

GBA variants in REM sleep behavior disorder

A multicenter study

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Neurology® 2020;95:e1008-e1016. doi:10.1212/WNL.0000000000010042

Abstract

Objective

To study the role of *GBA* variants in the risk for isolated REM sleep behavior disorder (iRBD) and conversion to overt neurodegeneration.

Methods

A total of 4,147 individuals were included: 1,061 patients with iRBD and 3,086 controls. *GBA* was fully sequenced using molecular inversion probes and Sanger sequencing. We analyzed the effects of *GBA* variants on the risk of iRBD, age at onset (AAO), and conversion rates.

Results

GBA variants were found in 9.5% of patients with iRBD compared to 4.1% of controls (odds ratio, 2.45; 95% confidence interval [CI], 1.87–3.22; $p = 1 \times 10^{-10}$). The estimated OR for mild p.N370S variant carriers was 3.69 (95% CI, 1.90–7.14; $p = 3.5 \times 10^{-5}$), while for severe variant carriers it was 17.55 (95% CI, 2.11–145.9; $p = 0.0015$). Carriers of severe *GBA* variants had an average AAO of 52.8 years, 7–8 years earlier than those with mild variants or noncarriers ($p = 0.029$). Of the *GBA* variant carriers with available data, 52.5% had converted, compared to 35.6% of noncarriers ($p = 0.011$), with a trend for faster conversion among severe *GBA* variant carriers. However, the results on AAO and conversion were based on small numbers and should be interpreted with caution.

Conclusions

GBA variants robustly and differentially increase the risk of iRBD. The rate of conversion to neurodegeneration is also increased and may be faster among severe *GBA* variant carriers, although confirmation will be required in larger samples. Screening for RBD in healthy carriers of *GBA* variants should be studied as a potential way to identify *GBA* variant carriers who will develop a synucleinopathy in the future.

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Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by The Charity Open Access Fund (COAF).

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Glossary

AAO = age at onset; **CI** = confidence interval; **DLB** = dementia with Lewy bodies; **GCase** = glucocerebrosidase; **GD** = Gaucher disease; **GWAS** = genome-wide association study; **iRBD** = isolated REM sleep behavior disorder; **MIP** = molecular inversion probe; **MSA** = multiple system atrophy; **NGS** = next-generation sequencing; **OR** = odds ratio; **PD** = Parkinson disease; **pRBD** = probable REM sleep behavior disorder; **RBD** = REM sleep behavior disorder.

Isolated REM sleep behavior disorder (iRBD) can be considered a prodromal synucleinopathy, because >80% of patients with iRBD will eventually convert to an overt neurodegenerative syndrome associated with α -synuclein accumulation—Parkinson disease (PD), dementia with Lewy bodies (DLB), or multiple system atrophy (MSA)¹—with a conversion rate of about 6% a year.² For unknown reasons, while some patients with iRBD convert rapidly, others can remain free from parkinsonism or dementia for decades.^{3,4}

Variants in the gene encoding for the lysosomal enzyme glucocerebrosidase, *GBA*, are strong and relatively common risk factors for PD^{5,6} and DLB,⁷ yet their role in MSA is unclear.^{8–10} Patients with PD who carry *GBA* variants, as a group, tend to have higher rates of nonmotor symptoms, including REM sleep behavior disorder (RBD), cognitive impairment, hyposmia, and autonomic dysfunction.¹¹ *GBA* variants can be classified as severe or mild based on the type of Gaucher disease (GD) associated with the variant.¹² Accordingly, patients with severe *GBA* variants have a higher risk for PD, an earlier average age at onset (AAO),⁵ and faster cognitive decline^{13,14} compared to patients with PD with mild or no *GBA* variants.

