The role of the melanoma gene *MC1R* in Parkinson disease and REM sleep Behavior Disorder

Ziv Gan-Or¹,²,³, Noreen Mohsin¹, Simon L. Girard², Jacques Y. Montplaisir⁴,⁵, Amirthagowri Ambalavanan¹,², Stephanie Strong¹, Victoria Mallett¹, Sandra B. Laurent¹, Cynthia V. Bourassa¹, Michel Boivin⁶,⁷, Melanie Langlois⁸, Isabelle Arnulf⁹, Birgit Högl¹⁰, Birgit Frauscher¹⁰, Christelle Monaca¹¹, Alex Desautels⁴,¹², Jean-François Gagnon⁴,¹³, Ronald B. Postuma¹⁴, Patrick A. Dion¹,³, Yves Dauvilliers¹⁵, Nicolas Dupre⁸, Roy N. Alcalay¹⁶, and Guy A. Rouleau¹,²,³,*  

¹ Montreal Neurological Institute, McGill University, Montréal, QC, Canada  
² Department of Human Genetics, McGill University, Montréal, QC, Canada  
³ Department of Neurology and Neurosurgery, McGill University, Montréal, QC, Canada  
⁴ Centre d’Études Avancées en Médecine du Sommeil, Hôpital du Sacré-Cœur de Montréal, Montréal, QC, Canada  
⁵ Department of Psychiatry, Université de Montréal, Montréal, QC, Canada  
⁶ GRIP, École de psychologie, Université Laval, Québec city, QC, Canada  
⁷ Institute of Genetic, Neurobiological and Social Foundations of Child Development, Tomsk State University, Tomsk, Russia  
⁸ Faculté de Médecine, Université Laval, CHU de Québec (Enfant-Jésus), Québec , QC, Canada  
⁹ Sleep Disorders Unit, Pitié Salpêtrière Hospital, Centre de Recherche de l’Institut du Cerveau et de la Moelle Epinière and Sorbonne Universities, UPMC Paris 6 univ, Paris, France  
¹⁰ Sleep Disorders Clinic, Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria  
¹¹ University Lille north of France, Department of clinical neurophysiology and sleep center, CHU Lille, France  
¹² Department of Neurosciences, Université de Montréal, Montréal, Canada  
¹³ Département de psychologie, Université du Québec à Montréal, Montréal, QC, Canada  

¹ Corresponding authors: Ziv Gan-Or, Montréal Neurological Institute and hospital, Department of Human Genetics, McGill University, Address: 1033 Pine Avenue, West, Ludmer Pavilion, room 327, Montreal, QC, H3A 1A1, Tel: +1-514-398-6821, Fax: +1-514-398-8248, ; Email: ziv.gan-or@mail.mcgill.ca, Guy A. Rouleau, Director, Montréal Neurological Institute and hospital, Address: 3801, University Street, Office 636, Montréal, Québec H3A 2B4, Tel: +1-514-398-2690, Fax: +1-514-398-8248, ; Email: guy.rouleau@mcgill.ca  

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Conflict of interest statement  
The authors report no conflict of interests.
Abstract

The MC1R gene, suggested to be involved in Parkinson disease (PD) and melanoma, was sequenced in PD patients (n=539) and controls (n=265) from New-York, and PD patients (n=551), rapid eye movement sleep behavior disorder (RBD) patients (n=351) and controls (n=956) of European ancestry. Sixty-eight MC1R variants were identified, including 7 common variants with frequency>0.01. None of the common variants was associated with PD or RBD in the different regression models. In a meta-analysis with fixed-effect model, the p.R160W variant was associated with an increased risk for PD (OR=1.22, 95%CI 1.02-1.47, p=0.03) but with significant heterogeneity (p=0.048). Removing one study that introduced the heterogeneity resulted in non-significant association (OR=1.11, 95%CI 0.92-1.35, p=0.27, heterogeneity p=0.57). Rare variants had similar frequencies in patients and controls (10.54% and 10.15%, respectively, p=0.75), and no cumulative effect of carrying more than one MC1R variant was found. The current study does not support a role for the MC1R p.R160W and other variants in susceptibility for PD or RBD.

Introduction

There is an unexplained yet well-validated association between Parkinson disease (PD, MIM no. 168600) and melanoma; patients with PD have an increased risk for developing melanoma, and melanoma patients have an increased risk for PD. (Liu, et al., 2011, Pan, et al., 2011) Several hypotheses were proposed in an attempt to explain the mechanism underlying this association; however, the exact causative factors are yet to be determined. One of the hypotheses is the existence of genetic pleotropy, i.e. the same genetic risk factors for both diseases.

