Anat Bar-Shira, PhD³, Avi Orr-Utreger, MD, PhD^{2,3}, Susan B Bressman, MD^{1,2}, Karen Marder, MD, MPH⁶, Nir Giladi, MD^{1,2}, and the AJ LRRK2 Consortium

¹Movement Disorders Unit, Neurological Institute, Tel Aviv Medical Center, Tel-Aviv, Israel

²Sackler School of Medicine, Sagol School for Neuroscience, Tel Aviv University, Tel-Aviv, Israel

³Genetics Institute, Tel Aviv Medical Center, Tel Aviv Israel

⁴Departments of Neurology, Mount Sinai Beth Israel Medical Center

⁵Icahn School of Medicine at Mount Sinai, New York, NY, USA

⁶Department of Neurology, College of Physicians and Surgeons, Taub Institute for Alzheimer's Disease and the Aging Brain, Columbia University, New York, NY, USA

⁷Department of Pathology and Cell Biology, Columbia University Medical Center, New York, NY, USA

Abstract

Background—In 2015 the Movement Disorder Society (MDS) Task Force recommended research criteria for the estimation of prodromal PD. We aimed to evaluate, for the first time, the criteria in first-degree relatives of Ashkenazi Jewish *G2019S-LRRK2* PD patients, who are considered a population at risk for developing PD, and assess the sensitivity and specificity of the criteria in identifying phenoconverters.

Methods—Participants were evaluated longitudinally over a period of 5 years (average follow-up 49.2±12.3 months). Likelihood ratios (LR) and probability estimations were calculated based on the MDS Research Criteria for Prodromal Parkinson's Disease markers and examined for each assessment point.

Results—120 healthy carriers (HC) (49.53±13.4 yrs; 54%F) and 111 healthy non-carriers (HNC) (48.43±15.79 yrs; 49%F) participated in this study. Probability scores were significantly higher in

Correspondence to: Anat Mirelman, PhD, Laboratory of Early Markers of Neurodegeneration, Center for the study of Movement, Cognition and Mobility, Neurological Institute, Tel Aviv Medical Center, 6 Weizmann Street, Tel Aviv 64239, Israel, fax: +972-3-697-4911, anatmi@tlvmc.gov.il.

Author Roles

A. M. (1A, 1B, 1C, 2AM 2CM 3A, 3B), R.S.P (1B, 1C, 3B), R.N.A (1B, 1C, 3B), S.S (2B, 3B), A.T (1B, 1C, 3B), T.G (1C, 3B), D.R (1B, 1C, 3B), H.M-S (1B, 1C, 3B), M.O.R (1B, 1C, 3B), L.O (1C, 3B), L.C (1C, 3B), M. G-W(1C, 3B), A. B-S (1C, 3B), A. O-U (1A, 1B, 1C, 3B), S.B.B(1A, 1B, 1C, 3B), K.S.M (1A, 1B, 1C, 3B), N.G. (1A, 1B, 1C, 3B).

HC than HNC ($p<0.0001$). Of the twenty participants (8.6%) who met criteria for probable prodromal PD at baseline, 17 were HC. Participants who reached the threshold were older ($p<0.0001$), had higher UPDRS-III ($p<0.001$), lower cognitive function ($p=0.001$) and more non-motor symptoms ($p<0.0001$), compared to those who did not. Ten participants were diagnosed with incident-PD within 5 years from baseline resulting in a specificity of 91.82% (95%CI:86.69–96.94), sensitivity of 80% (95%CI:55.21–100%), PPV of 47.06% (95%CI:23.33–70.79) and NPV of 98.06% (95%CI:95.39–100). All 10 phenoconvertors were G2019S-*LRRK2* carriers.

Conclusions—The results showed the utility of using the criteria and high sensitivity and specificity in identifying prodromal PD in this high risk unique cohort. These results may be valuable for future disease modification clinical trials.

Keywords

LRRK2; Parkinson's disease; Prodromal; MDS prodromal criteria; G2019S; Progression

Introduction

The pathological changes of Parkinson's disease (PD) can start decades before the appearance of cardinal motor symptoms. Detecting patients at the premotor stage will be crucial for future clinical trials aiming at modifying progression at the earliest stages of the disease. In 2015, the International Parkinson and Movement Disorder Society (MDS) Task Force recommended research criteria using probability estimation for the diagnosis of prodromal PD¹. The criteria includes risk factors as well as motor and non-motor prodromal markers. These prodromal criteria need to be validated in cohorts at increased risk of developing PD.

The MDS Research Criteria for Prodromal PD has been examined in four different high risk cohorts: individuals with diagnosed REM sleep Behavior Disorder (RBD)²; Early Detection of Neurodegeneration cohort (TREND study³: the presence of probable RBD, depression, and/or hyposmia); the population-based Prospective Evaluation of Risk Factors for Idiopathic Parkinson's Syndrome (PRIPS)³; and a general elderly population (Bruneck study)⁴. Based on their available data, these studies reported a wide range of sensitivity (14–81.3%) and positive predictive value (19–81%) for the prediction of PD but relatively high specificity (67.9–99.2%).