Few studies with small sample size have examined the role of *GBA* in iRBD, including studies of 69,¹⁵ 171,¹⁶ and 265 patients with iRBD,¹⁵ all supporting an association between *GBA* variants and iRBD but with different risk estimates. It has been shown that in PD cohorts with available data on probable RBD (pRBD), *GBA* variants are more frequent in the group with pRBD.¹⁵ However, there are no accurate estimates of the risk of iRBD among *GBA* variant carriers and there have been no studies separately analyzing severe and mild *GBA* variants. It is not clear whether *GBA* variants affect the rate of conversion from iRBD to overt synucleinopathies, as only 2 small sample size studies with contradicting results examined this hypothesis. In one, there was no association with the rate of conversion in 8 *GBA* variant carriers with iRBD¹⁶; in the other, a faster conversion was shown for 13 *GBA* variant carriers with iRBD compared to noncarriers.¹⁷

In this study, we analyzed *GBA* variants in a large, multicenter study including 1,061 patients with iRBD, more than double the sample than all previous studies combined, and 3,086 controls, all of European origin. We further examined the effects of severe vs mild *GBA* variants on risk of iRBD,

reported AAO of iRBD, and the potential effects on conversion from iRBD to an overt neurodegenerative disease.

Methods

Population

The patient population included 1,061 individuals diagnosed with iRBD with video-polysomnography according to the International Classification of Sleep Disorders, version 2 or 3 criteria.¹⁸ The recruiting centers and the number of patients from each center are detailed in table 1. Additional data were available for subsets of samples, including reported AAO of RBD (*n* = 594), age at diagnosis of iRBD (*n* = 599), eventual phenocconversion to an overt neurodegenerative disease (data available for *n* = 584, converted *n* = 218), and rate of phenocconversion (*n* = 217). The average follow-up period for *GBA* carriers was 4.8 years and for noncarriers it was 4.1 years (*p* = 0.22).

The data on these variables were collected in 2018. The control population included a total of 3,086 individuals, comprised of 1,317 in-house controls of European origin (confirmed by principal component analysis using available genome-wide association study [GWAS] data compared to data from HapMap v.3 and hg19/GRCh37) and an additional 1,769 previously published European controls in which *GBA* was fully sequenced and all the variants were reported (table e-1 details these controls and the reported *GBA* variants in each of the articles; github.com/gan-orlab/GBA_RBD/). The in-house controls had a mean age of 46.5 ± 15.0 years and included 46.6% men, compared to 60.5 ± 9.9 and 81% men in the patients, therefore when analyzing these populations, adjustment for age and sex was performed (see Statistical analysis and Results).

GBA sequencing and classification of GBA variants

GBA was fully sequenced as described previously¹⁹ and the full protocol is available upon request. In brief, we designed molecular inversion probes (MIPs) targeting the coding sequence of *GBA* and performed next-generation sequencing (NGS) post capture. Alignment, variant calling, and annotations were done as previously described¹⁹ using a standard pipeline. Exons 10 and 11 were also sequenced using Sanger sequencing since the coverage of NGS of these exons was low. Table e-2 (github.com/gan-orlab/GBA_RBD/) details the probes used for the MIPs capture. Classification of *GBA* variants as severe or mild was performed as described