Large genetic studies have identified various risk factors for PD, including genome wide associated loci (Do, et al., 2011 International Parkinson Disease Genomics, et al., 2011 Nalls, et al., 2014 Satake, et al., 2009 Simon-Sanchez, et al., 2009) or mutations in specific genes such as GBA, LRRK2, SNCA, VPS35, SMPD1, PARK2, PINK1, PARK7 and others (reviewed in (Gan-Or, et al., 2015 Trinh and Farrer, 2013)). However, none of these genetic loci or genes can currently explain the association between PD and melanoma. Recently, it was suggested that the melanoma-related MC1R gene, encoding the melanocortin 1 receptor, is associated with PD, (Tell-Marti, et al., 2015b) but this association is currently controversial. (Dong, et al., 2014 Elincx-Benizri, et al., 2014 Lubbe, et al., 2015 Tell-Marti, et al., 2015a) In a Spanish cohort of PD patients and controls, the melanoma-associated MC1R p.R160W variant was associated with a 2-fold increased risk for PD, (Tell-Marti, et al., 2015b) However, a previous, larger case-control study that included the MC1R p.R160W variant did not identify this association. (Dong, et al., 2014) Moreover, in a smaller study that included patients with PD alone, PD with melanoma, and melanoma alone, neither this
variant nor other MC1R variants were associated with PD. (Elincx-Benizri, et al., 2014) In a Chinese cohort, in which the MC1R p.R160W was absent, other MC1R variants were also not associated with an increased risk for PD. (Foo, et al., 2015) Furthermore, the MC1R gene was not identified in any of the large genome wide association studies (GWAS) (Do, et al., 2011 International Parkinson Disease Genomics, et al., 2011 Nalls, et al., 2014 Satake, et al., 2009 Simon-Sanchez, et al., 2009), and no single nucleotide polymorphism (SNP) in the MC1R locus was associated with PD, even without correction for multiple comparisons in the PDGene database (www.pdgene.org).

In the current study, we aimed to examine the role of the MC1R gene in PD. Furthermore, since rapid eye movement (REM) sleep behavior disorder (RBD), a parasomnia that is a prodromal disorder for PD and other synucleinopathies, (Postuma, 2014 Postuma, et al., 2015b) the association between MC1R variants and RBD was also studied.

Methods

Study populations

Three populations were included in the current study: 1) a cohort of unrelated, consecutively recruited PD patients (n=539) and controls (n=265) from Columbia University, New-York, NY, USA (more details on the recruitment of cohort 1, termed “SPOT” cohort, were previously published (Alcalay, et al., 2015)). 2) a cohort of unrelated, consecutively recruited PD patients (n=551) and controls (n=956) of European ancestry, mainly French-Canadian and French, and 3) a cohort of unrelated, consecutively recruited RBD patients (n=351) of European ancestry, also mainly French-Canadian and French. Cohort 2 was collected through a network of collaborators from France and Quebec, including the Quebec Parkinson’s Network (http://rpq-qpn.ca/). Cohort 3 was collected at the Montreal Neurological Institute (MNI), Montreal, Canada, by collaborators from the International RBD Study Group (Postuma, et al., 2015b Schenck, et al., 2013) from Europe and Canada. Basic demographic characteristics of these cohorts are detailed in Table 1. The control population from the MNI was composed of ethnicity-matched elderly controls (n=553, average age 51.8 ± 13.2 years) and young controls (n=403, average age 31.9 ± 4.9 years). Since the frequencies of the tested variants were nearly identical in these two control populations (see results), they could be reliably combined for the analysis, after adjusting for the age differences in the association analyses (see methods). Lack of relatedness and the ancestry in cohorts 2 and 3 were ascertained by unpublished genome-wide association study data, and in cohort 1 it was ascertained by the clinician who recruited and routinely treating the patients. PD patients were diagnosed according to the UK Brain Bank Criteria (but without excluding patients who reported family history of PD) by neurologists specialized in movement disorders. RBD was diagnosed according to the International Classification of Sleep Disorders criteria (ICSD-2) by neurologists specialized in sleep disorders, based on both history and polysomnography showing REM sleep without atonia. All patients and controls signed an informed consent form before entering the study, and the protocols were approved by the respective institutional review boards.
Sequencing of the MC1R gene

DNA was extracted by using a standard salting-out protocol. The entire coding sequence of the MC1R gene (NM_002386) was amplified by using the forward primer 5’ GCAGCACCATGAACTAAGCA 3’ and the reverse primer 5’ CAGGGTCACACAGGAACCA 3’ with the AmpliTaq Gold DNA Polymerase (Applied Biosystems, CA, USA) or the Taq DNA polymerase (Qiagen, Maryland, USA). The amplified products were then sequenced using the forward primer 5’ AACCTGCACCTCACCATTG3’ and the reverse primer 5’ TTTAAGGCCAAAGCCCTGGT 3’ at the Genome Quebec Innovation Centre (Montréal, QC, Canada) using a 3730XL DNA analyzer (Applied Biosystems, CA, USA). The sequences were analyzed using the Genalys 3.3b software. All variants that were identified in the forward sequencing were also identified in the reverse sequencing in the overlapping region. Furthermore, forward and reverse sequencing of 40 samples was repeated from another tube of DNA that was taken in another visit of the patient, with a 100% match. Only samples with both forward and reverse sequencing were included in the analysis.