The autosomal dominant G2019S mutation in exon 41 (leucine rich repeat kinase 2-*LRRK2*) is increased in Ashkenazi Jewish (AJ) PD patients⁵, where rates approach as high as 26% in familial and 14% in apparently sporadic PD^{5,6}. The asymptomatic first-degree relatives of AJ PD patients with the G2019S-*LRRK2* mutation, represent a population at risk for developing PD. Yet, penetrance is incomplete and age-dependent, estimated at 80 years of age as 26% (95%CI 0.18–0.36) among AJ⁷ and 42.5% (95%CI: 26.3 – 65.8%) in G2019S-*LRRK2* carriers who are non-AJ⁸. The value of the MDS Research Criteria in such a unique population is of special importance for disease prevention and modification trials. The estimated low penetrance further highlights the need to identify mutation carriers at risk for development of PD for future trials.

Thus the aims of this study were to: 1) evaluate the likelihood ratio (LR) and PD probability in unaffected AJ, carriers and non-carriers of the G2019S-*LRRK2* mutation, 2) explore the change in LR's and probability over time in this cohort and 3) assess the sensitivity and specificity of the MDS prodromal criteria in identifying phenoconverters (incident PD) in this unique cohort.

Methods

Participants

The study was conducted by the *LRRK2* AJ Consortium which includes centers in Israel (Tel Aviv Medical Center; TLVMC) and New York (Beth Israel Medical Center; BI and Columbia University Medical Center; CU). 231 healthy AJ relatives of PD patients, who were carriers of the G2019S *LRRK2* mutation, participated in this double blind (to mutation status) observational longitudinal study (BI=30, CU=46 and TLVMC=155) (Table 1). Participants were excluded if they were diagnosed with PD or dementia or any symptoms suggesting possible parkinsonism (UPDRS-III>7) at baseline, or if they carried one of the 7 common mutations among AJ in the glucocerebrosidase 1 gene (*GBA1*). The study was approved by the Institutional Review Boards at all sites. All participants provided informed consent. Participants were followed every 18–24 months, (average duration: 49.2 months, range: 17–64 months). During each follow-up visit, all participants were assessed again for parkinsonism by a movement disorders specialist blinded to genetic status to assess phenoconversion (based on the UK Brain Bank criteria⁹).

Outcomes

In order to calculate the post-test probability for conversion to PD for each participant, individualized Likelihood Ratios (LR) were calculated, at baseline and during each follow-up visit, for each MDS prodromal criterion according to the recommended scores¹. Except SN hyperechogenicity and single-photon emission computed tomography (SPECT)/PET, all items of the MDS prodromal criteria were evaluated in our cohort. Risk markers included: age, sex, family history, G2019S-*LRRK2* genetic status, habits and occupational exposure. Prodromal markers included subtle motor and non-motor symptoms with the specified cut-offs: Motor function was tested using the UPDRS-Part III⁹ with a cut-off score of >3 (excluding action tremor). Olfactory function: a score <20th percentile for the individual's age group and sex on the University of Pennsylvania Smell Identification Test (UPSIT)¹⁰ was considered high risk. REM sleep Behavior Disorder (RBD) was assessed using the RBDQ¹¹ with a score of ≥6 reflecting RBD based on the exploration of PD related dysfunction¹⁸. Urinary, erectile, and bowel symptoms received a high risk LR if scored 1 on the specified item on the Non-Motor Symptom Questionnaire (NMS)¹² or ≥2 on the corresponding item on the Scale for Autonomic Function (SCOPA-AUT)¹³; orthostatic hypotension was tested by manual measurement of blood pressure in supine position and after 1 minute of standing. A drop in systolic blood pressure >20mm Hg or >10mm Hg with positive symptoms was considered high risk. A score of ≥14 on the Beck Depression Inventory-II (BDI-II)¹⁴ or ≥6 on the Geriatric Depression Scale-15 (GDS-15)¹⁵ were used as the cut-off for depression while a score of >10 on the Epworth Sleepiness Scale (ESS)¹⁶ reflected somnolence. Smoking, caffeine consumption and pesticide and occupational

exposure were evaluated using the PD Risk Factor Questionnaire (RFQ)¹⁷. Table 2 summarizes the list of the items evaluated in our cohort and their pre-recommended LR for each corresponding status. As recommended, missing values were awarded a score of 1¹.

Prior-probability was based on the recommended age related criterion, this was combined with the minimum required LR for prodromal PD to calculate post-probability of disease using the 80% threshold as a marker for prodromal likelihood¹. This procedure was re-performed with updated information on age and prodromal features at each follow-up point. Note that all of the participants in our study were first-degree relatives of patients with PD which awards a 2.5 point score (or 7.5 if sibling had PD with age of onset <50) if genotype is not added. 52% of our cohort were carriers of the G2019S-*LRRK2* mutation which awarded a 25 point LR score already at the time of recruitment. For individuals under the age of 50 we used prior probability of 0.2% and an LR threshold of 1200 based on sensitivity assessment.

Statistical Analysis

Mean (standard deviation; SD) and frequency percentages were used to describe numeric and categorical variables, respectively. Univariate comparisons between the LRs of healthy carriers (HC) and healthy non-carriers (HNC) of the G2019S-*LRRK2* mutation were performed using independent samples t tests, Pearson chi-square, or Fisher's exact test, where appropriate.