Table 1 *GBA* variants in the participating centers

Center	<i>GBA</i> variant carriers, n (%) / n total patients with iRBD	<i>GBA</i> variants identified		Conversion data available for patients, n	Conversion in <i>GBA</i> carriers: condition (n converted)	
		Mild	Severe		Mild	Severe
Montreal, Canada	20 (15)/138	p.N370S-3 p.E326K-5 p.T369M-7 p.W378G-2	p.L444P-1 p.H255Q-1 p.W291X-1	125	p.E326K-DLB (2), PD (1), dementia (1) p.T369M-PD (3), MSA (1), dementia (1) p.W378G-DLB (2)	p.L444P-PD (1) p.H255Q-PD (1) p.W291X-PD (1)
Innsbruck, Austria	7 (9)/80	p.E326K-7		69	p.E326K-PD (1)	
Bologna, Italy	2 (7)/28	p.E326K-1 p.R2L-1		19	—	
Prague, Czech Republic	3 (6)/47	p.E326K-1 p.T369M-2		46	p.T369M-dementia (1)	
Paris, France	14 (6)/219	p.E326K-8 p.N370S-4 p.T369M-2		77	p.E326K-PD (1), dementia (1) p.N370S-PD (1)	
Montpellier, France (Beau Soleil Clinic)	5 (19)/26	p.E326K-2 p.N370S-1 p.T369M-1 p.R502C-1		2	p.R502C-PD (1)	
Lille, France	5 (22)/23	p.E326K-2 p.N370S-2	p.R131L-1	15	p.N370S-PD (1), MSA (1)	p.R131L-PD (1)
Montpellier, France (CHU Montpellier)	8 (8)/96	p.E326K-5 p.N370S-2 p.T369M-1		14	p.T369M-DLB (1)	
Kessel, Germany	3 (11)/27	p.E326K-2 p.T369M-1		27	p.T369M-DLB (1)	
Udine, Italy	6 (7)/83	p.E326K-2 p.N370S-2 p.T369M-1	p.D409H-1	25	p.E326K-unknown (1) p.N370S-unknown (1)	p.D409H-unknown (1)
Milan, Italy	1 (5)/19	p.T369M-1		19	None	
Oxford, United Kingdom	27 (15)/181	p.E326K-12 p.N370S-6 p.N227S-1 p.T369M-4 p.T369M/ p.E326K-1 p.R2L-1 p.Y212H-1	p.D409H-1	97	p.E326K-PD (2) p.N370S-PD (1)	

Abbreviations: DLB = dementia with Lewy bodies; iRBD = isolated REM sleep behavior disorder; MSA = multiple system atrophy; Parkinson disease. Centers with no *GBA* variant carriers are excluded from the table: Geel, Belgium (n = 9); Nimes, France (n = 5); Marburg, Germany (n = 29); Munster, Germany (n = 23); Cagliari, Italy (n = 28).

previously^{5,12} based on the occurrence of these variants in the severe (type II and type III) and mild (type I) forms of GD. The p.E326K and p.T369M variants, which do not cause GD but have a comparable risk as that of the p.N370S variants in PD,^{20,21} were therefore included in the mild variant group.

Statistical analysis

To examine the association between *GBA* variants and risk of iRBD and controls, we performed association tests (χ^2 or Fisher exact test), logistic regression adjusted for sex and age, and burden tests. To examine the association of *GBA* variants with risk of iRBD comparing all controls, we used χ^2 or Fisher

exact tests since there were no available data on age and sex from the controls collected from the literature to perform adjusted logistic regression. We therefore also performed this association using only our in-house European controls, for which data on age and sex were available, using logistic regression model adjusted for age and sex. Of note, having younger controls may result in underestimation of the risk, as some of the young controls with *GBA* variants may develop iRBD or overt neurodegeneration in the future. Therefore, if the statistical adjustment is not complete, the risk estimations that were calculated could be slightly lower (i.e., false-positive results are not likely; rather, underestimated risk is likely). We

also performed burden tests using the R package SKAT. Association with AAO and specific types of *GBA* variants (severe or mild) was tested using the nonparametric Kruskal-Wallis test since the group of severe *GBA* variants included only 5 patients. The association with conversion was tested using a χ^2 test for the total number of conversions, and Kaplan-Meier survival analysis was performed to examine the rate of conversion. All statistical analyses were performed using R or SPSS v24 (IBM, Armonk, NY).

Standard protocols approvals, registrations, and patient consents

All study participants signed informed consent forms, and the study protocol was approved by the institutional review boards.

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

GBA variants are associated with increased risk of iRBD with differential effects of severe and mild variants.