Statistical analysis

To compare single categorical variables, χ² or Fisher’s exact test was used, and to compare continuous variables, Student’s t-test or ANOVA was used. χ² with one degree of freedom was used to determine whether the observed genotype frequencies of the common MC1R variants deviate from the expected frequencies based on Hardy-Weinberg Equilibrium (HWE). To estimate the association between the detected common MC1R variants and PD or RBD, binary logistic regression with the status of the individual (patient or control) as the dependent variable was used. When patients and controls did not match for sex or age, these variables were added as covariates for the analysis to adjust for their effects. When a regression model for all patients from both centers (NY and Montreal) was performed, the site was also added as covariate to adjust for the differences in the genetic background of the two populations from the two centers. Power analysis demonstrated that our population had a power of >98% to detect the originally reported association between the MC1R p.R160W and PD (Tell-Marti, et al., 2015b). Furthermore, our PD population (1090 patients and 1221 controls) had a power of >80% to detect a much lower odds ratio of 1.4. All the statistical analysis, except for the meta-analysis, was performed using the SPSS v.21 software (IBM, Ltd.). The meta-analysis was performed by using an R package (Metafor). Data for the meta-analysis were collected and weighted at the individual level, and heterozygous and homozygous carriers were considered as carriers for the analysis. The Cochran-Mantel-Haenszel test was used to pool the studied and calculate the odds ratios (OR) using either the fixed-or random-effect models. Tarone’s test was applied to estimate heterogeneity, and in case of significant heterogeneity, the source of heterogeneity was identified by excluding studies one by one, and re-calculating the Tarone’s test for heterogeneity. The online tools SIFT (Kumar, et al., 2009) and PolyPhen-2 (Adzhubei, et al., 2010) were used to predict the effects of the MC1R variants.
Results

Common and rare MC1R variants have no or minimal association with the risk for PD or RBD

A total of 68 MC1R variants were identified in patients and controls. Supplementary Table 1 details these variants, their predicted effect on the protein, and their distribution among patients and controls. Seven common variants with allele frequency > 0.01 were included in logistic regression models to determine their association with the risk for PD and RBD (Table 2). None of these variants deviated from Hardy-Weinberg equilibrium (HWE). First, PD patients and RBD patients were separately compared to their respective control populations from each center. Subsequently, a combined analysis of the PD and RBD patients from Montreal vs. their controls, and a combined analysis of all PD and RBD patients and controls from both centers were performed. The elderly and young controls from Montreal had nearly identical frequencies for the seven common variants (0.29 and 0.30 for the p.V60L variant, respectively, 0.13 and 0.13 for p.V92M, 0.11 and 0.10 for p.R151C, 0.08 and 0.08 for p.R160W, 0.07 and 0.08 for p.R163Q, 0.04 and 0.04 for p.D294H, and 0.17 and 0.17 for p.T314T) and could therefore be combined reliably as one control group. None of the seven common MC1R variants was associated with risk for PD or RBD in any of the models (Table 2). The MC1R p.R160W, which was suggested to be associated with PD,(Tell-Marti, et al., 2015b) had non-significant odd ratios (ORs) ranging between 0.76-1.13 in the different analyses (uncorrected p value > 0.45 in all the analyses, Table 2). Of the seven common variants, six were nonsynonymous, and similar analysis of these six variants alone resulted in very similar, non-significant results (data not shown).

The combined frequency of all the rare variants (allele frequency < 0.01) was nearly identical among patients and controls (10.54% and 10.15%, respectively, p=0.75, Fischer exact test). The combined frequency of rare nonsynonymous, frameshift or stop mutations was also very similar among patients and controls (8.53% and 8.68%, respectively, p=0.44, Fisher’s exact test). Furthermore, no cumulative effect of carrying more than one MC1R variant was found (Figure 1). Several rare variants had higher frequencies in patients compared to controls (Supplementary Table 1), but none of these variants reached statistical significance after correction for multiple comparisons.