Linear mixed model analysis was used to evaluate change in LR over time with random intercepts allowed in order to improve model estimations. Change between assessment points was calculated. Individuals were then stratified into either incident PD or non-converters (PD-free) according to the presence of PD clinical diagnosis at last follow-up. Differences between groups (i.e., incident PD vs. PD-free) in categorical variables at baseline were tested using the Fisher exact test and the Mann-Whitney U test, respectively. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and relative risk probability for the diagnosis of incident PD were calculated. We used SPSS for Windows version 22.0 for all statistical analyses. The level of significance was set to $P < .05$.

Results

Participant characteristics are detailed in table 1. Subjects were similar between sites in terms of age and gender, and average UPDRS-III was 1.82 ± 1.94 . Participants in Tel Aviv had lower UPSIT scores than the two groups from the USA ($p=0.001$) while participants at CU had higher MoCA scores ($p < 0.001$) and participants at BI were more likely to report RBD than the 2 other sites ($p=0.009$).

Comparison between healthy carriers (HC) and healthy non-carriers (HNC) at baseline revealed that HC had a higher frequency of constipation ($p=0.041$) and a trend for depression ($p=0.071$) but less frequent reports of RBD ($p=0.07$). As expected based on presence of mutation, HC had higher LR ($p=0.001$) and post-probability scores ($p < 0.001$), compared to HNC (Table 2). When removing *LRRK2* mutation status from the LR

calculation, post-probability was slightly higher in HC than HNC (11.77 ± 25.9 vs. 8.65 ± 29.65) while LR scores showed high variability (37.26 ± 113.44 vs. 24.76 ± 73.48 , respectively) with no between group differences ($p > 0.101$).

A total of 20 participants met criteria for probable prodromal PD (>80% of threshold) at baseline (prevalence, 8.6%; 95% CI, 6.1%–13.9%), 3(15%) were parents of patients with PD, 12(60%) were siblings and 5(25%) were children of patients with PD. Seventeen (85%) of these participants were mutation carriers (Figure 1). Participants who reached the threshold for probable prodromal PD were older (mean age 70.05 ± 12.46 vs. 48.36 ± 12.94 ; $p < 0.0001$), had higher scores on the UPDRS-III (5.25 ± 1.37 vs. 1.49 ± 1.66 ; $p < 0.001$) and lower cognitive scores (mean MOCA: 24.90 ± 3.21 vs. 26.77 ± 2.40 ; $p = 0.001$), compared to those below the threshold. In addition, a higher frequency of constipation (95% vs. 25.4%; $p < 0.0001$), somnolence (15.0% vs. 3.3%; $p = 0.014$), erectile dysfunction (69.2% vs. 19.4%; $p < 0.0001$), and hyposmia (50.0% vs. 20.9%; $p = 0.001$) was reported by prodromal participants than PD-free. Mean number of prodromal markers was greater for HNC who reached the threshold but remained PD-free than PD-free HC (5.3 vs. 4) (Supplementary figure 1). Thirty participants reached scores above 50% of post-probability prodromal PD. Within this group 8 were HNC and 22 were HC. (Supplementary figure 2).

LR scores tended to slightly increase with follow-up with an average increase of $129\% \pm 380\%$ in both HC and HNC for the total follow-up period (Mean follow-up duration HC group 47.7 ± 13.2 months; HNC 50.1 ± 11.3 months), with no difference in change over time between groups ($p = 0.63$). Contrarily, a significant increase in LR scores was observed in the 20 probable prodromal subjects from baseline to last follow-up ($p < 0.0001$). This change was significantly greater than that of all PD-free subjects even when genetic status was not included, reflecting a higher frequency of non-motor symptoms ($p < 0.0001$) (Figure 2).

Of the 231 participants, 10 were diagnosed with incident PD during follow-up (4 after 3 years and 6 after 5 years). Six were children and 4 were siblings of PD patients. None of the phenoconvertors were related to each other and all 10 phenoconvertors were carriers of the G2019S-*LRRK2* mutation, thus they had significantly higher LRs and posttest probabilities even at baseline assessment. Eight out of these 10 subjects reached the 80% threshold for prodromal PD already at baseline assessment resulting in specificity of 91.82% (95%CI: 86.69–96.94), sensitivity of 80% (95%CI: 55.21–99%), PPV of 47.06% (95%CI: 23.33–70.79) and NPV of 98.06% (95%CI: 95.39–100%) (Table 3).

Most of the single markers were more frequent in incident-PD cases compared with those who remained disease free, with the following reaching statistical significance: UPDRS-III scores ($P < 0.001$), somnolence ($p = 0.001$), constipation ($p < 0.0001$), and erectile dysfunction ($p = 0.003$). The two phenoconvertors who did not reach the 80% threshold at baseline assessment, scored post-probabilities of 67% and 52.8%. These subjects were 45 and 30 years of age at baseline assessment and developed PD within 38 months. Expanding the threshold to 50% slightly decreased specificity while sensitivity increased to 100%. When exploring the classification function without the genetic status, sensitivity markedly declined (table 3 and supplementary figure 2).

Discussion

The present study is the first to evaluate the MDS Research Criteria for Prodromal PD in carriers of the G2019S –*LRRK2* mutation and the first among Ashkenazi Jews. Our study investigated the utility and validity of using the MDS Research Criteria in this at risk population and the sensitivity of the criteria in identifying prodromal PD in this unique cohort.