The variants in *GBA* identified in each of the participating centers are detailed in table 1, with a total of 17 distinct variants found in patients and controls (table 2). Table e-1 details the variants found in each of the previously published control populations. Out of 1,061 patients with iRBD, 101 *GBA* variant carriers (9.5%) were identified, compared to 126 out of 3,086 (4.1%) controls (table 2; odds ratio [OR], 2.45; 95% confidence interval [CI], 1.87–3.22; $p = 1 \times 10^{-10}$). We repeated this analysis using a logistic regression model adjusted for age and sex using the controls with available data ($n = 1,317$), which yielded very similar results (OR, 2.12; 95% CI, 1.34–3.36; $p = 0.001$). Burden tests using the R package SKAT also yielded similar results ($p = 2.6 \times 10^{-6}$ using the in-house controls and $p = 1.7 \times 10^{-12}$ using all controls). Similar to previous observations in PD, different *GBA* variants have different effects on the risk of iRBD. The mild p.N370S variant was found in 20 patients with iRBD (1.9%) compared to 16 (0.5%) controls (OR, 3.69; 95% CI, 1.90–7.14; $p = 3.5 \times 10^{-5}$), while severe variants (p.L444P, p.D409H, p.W291X, p.H255Q, and p.R131L) were found in 6 (0.6%) patients with iRBD and in 1 (p.L444P, 0.03%) control (OR, 17.55; 95% CI, 2.11–145.9; $p = 0.0015$). Of the 2 polymorphisms known to be risk factors for PD, p.E326K and p.T369M, only p.E326K was associated with iRBD (4.4% vs 1.5% in patients and controls; OR, 3.2; 95% CI, 2.12–4.84; $p = 6 \times 10^{-9}$), and the carrier frequency of p.T369M was only slightly elevated in iRBD but not statistically significant (1.9% vs 1.7%; OR, 1.13; 95% CI, 0.68–1.89; $p = 0.6$). The carrier frequencies of the p.N370S, p.E326K, and p.T369M variants in gnomAD (gnomad.broadinstitute.org/) in the European population are 0.4%, 2.4%, and 1.9%, respectively, similar to the frequencies in our controls.

Estimated AAO of iRBD may be affected by the type of *GBA* variant

AAO as reported by the patients could be an unreliable estimate and data were not available for all patients. Therefore, the following results should be considered with caution. Carriers of the severe *GBA* variants had an average AAO of 52.8 ± 2.8 years (data were available for 5 out of 6 patients with a severe *GBA* variant), carriers of all other variants had an average AAO of 59.7 ± 9.6 years (data were available for 58 patients), and noncarriers of *GBA* variants had an average AAO of 60.6 ± 9.9 years (data were available for 531 patients). Because there were only 5 patients in the severe variants group, the nonparametric Kruskal-Wallis test was performed, demonstrating a possible association with the type of variant ($\chi^2 = 7.083$, $df = 3$, $p = 0.029$), which will benefit from replication in a larger sample size.

Do *GBA* variants affect the rate of conversion of iRBD to overt neurodegenerative diseases?

Data on conversion of iRBD was available for 59 *GBA* variant carriers and 525 noncarriers of *GBA* variants. Of the *GBA* variant carriers, 31 (52.5%) had converted, and in noncarriers 187 (35.6%) had converted ($p = 0.011$). Data on time from iRBD diagnosis to phenoconversion or last follow-up was available for 29 *GBA* variant carriers and for 276 noncarriers. Kaplan-Meier survival analysis suggested that *GBA* variant carriers progressed faster but the difference vs noncarriers of *GBA* variants was not statistically significant (figure). When severe *GBA* variant carriers were compared to mild *GBA* carriers and noncarriers, a possible association was demonstrated, as the Breslow test was statistically significant and the Tarone-Ware test was at near statistical significance, while the log-rank test did not reach statistical significance (figure; Breslow $p = 0.017$, Tarone-Ware $p = 0.051$, log-rank $p = 0.24$).

Discussion

Our results confirm the association between *GBA* variants and increased risk of iRBD and suggest that severe and mild *GBA* variants have differential effects on risk, similar to previous reports in PD.⁵ These results also suggest that patients with iRBD with severe *GBA* variants may have earlier AAO and may convert faster to overt neurodegenerative disease. However, the results on AAO and conversion should be considered as preliminary only and with caution, due to several limitations discussed below.