As expected, HC had higher LR and post-probability scores compared to HNC. This is not surprising as the presence of the *LRRK2* G2019S mutation, even without additional symptoms, increases the LR. Mathematically, carriers can meet the threshold for prodromal PD with just 3–4 additional prodromal markers. By contrast, HNC need to have a larger number of prodromal markers to reach the 80% post-probability threshold (recall supplementary figure 1). In accordance with earlier reports¹⁹, HC demonstrated slightly more non-motor symptoms such as constipation and depression compared to HNC. Previous studies reported less hyposmia and RBD in patients with AJ and non AJ *LRRK2*-PD, as compared to idiopathic PD cases^{18, 20–22}. Consistent with these findings, olfaction did not differ between HC and HNC while there was a trend for less RBD in HC than HNC.

Change in post-probability scores between PD-free HC and HNC over the 5 year follow-up period was similar. The assumption underlying the MDS Research Criteria for Prodromal PD is that time-dependent prodromal markers should have a steeper increase in prodromal subjects as opposed to low-risk groups. Indeed rate of change in the prodromal subjects was significantly faster than in the PD-free subjects. This difference between groups was already observed at the initial follow-up assessment (19 months post-baseline), suggesting that exploring change in individuals with minimal symptoms, even after short periods of time, can help increase the likelihood of identifying potential phenoconversion.

These findings attest to the stability of the criteria, but highlight the limitations of some of the time-dependent clinical markers used for the criteria. Many of these markers are measured using self-report questionnaires (i.e., RBDQ, SCOPA-AUT, NMSQ, ESS) which may impact the validity and accuracy of the information as compared to quantitative measures (i.e., PSG). In our study, motor function was assessed using the UPDRS-III which lacks sensitivity for mild motor changes. The MDS Research Criteria for Prodromal PD defined LR for quantitative motor tests of the upper extremity but not lower extremity function or gait¹. Previous studies have shown subtle motor changes in *LRRK2* carriers and individuals with SN hyperechogenicity using instrumented gait and motor function assessment^{23–27}. Adding such objective quantitative measures may enhance the sensitivity of the criteria for change overtime.

We found a prevalence of probable prodromal PD¹ in 8.6% of our cohort. This prevalence is much higher than the 2.2% reported in the general older population⁴ and 0.77% in the TREND study³ but significantly lower than the 60.3% reported in confirmed RBD cases². Specificity predicting incident PD in our carrier group was high at 91.8% and NPV of 98% while sensitivity was slightly lower at 80%, similar to that of RBD cases², demonstrating the value of this approach. When we expanded the threshold for possible prodromal (>50%

probability), we found a prevalence of 12.9% in the cohort, with 22 subjects in the HC group (18.3%) and 8 of the HNC's (7.2%) reaching the threshold. This approach slightly decreased specificity (88.18%) but increased sensitivity to 100%. The MDS Research Criteria for Prodromal PD set an 80% threshold for posttest probability in order to enhance specificity to define target populations for future disease-prevention trials. However, similar to the findings reported by Mahlke et al⁴, using a post-probability threshold of 50% significantly enhanced sensitivity while the decrease in specificity was minute. Applying a broader definition may assist in recruitment and account for variability in clinical trials. Interestingly, when we calculated classification functions without accounting for genetic status, sensitivity significantly declined by approximately 50%. Considering the low penetrance of the G2019S-*LRRK2*, the NPV may be highly valuable in future disease prevention clinical trials as it may be useful in identifying, with high probability, those individuals who are unlikely to manifest.

Two of the incident-PD subjects were not identified as prodromal PD at the time of initial assessment. Both individuals were younger than 50 years of age which was the minimum prior-probability set by the MDS task force. This is an important observation as approximately 10% of all patients with PD are diagnosed before the age of 50²⁸. Thus, it seems likely that prodromal symptoms could be detected at a much younger age and perhaps the criteria should be expanded. On the other hand, higher post-probability scores were observed in older individuals above 80 years of age. It is important to consider that a score of 4 points on the UPDRS-III increases the LR 10-fold. Many older adults are likely to present motor impairments that can result in a higher UPDRS-III score, while the frequency of non-motor symptoms increases with age. Interestingly, the median LR scores of our older group (>80 years of age) was higher than the threshold for probable PD defined by the MDS Research Criteria for Prodromal PD (recall figure 1). This may likely have an effect on the specificity of the criteria. The Bruneck study⁴, evaluated the criteria in older adults. However, the age range of the participants in that study was between 61.4–78.8 years. Thus further investigation of the criteria in older and younger adults is needed to fully assess the advantages and limitations of the criteria in these populations²⁹ and their applicability to broad clinical cohorts.

The research approach to develop this prodromal probability for the general population is certainly comprehensive but may need to be modified for use in specific genetic groups. For example, previous studies have shown a similar gender ratio in G2019S-*LRRK2* PD³⁰. The risk scores provided in the criteria award higher risk to males than females based on the ratio observed in IPD. This should probably be modified to improve sensitivity. Further, current estimations regarding G2019S penetrance in AJ is 26% at age 80⁷. Presently, penetrance estimations are not incorporated into the Research Criteria for Prodromal PD meaning, the existence of genetic mutation awards a flat LR score regardless of age. This method assumes a linear relationship while risk distribution of carrying the mutation varies based on age. It would be of interest to include estimations of penetrance and distribution as it may improve the accuracy, sensitivity and specificity of the criteria and is highly important to enable the estimation of time to phenoconversion and identifying potential participants for future disease modifying clinical trials. Nevertheless, the sensitivity observed in our cohort without

including the genetic status was still higher (40%) than that seen in other risk cohorts³, reaffirming the suitability of the criterion for such genetic cohorts.