Three previous small sample size studies have examined the association between *GBA* variants and iRBD.^{15,16,22} Two of these studies included full sequencing of the gene^{15,16} and the third only examined 2 specific variants (p.N370S and p.L444P).²² Due to their size, analyses of specific variants or types of variants, such as severe or mild, were not possible. The current study includes 2 of the previously published cohorts^{15,22} and additional cohorts of European ancestry. With the larger sample size accrued, we were able to

Table 2 *GBA* variants in patients with isolated REM sleep behavior disorder (iRBD) and controls

<i>GBA</i> variant ^a	Patients with iRBD, n (%) (n = 1,061)	All controls, n (%) (n = 3,086)	In-house controls, n (%) (n = 1,317)	Literature controls, n (%) (n = 1,769)
Heterozygous				
p.R2L	2 (0.2)	2 (0.06)	1 (0.08)	1 (0.06)
p.K79M	—	1 (0.03)	—	1 (0.06)
p.R131L	1 (0.1)	—	—	—
p.Y212H	1 (0.1)	—	—	—
p.N227S	1 (0.1)	—	—	—
p.H255Q	1 (0.1)	—	—	—
p.W291X	1 (0.1)	—	—	—
p.E326K	47 (4.4)	45 (1.4)	18 (1.4)	27 (1.5)
p.T369M	20 (1.9)	54 (1.7)	35 (2.7)	19 (1.1)
p.N370S	20 (1.9)	16 (0.5)	10 (0.8)	6 (0.3)
p.W378G	2 (0.2)	1 (0.03)	1 (0.08)	—
p.E388K	—	3 (0.09)	—	3 (0.17)
p.D409H	2 (0.2)	—	—	—
p.L444P	1 (0.1)	1 (0.03)	—	1 (0.06)
p.V460L	—	2 (0.06)	—	2 (0.11)
p.T482K	—	1 (0.03)	—	1 (0.06)
p.R502C	1 (0.1)	—	—	—
Homozygous/compound heterozygous				
p.E326K/p.T369M	1 (0.1)	—	—	—
Total	101 (9.5)	126 (4.1)	65 (4.9)	61 (3.4)

^a Variants nomenclature is according to the nomenclature typically used for *GBA* variants, of the active enzyme (497 amino acids) after the removal of the 39 amino acids of the leader peptide.

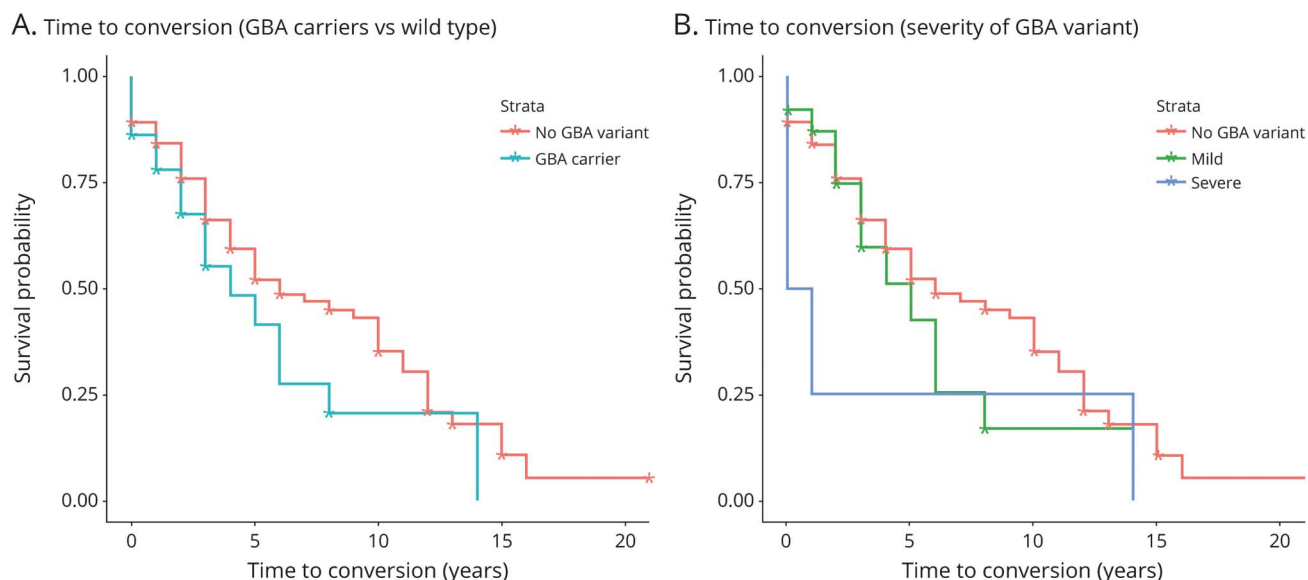
demonstrate a much larger risk in carriers of severe *GBA* variants. Given the small numbers of these variants and the wide range of the CIs, the risk estimates may be different in future, larger studies. The current results are in line with previous results from PD, which clearly demonstrated similar relationships between severe and mild *GBA* variants and risk for PD.⁵ Previous studies have also suggested that the type of *GBA* variants may affect PD progression,^{13,14} which is further supported by our preliminary findings on AAO and conversion of iRBD.

In recent years it has been demonstrated that the coding variants p.E326K and p.T369M, which do not cause GD, are risk factors for PD.^{20,21,23} In DLB, the association between p.E326K and risk for the disease is clear, yet it is still unclear whether p.T369M is a risk factor for DLB. Only a few studies that examined p.T369M in DLB have been performed and in most of them there was no association. A multicenter study that included over 700 patients with DLB reported lack of association, and in a GWAS with over 1,700 patients with

DLB, only the p.E326K variant was reported to be associated with the disease.⁷ Conversely, recent data from 556 patients with DLB did suggest an association.²⁴ The lack of association in the current study in iRBD may also provide further support for lack of association of p.T369M with iRBD and DLB. However, it is important to keep in mind that the association of this variant with PD was only reported in much larger studies^{20,21} due to its lower effect on risk compared to other *GBA* variants. Only much larger studies can determine conclusively whether p.T369M is associated with iRBD and DLB. There was a large difference between the frequency of p.T369M in our in-house controls (2.7%) and the controls from the literature (1.1%), perhaps due to population structure, but the combined frequency (1.7%) is comparable to that seen in the gnomAD European population (1.9%), rendering our results for this variant as likely unbiased.

Our study has several limitations. The possible association between *GBA* variants and rate of conversion reported here,

Figure Conversion to overt neurodegenerative disease in patients with iRBD with and without *GBA* variants



(A) Survival plot comparing *GBA* variant carriers (blue) and noncarriers (red) from diagnosis until conversion or recent follow-up. Log-rank $p = 0.13$, Breslow $p = 0.32$, Tarone-Ware $p = 0.22$. (B) Survival plot comparing carriers of severe *GBA* variants (blue), mild/other *GBA* variants (green), and noncarriers (red). Log-rank $p = 0.24$, Breslow $p = 0.017$, Tarone-Ware $p = 0.051$.

although potentially interesting, should be taken with caution for several reasons. (1) The results include the cohort from Montreal, in which it was previously reported that *GBA* variants are associated with rate of conversion, but it does not include the negative study from Barcelona (data could not be shared). (2) The results are based on a small number of variant carriers (4 patients with a severe *GBA* variant, 25 with other *GBA* variants). Larger studies will be required to determine conclusively whether *GBA* variants are associated with the rate of phenoconversion. An additional potential limitation is that the measured duration from age at diagnosis or iRBD to conversion might not reflect the actual length of disease duration, as patients can remain unaware for many years about their dream-enactment behaviors, especially if they do not have a bed partner or if they do not have very active or violent dreams. The small number of severe *GBA* variants is also a limitation in the risk analysis, as it created a wide CI. Since the effect of severe vs mild variants is in line with previous studies in PD, it is likely that these risk estimates of iRBD are overall correct, yet the precise estimate might change in future, larger studies.