Limitations and Strengths

This study was conducted in AJ carriers and non-carriers of the G2019S-*LRRK2* mutation. All of our subjects were first-degree relatives of PD patients, thus sensitivity and specificity estimates would be different if these conditions do not apply. Nevertheless, using such a population allowed us to investigate diagnostic accuracy with higher statistical power. Our study lacked data on some high-LR markers namely, dopaminergic PET/SPECT and polysomnography. Including such data would likely improve estimation even further. Lastly, the time to develop PD is still unclear and may rely on many aspects including for example reserve capacity. Twelve of our prodromal subjects remained PD-free at 5 years follow-up. It is likely that with a longer follow-up, additional prodromal subjects would have developed the disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the participants of this project for their invaluable contribution and the staff of the AJ *LRRK2* consortium for their effort and support.

Study Funding

This study was funded by the Michael J Fox Foundation for Parkinson's Research, the National Institute of Health (through Grant Numbers K02-NS073836, R56NS036630, K02NS080915, NS050487, NS060113, UL1 TR001873, UL1 RR024156 and NINDS 10628097) as well as by grants from the Tel Aviv Sourasky Medical Center Grant of Excellence, Khan Foundation, and the Israel Science Foundation Heritage Legacy. The funding sources had no involvement in the design, interpretation or writing of this manuscript.

Reference List

1. Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, Gasser T, Goetz CG, Halliday G, Joseph L, Lang AE, Liepelt-Scarfone I, Litvan I, Marek K, Obeso J, Oertel W, Olanow CW, Poewe W, Stern M, Deuschl G. MDS research criteria for prodromal Parkinson's disease. *Mov Disord*. 2015 Oct; 30(12):1600–11. [PubMed: 26474317]
2. Fereshtehnejad SM, Montplaisir JY, Pelletier A, Gagnon JF, Berg D, Postuma RB. Validation of the MDS research criteria for prodromal Parkinson's disease: Longitudinal assessment in a REM sleep behavior disorder (RBD) cohort. *Mov Disord*. 2017 Jun; 32(6):865–73. [PubMed: 28429825]
3. Pilotto A, Heinzel S, Suenkel U, Lerche S, Brockmann K, Roeben B, Schaeffer E, Wurster I, Yilmaz R, Liepelt-Scarfone I, von Thaler AK, Metzger FG, Eschweiler GW, Postuma RB, Maetzler W, Berg D. Application of the movement disorder society prodromal Parkinson's disease research criteria in 2 independent prospective cohorts. *Mov Disord*. 2017 Jul; 32(7):1025–34. [PubMed: 28509336]
4. Mahlknecht P, Gasperi A, Willeit P, Kiechl S, Stockner H, Willeit J, Rungger G, Sawires M, Nocker M, Rastner V, Mair KJ, Hotter A, Poewe W, Seppi K. Prodromal Parkinson's disease as defined per MDS research criteria in the general elderly community. *Mov Disord*. 2016 Sep; 31(9):1405–8. [PubMed: 27273736]
5. Orr-Urtreger A, Shifrin C, Rozovski U, Rosner S, Bercovich D, Gurevich T, Yagev-More H, Bar-Shira A, Giladi N. The *LRRK2* G2019S mutation in Ashkenazi Jews with Parkinson disease: is there a gender effect? *Neurology*. 2007 Oct 16; 69(16):1595–602. [PubMed: 17938369]