The mechanisms underlying the association between *GBA* variants, the enzyme encoded by *GBA*, glucocerebrosidase (GCase), and the development of neurodegeneration are unknown.¹¹ Several mechanisms have been proposed, including interaction of GCase substrates with α -synuclein, which may lead to its accumulation,²⁵ changes in the lysosomal membrane composition, which may lead to reduced autophagy and mitophagy,^{26,27} accumulation of misfolded

GCase and endoplasmic reticulum stress,²⁸ and others. The association with iRBD may suggest that studying these mechanisms in nondopaminergic neuronal models that are involved in RBD could lead to new discoveries and better understanding of these potential mechanisms.

Our results demonstrate that *GBA* variants are associated with increased risk of iRBD. These results may also suggest that severe and mild *GBA* variants may have differential effects on the risk, and possibly on AAO, of iRBD and its conversion to overt neurodegenerative disease. Due to the limitations mentioned above, the latter associations should be considered as preliminary with additional, larger studies on *GBA* in iRBD required to confirm or refute them. One important implication of the association between *GBA* variants and iRBD is the possibility to perform screening for iRBD in healthy *GBA* variant carriers. This may allow for even earlier detection of prodromal neurodegeneration and could be especially useful when home detection of iRBD will be made possible.

Acknowledgment

The authors thank the patients and controls for participation and Helene Catoire, Sandra B. Laurent, and Dan Spiegelman for assistance. J.-F.G. holds a Canada Research Chair in Cognitive Decline in Pathological Aging. W.O. is Hertie Senior Research Professor, supported by the Charitable Hertie Foundation, Frankfurt/Main, Germany. G.A.R. holds a Canada Research Chair in Genetics of the Nervous System and the Wilder Penfield Chair in Neurosciences. Z.G.-O. is supported by the Fonds de Recherche du Québec-Santé (FRQS) Chercheurs-Boursiers Award given in collaboration

with Parkinson QC, and is a Parkinson Canada New Investigator awardee.

Study funding

This work was supported financially by Parkinson Canada, the Michael J. Fox Foundation, the Canadian Consortium on Neurodegeneration in Aging (CCNA), the Canadian Glycomics Network (GlycoNet), the Canada First Research Excellence Fund (CFREF), awarded to McGill University for the Healthy Brains for Healthy Lives (HBHL) program, the Canadian Institutes for Health Research (CIHR), Weston Foundation, and Fonds de Recherche du Québec–Santé (FRQS) Chercheurs-Boursiers. The Oxford Discovery study is funded by the Monument Trust Discovery Award from Parkinson’s UK and supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre based at Oxford University Hospitals NHS Trust and University of Oxford, the NIHR Clinical Research Network, and the Dementias and Neurodegenerative Diseases Research Network (DeNDRoN).

Disclosure

L. Krohn, J. Ruskey, U. Rudakou, E. Leveille, and F. Asayesh report no disclosures relevant to the manuscript. M. Hu received consultancy fees from Roche and Biogen Pharmaceuticals. I. Arnulf received fees for speaking engagements from UCB Pharma and consultancy for Roche, Novartis, and Ono Pharma. Y. Dauvilliers reports no disclosures relevant to the manuscript. B. Högl received consultancy fees from Axovant, benevolent Bio, Takeda, Roche, and Ono Pharma, and received speaker honoraria from Eli Lilly, Mundipharma, UCB, AbbVie, Inspire, and Lundbeck. A. Stefani, C. Monaca, B. Abril, G. Plazzi, E. Antelmi, and L. Ferini-Strambi report no disclosures relevant to the manuscript. A. Heidebreder received honoraria for lectures from UCB, Bioprojet, Servier, and Medice and consultancy fees from UCB. B. Boeve has served as an investigator for clinical trials sponsored by Biogen and Alector; serves on the Scientific Advisory Board of the Tau Consortium; and receives research support from the NIH, the Mayo Clinic Dorothy and Harry T. Mangurian Jr. Lewy Body Dementia Program, the Little Family Foundation, and the LBD Functional Genomics Program. A.J. Espay received grant support from the NIH and the Michael J. Fox Foundation; personal compensation as a consultant/scientific advisory board member for AbbVie, Adamas, Acadia, Acorda, Neuroderm, Neurocrine, Impax/Amneal, Sunovion, Lundbeck, Osmotica Pharmaceutical, and USWorldMeds; publishing royalties from Lippincott Williams & Wilkins, Cambridge University Press, and Springer; and honoraria from USWorldMeds, Lundbeck, Acadia, Sunovion, the American Academy of Neurology, and the Movement Disorders Society. V. Cochen De Cock reports no disclosures relevant to the manuscript. B. Mollenhauer has received honoraria for consultancy from Roche, Biogen, UCB, and Sun Pharma Advanced Research Company; is a member of the executive steering committee of the Parkinson Progression Marker Initiative and PI of the Systemic Synuclein Sampling