6. Ozelius LJ, Senthil G, Saunders-Pullman R, Ohmann E, Deligtisch A, Tagliati M, Hunt AL, Klein C, Henick B, Hailpern SM, Lipton RB, Soto-Valencia J, Risch N, Bressman SB. LRRK2 G2019S as a cause of Parkinson's disease in Ashkenazi Jews. *N Engl J Med*. 2006 Jan 26; 354(4):424–5. [PubMed: 16436782]
7. Marder K, Wang Y, Alcalay RN, Mejia-Santana H, Tang MX, Lee A, Raymond D, Mirelman A, Saunders-Pullman R, Clark L, Ozelius L, Orr-Urtreger A, Giladi N, Bressman S. Age-specific penetrance of LRRK2 G2019S in the Michael J. Fox Ashkenazi Jewish LRRK2 Consortium. *Neurology*. 2015 Jul 7; 85(1):89–95. [PubMed: 26062626]
8. Lee AJ, Wang Y, Alcalay RN, Mejia-Santana H, Saunders-Pullman R, Bressman S, Corvol JC, Brice A, Lesage S, Mangone G, Tolosa E, Pont-Sunyer C, Vilas D, Schule B, Kausar F, Foroud T, Berg D, Brockmann K, Goldwurm S, Siri C, Asselta R, Ruiz-Martinez J, Mondragon E, Marras C, Ghate T, Giladi N, Mirelman A, Marder K. Penetrance estimate of LRRK2 p.G2019S mutation in individuals of non-Ashkenazi Jewish ancestry. *Mov Disord*. 2017 Jun 22.
9. Fahn S, Elton R. Members of the UPDRS development committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne D, Goldstein M, editors *Recent developments in Parkinson's disease*. Florham Park, NJ: Macmillan Health Care Information; 1987. 153–63.
10. Doty RL, Frye RE, Agrawal U. Internal consistency reliability of the fractionated and whole University of Pennsylvania Smell Identification Test. *Percept Psychophys*. 1989 May; 45(5):381–4. [PubMed: 2726398]
11. Stiasny-Kolster K, Mayer G, Schafer S, Moller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire--a new diagnostic instrument. *Mov Disord*. 2007 Dec; 22(16):2386–93. [PubMed: 17894337]
12. Chaudhuri KR, Martinez-Martin P, Schapira AH, Stocchi F, Sethi KD, Odin P, Brown RG, Koller W, Barone P, MacPhee G, Kelly L, Rabey M, MacMahon D, Thomas S, Ondo WG, Rye D, Forbes A, Tluk S, Dhawan V, Bowron A, Williams AJ, Olanow CW. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. *Mov Disord*. 2006; 21(7):916–23. [PubMed: 16547944]
13. Visser M, Marinus J, Stiggelbout AM, Van Hilten JJ. Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. *Mov Disord*. 2004 Nov; 19(11):1306–12. [PubMed: 15390007]
14. Steer RA, Rissmiller DJ, Beck AT. Use of the Beck Depression Inventory-II with depressed geriatric inpatients. *Behav Res Ther*. 2000 Mar; 38(3):311–8. [PubMed: 10665163]
15. Meara J, Mitchelmore E, Hubson P. Use of the GDS-15 geriatric depression scale as a screening instrument for depressive symptomatology in patients with Parkinson's disease and their carers in the community. *Age Ageing*. 1999; 28:35–8. [PubMed: 10203202]
16. Hagell P, Broman JE. Measurement properties and hierarchical item structure of the Epworth Sleepiness Scale in Parkinson's disease. *J Sleep Res*. 2007 Mar; 16(1):102–9. [PubMed: 17309769]
17. Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Richardson RJ. The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. *Neurology*. 1998 May; 50(5):1346–50. [PubMed: 9595985]
18. Saunders-Pullman R, Alcalay RN, Mirelman A, Wang C, Luciano MS, Ortega RA, Glickman A, Raymond D, Mejia-Santana H, Doan N, Johannes B, Yasinovsky K, Ozelius L, Clark L, Orr-Urtreger A, Marder K, Giladi N, Bressman SB. REM sleep behavior disorder, as assessed by questionnaire, in G2019S LRRK2 mutation PD and carriers. *Mov Disord*. 2015 Nov; 30(13):1834–9. [PubMed: 26366513]
19. Mirelman A, Alcalay RN, Saunders-Pullman R, Yasinovsky K, Thaler A, Gurevich T, Mejia-Santana H, Raymond D, Gana-Weisz M, Bar-Shira A, Ozelius L, Clark L, Orr-Urtreger A, Bressman S, Marder K, Giladi N. Nonmotor symptoms in healthy Ashkenazi Jewish carriers of the G2019S mutation in the LRRK2 gene. *Mov Disord*. 2015 Jun; 30(7):981–6. [PubMed: 25809001]
20. Pont-Sunyer C, Tolosa E, Caspell-Garcia C, Coffey C, Alcalay RN, Chan P, Duda JE, Facheris M, Fernandez-Santiago R, Marek K, Lomena F, Marras C, Mondragon E, Saunders-Pullman R, Waro B. The prodromal phase of leucine-rich repeat kinase 2-associated Parkinson disease: Clinical and imaging Studies. *Mov Disord*. 2017 May; 32(5):726–38. [PubMed: 28370517]