Study of the Michael J. Fox Foundation for Parkinson’s Research; and has received research funding from the Deutsche Forschungsgemeinschaft (DFG), EU (Horizon2020), Parkinson Fonds Deutschland, Deutsche Parkinson Vereinigung, and the Michael J. Fox Foundation for Parkinson’s Research. F. Sixel-Döring has received honoraria for lectures from Abbott, Desitin, Grünenthal, Licher MT, STADA Pharm, and UCB; seminar fees from Boston Scientific and Licher MT; serves on an advisory board for STADA Pharm; and reports no conflict of interest with the presented study. C. Trenkwalder has received honoraria for lectures from UCB, Grünenthal, and Otsuka and consultancy fees from Britannia Pharmaceuticals and Roche. K. Sonka, D. Kemlink, M. Figorilli, M. Puligheddu, F. Dijkstra, and M. Viaene report no disclosures relevant to the manuscript. W. Oertel received consultancy or speaker fees from Adamas, AbbVie, Desitin, Novartis and Roche, and reports no conflicts of interest related to the study. M. Toffoli, G. Luigi Gigli, and M. Valente report no disclosures relevant to the manuscript. J.F. Gagnon reports research funding from the Canadian Institutes for Health Research (CIHR). A. Desautels received grants from Flamel Ireland, Pfized, Biron, and Canopy Growth, as well as fees for speaking engagements from Biogen and consultancy from UCB Pharma. J. Montplaisir reports no disclosures relevant to the manuscript. R. Postuma reports grants from Fonds de la Recherche en Sante, the Canadian Institute of Health Research, The Parkinson Society of Canada, the Weston-Garfield Foundation, the Michael J. Fox Foundation, and the Webster Foundation, as well as personal fees from Takeda, Roche, Teva Neurosciences, Novartis Canada, Biogen, Boehringer Ingelheim, Theranexus, GE HealthCare, Jazz Pharmaceuticals, AbbVie, Janssen, Otsuko, Phytopharmics, and Inception Sciences. G. Rouleau reports no disclosures relevant to the manuscript. Z. Gan-Or received consultancy fees from Lysosomal Therapeutics Inc. (LTI), Idorsia, Prevail Therapeutics, Inceptions Sciences (now Ventus), Denali, and Deerfield. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

Publication history

Received by *Neurology* October 30, 2019. Accepted in final form February 14, 2020.

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Lynne Krohn, MSc	McGill University, Montréal, Canada	Designed and conceptualized study, analyzed the data, drafted the manuscript for intellectual content
Jennifer A. Ruskey, MSc	McGill University, Montréal, Canada	Major role in the acquisition of data, revised the manuscript for intellectual content
Uladislaw Rudakou, BSc	McGill University, Montréal, Canada	Analyzed the data, revised the manuscript for intellectual content

Appendix (continued)

Name	Location	Contribution
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Appendix (continued)

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Continued

Appendix (continued)

Name	Location	Contribution
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Neurology 2020;95:e1008-e1016 Published Online before print June 26, 2020

DOI 10.1212/WNL.0000000000010042

This information is current as of June 26, 2020

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