21. Saunders-Pullman R, Mirelman A, Wang C, Alcalay RN, San LM, Ortega R, Raymond D, Mejia-Santana H, Ozelius L, Clark L, Orr-Urtreger A, Marder K, Giladi N, Bressman SB. Olfactory identification in LRRK2 G2019S mutation carriers: a relevant marker? *Ann Clin Transl Neurol*. 2014 Sep; 1(9):670–8. [PubMed: 25493281]
22. Marras C, Alcalay RN, Caspell-Garcia C, Coffey C, Chan P, Duda JE, Facheris MF, Fernandez-Santiago R, Ruiz-Martinez J, Mestre T, Saunders-Pullman R, Pont-Sunyer C, Tolosa E, Waro B. Motor and nonmotor heterogeneity of LRRK2-related and idiopathic Parkinson's disease. *Mov Disord*. 2016 Aug; 31(8):1192–202. [PubMed: 27091104]
23. Lerche S, Hobert M, Brockmann K, Wurster I, Gaenslen A, Hasmann S, Eschweiler GW, Maetzler W, Berg D. Mild parkinsonian signs in the elderly--is there an association with PD? Cross-sectional findings in 992 individuals. *PLoS One*. 2014; 9(3):e92878. [PubMed: 24675747]
24. Maetzler W, Hausdorff JM. Motor signs in the prodromal phase of Parkinson's disease. *Mov Disord*. 2012 Apr 15; 27(5):627–33. [PubMed: 22437964]
25. Mirelman A, Gurevich T, Giladi N, Bar-Shira A, Orr-Urtreger A, Hausdorff JM. Gait alterations in healthy carriers of the LRRK2 G2019S mutation. *Ann Neurol*. 2011 Jan; 69(1):193–7. [PubMed: 21280089]
26. Mirelman A, Bernad-Elazari H, Thaler A, Giladi-Yacobi E, Gurevich T, Gana-Weisz M, Saunders-Pullman R, Raymond D, Doan N, Bressman SB, Marder KS, Alcalay RN, Rao AK, Berg D, Brockmann K, Aasly J, Waro BJ, Tolosa E, Vilas D, Pont-Sunyer C, Orr-Urtreger A, Hausdorff JM, Giladi N. Arm swing as a potential new prodromal marker of Parkinson's disease. *Mov Disord*. 2016 Oct; 31(10):1527–34. [PubMed: 27430880]
27. Postuma RB, Aarsland D, Barone P, Burn DJ, Hawkes CH, Oertel W, Ziemssen T. Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. *Mov Disord*. 2012 Apr 15; 27(5):617–26. [PubMed: 22508280]
28. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol*. 2006 Jun; 5(6):525–35. [PubMed: 16713924]
29. Saunders-Pullman R, Lipton RB, Senthil G, Katz M, Costan-Toth C, Derby C, Bressman S, Verghese J, Ozelius LJ. Increased frequency of the LRRK2 G2019S mutation in an elderly Ashkenazi Jewish population is not associated with dementia. *Neurosci Lett*. 2006 Jul 10; 402(1–2):92–6. [PubMed: 16632201]
30. Gan-Or Z, Leblond CS, Mallett V, Orr-Urtreger A, Dion PA, Rouleau GA. LRRK2 mutations in Parkinson disease; a sex effect or lack thereof? A meta-analysis. *Parkinsonism Relat Disord*. 2015 Jul; 21(7):778–82. [PubMed: 25962553]

Figure 1.

Violin plots of LR for prodromal PD based on age criteria at initial assessment. The orange line represents the threshold per age. The contour of the figure is based on frequency with wider areas representing more individuals and the widest area represents the median of the group per age. The green dots represent the HNC and the blue dots are the HC. Dots circles in black are the subjects who were diagnosed with PD during follow-up. Note that the median score in the over 80 years of age group is higher than the threshold.

Figure 2.

Change in LR over time in prodromal cases (n=20) and in PD-free subjects(n=211). Prodromal PD cases were identified during T1 (initial assessment). T2 follow-up was on average 19.4 months post T1 and 23.3 months before T3. Note within the group of probable prodromal cases at T1, 8 subjects were diagnosed with incidence-PD by last follow-up. LR scores in this figure do not include the genetic status in order to evaluate the slope of change as a function of the increase in clinical symptoms. Mean and SE are presented.

Table 1

Participant characteristics. Mean and SD are provided as well as range and percent.

	All subjects (n=231)	Beth Israel (n=30)	Columbia U (n=46)	Tel Aviv (n=155)	P value
Degree of relation (Parents/ siblings/ children of patients)	6% / 26.5% / 67.5%	10% / 30 % / 60%	8.7% / 30 % / 61%	4% / 25.2% / 71%	0.454
Carriers of LRRK2-G2019S mutation (carriers/ non-carriers) (n, % for Parents/ siblings/ children within carriers)	120/1117 (51%) / 30 (50%) / 83 (53.2%)	17/131 (5.9%) / 5 (29.4%) / 11 (64.7%)	24/223 (12.5%) / 8 (33.3%) / 13 (54.2%)	79/762 (2.5%) / 18 (22.8%) / 59 (74.7%)	0.849
Age (y)	50.3 ± 14.2 (21–89)	48.8 ± 16.5 (21–86)	52.8 ± 15.5 (25–89)	49.5 ± 13.4 (30–85)	0.352
Sex (M/F)	113/118	16/14	18/28	78/77	0.279
Years of education (y)	12.7 ± 5.8 (9–22)	13.6 ± 5.3 (10–21)	12.9 ± 6.0 (9–21)	11.6 ± 6.1 (9–22)	0.163
UPDRS III	1.8 ± 1.9 (0–7)	1.4 ± 1.6 (0–7)	1.2 ± 1.9 (0–7)	2.1 ± 1.9 (0–7)	0.012
MOCA	26.6 ± 2.5 (18–30)	26.6 ± 2.6 (19–30)	28.4 ± 1.4 (25–30)	26.1 ± 2.5 (18–30)	<0.0001
Olfaction: % Normosmic / % hyposmic / % anosmic	81.7% / 15.6% / 2.7%	90.9% / 4.5% / 4.6%	91.7% / 5.5% / 2.8%	62.6% / 36.7% / 0.7%	0.034
Ever Smoked (%)	43.3%	44.4%	47.9%	37.5%	0.864
Positive RBDQ (6)	6.1%	10%	6.5%	5.2%	0.590

UPDRS-III- Unified Parkinson's Disease Rating Scale part III; MOCA- Montreal Cognitive Assessment; RBDQ- REM Sleep Behavior Disorder Questionnaire.

Frequency of prodromal symptoms in carriers and non-carriers. Assigned LR based on the MDS Research Criteria for Prodromal PD is presented for each criteria.

Table 2

Characteristics	MDS prodromal criteria	Total population (N =231)	HNC (N =111)	HC (N= 120)	Between group p value
Genetic mutation LRRK2 G2019S	Positive – 25	120 (52.1%)	---	100%	<0.001
	Negative - NA	111 (47.9%)	100%	----	
Sex	Male - 1.2	113 (48.9%)	57 (50.4%)	56 (49.6%)	0.477
	Female - 0.8	118 (50.8%)	54(48.6%)	64 (53.3%)	
	Current - 0.45	40 (18.0%)	20 (19 %)	20 (17.1%)	
	Never smoked - 1.25	128 (57.7%)	60 (57.1%)	68 (58.1%)	
Smoking	Former smoker- 0.8	54 (24.3%)	25 (23.8%)	29 (25 %)	0.929
	Non-Use – 1.35	23 (10 %)	11 (10.6%)	12 (10.2 %)	
Caffeine	Use – 0.88	199 (89.6%)	93 (89.4%)	106 (89.8%)	0.921
	Loss or impaired - 4.0	54 (23.4%)	29 (26.1%)	25 (20.8%)	
Olfactory function	Normal - 0.43	154 (66.7%)	69 (62.2%)	85 (70.8%)	0.175
	Positive - 2.2	83 (31.7%)	33 (31.4%)	50 (41.6%)	
Constipation	Negative - 0.8	148 (64.0%)	78 (70.2%)	70 (58.3%)	0.041
	Positive- 2.2	10 (4.3%)	5 (4.5%)	5 (4.2%)	
Somnolence	Negative- 0.88	221 (95.7%)	106 (95.5%)	115 (95.8%)	0.900
	Positive- 2.1	35 (38.0%)	17 (37.8%)	18 (38.3%)	
Orthostatic Hypotension	Negative- 0.87	57 (62.0%)	28 (62.2%)	29 (61.7%)	0.976
	Positive- 2.0	29 (26%)	12 (21.8%)	17 (30.3%)	
Erectile dysfunction	Negative- 0.90	76 (68.4 %)	40 (73.0%)	36 (64.2 %)	0.391
	Positive- 2.3	14 (6.1%)	10 (9.0%)	4 (2.2 %)	
RBDQ (6)	Negative- 0.76	217 (93.9%)	101 (91.0%)	116 (96.7%)	0.070
	Positive-1.8	99 (43%)	42 (38.2%)	57 (45.5%)	
Depression	Negative- 0.85	112 (48.7%)	57 (51.8%)	55 (45.8%)	0.071
	Positive- 1.90	48 (21%)	22 (20.2%)	26 (21.7%)	
Urinary dysfunction	Negative- 0.90	173 (75.5%)	83 (76.1%)	90 (75%)	0.957
	> 3 - 10.0	43 (18.6%)	17 (15.3%)	26 (21.7%)	
UPDRS - III					0.215

Characteristics	MDS prodromal criteria	Total population (N =231)	HNC (N =111)	HC (N= 120)	Between group p value
	3- 0.7	188 (81.4%)	94 (84.7%)	94 (78.3%)	
Exposure (occupational and pesticides)	Positive – 1.5	25 (10.4%)	12 (11.0%)	13 (10.9%)	0.833
	Negative or missing - NA	206 (89.1%)	103 (92.7%)	103 (85.8%)	
	-----	205.4±835.9	24.8±73.5	372.5±1134.5	
LR	-----				0.001
Post-probability (%)	-----	16.7 ± 28.1.30	8.3±19.5	24.5±32.4	<0.001
Frequency of Prodromal within groups based on age N(% of total)	Below 50 yrs		0 (0%)	1 (0.8%)	<0.001
	50 to 54 yrs;		0 (0%)	0 (0%)	
	55 to 59 yrs;		0 (0%)	3 (2.4%)	
	60 to 64 yrs;		0 (0%)	3 (2.4%)	
	65 to 69 yrs;		0 (0%)	3(2.4%)	
	70 to 74 yrs;		0 (0%)	2 (1.6%)	
	75 to 79 yrs;		1 (0.8%)	2 (1.6%)	
	80 yrs and over.		2 (1.6%)	3 (2.4%)	

Missing values were not imputed.

Table 3

Specificity and Sensitivity of detecting phenococonversion (%) and 95%CI are presented)

		Specificity	Sensitivity	PPV	NPV
HC (n=120)	At 80% Threshold	91.82% (86.69–96.94)	80% (55.21–100%)	47.06% (23.33–70.79)	98.06% (95.39–100%)
	At 50% Threshold	88.18% (82.15–94.21)	100% (100–100)	43.48% (23.22–63.74)	100 (100–100)
	At 80% Threshold without genetic status	98.18% (95.69–100)	40% (9.64–70.36)	66.66% (29.95–100)	94.74% (90.64–98.84)
	At 50% Threshold without genetic status	95.45% (91.56–99.35)	70% (41.59–98.40)	58.33% (30.44–86.23)	97.22% (94.12–100)
HNC (n=111)	At 80% Threshold	97.29% (94.28–100)	----	----	100
	At 50% Threshold	93.69% (89.17–98.22)	----	----	100
	At 80% Threshold without genetic status	97.29% (94.28–100)	----	----	100
	At 50% Threshold without genetic status	93.69% (89.17–98.22)	----	----	100

PPV- Positive Predictive Value, NPV- Negative Predictive Value