Meta-analysis of the effect of the MC1R p.R160W variant on PD risk demonstrates minimal or no effect

In order to further determine whether the MC1R p.R160W is associated with the risk for PD as was previously suggested,(Tell-Marti, et al., 2015b) a meta-analysis of four populations where this variant was specifically analyzed (two that were previously published and two from the current study, Table 3) was performed. Both fixed-and random-effect models were used (Figure 2A and 2B, respectively). In the fixed-effect model, the MC1R p.R160W was associated with an increased risk for PD (OR = 1.22, 95% CI 1.02-1.47, p=0.03, Figure 2A). However, there was significant heterogeneity in this model (p=0.048), which was introduced by the only study that had previously demonstrated an association between this variant and PD,(Tell-Marti, et al., 2015b) rendering the meta-analysis results less reliable. After the exclusion of this study, there was no significant association (OR = 1.11, 95% CI 0.92-1.35,
The current study demonstrates that variants in the \textit{MC1R} gene have minimal or no association with the risk for PD or RBD. More specifically, the \textit{MC1R} p.R160W variant, which was suggested to be a risk factor for PD,\cite{Tell-Marti, et al., 2015b} was not associated with PD or RBD when comparing specific populations or in the meta-analysis. The discrepancies between the single study that suggested an association between the \textit{MC1R} p.R160W variant and the current study could be explained by the different populations used. It is possible, for example, that in different populations, other genetic or environmental factors exist that differentially modify the association of \textit{MC1R} with PD. However, if this variant is hypothesized to be the functional variant that increases the risk for PD, by affecting the function of the melanocortin 1 receptor, it should have relatively similar effects in each population. Further support for the lack of association of \textit{MC1R} with PD is provided by the meta-OR previously reported for this variant (OR=0.98, 95% CI 0.89-1.07, \textit{p}=0.62) in the International PD Genomic Consortium data,\cite{Dong, et al., 2014} and the lack of signal in this locus in the PDGene database (www.pdgene.org). Although we cannot decisively rule out that this variant has a minor role in PD susceptibility that can only be detected in a much larger meta-analysis, the current data suggest that the \textit{MC1R} gene, and specifically the p.R160W variant, are probably not associated with PD, or have a very small effect. A previous observation from a cohort of 272 PD patients and 1185 controls, which suggested that the p.R151C variant is associated with PD,\cite{Gao, et al., 2009b} was also not supported by our results.

From a purely genetic perspective, there is not enough evidence that currently points to a specific shared genetic background; however, a few interesting observations were made. The largest GWASs from both diseases showed no overlap between the associated loci,\cite{Law, et al., 2015,Nalls, et al., 2014} and a study that specifically targeted known PD loci in a large melanoma cohort failed to identify an association.\cite{Meng, et al., 2012} However, one of the GWAS loci that was identified in melanoma\cite{Meng, et al., 2012} and melanocytic cutaneous nevi\cite{Falchi, et al., 2009} cohorts is the \textit{PLA2G6} locus. Interestingly, mutations in \textit{PLA2G6} may cause PD or Parkinsonism-dystonia syndrome,\cite{Gui, et al., 2013,Kauther, et al., 2011,Malaguti, et al., 2015,Paisan-Ruiz, et al., 2009} suggesting a potential genetic link between the two conditions.\cite{Paisan-Ruiz and Houlden, 2010} Another intriguing locus that was identified in PD GWAS is around the \textit{GPNMB} gene,\cite{Nalls, et al., 2014} which codes for the glycoprotein non-metastatic melanoma protein B, which may have an important role in melanoma.\cite{Maric, et al., 2013,Tomihari, et al., 2010} Additional studies are needed to
determine if these genes may contribute to the co-occurrence of PD and melanoma. In the current study, data on melanoma occurrence in the PD and RBD cohorts were not available.

In order to determine whether genetics, environmental factors, or their interaction leads to the co-occurrence of PD and melanoma, large genetic-environmental studies are needed. To reach statistical power that will allow drawing strong conclusions, large collaborations between different centers are needed to reach the number of patients required for such analysis. Understanding the underlying causes of this co-morbidity is of great importance, since it may allow specific interventions in PD patients or in prodromal PD to prevent melanoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the patients and controls for their participation in this study. This work was financially supported by the Canadian Institutes of Health Research (CIHR) and by the Michael J. Fox Foundation. The cohort from Columbia, NY, was funded by Parkinson's Disease Foundation and the NIH (K02NS080915, and UL1 TR000040). ZGO is supported by a postdoctoral fellowship from the Canadian Institutes for Health Research (CIHR). JFG holds a Canada Research Chair in Cognitive Decline in Pathological Aging. GAR holds a Canada Research Chair in Genetics of the Nervous System and the Wilder Penfield Chair in Neurosciences. We thank Daniel Rochefort, Pascale Hince, Helene Catoire, Cathy Mirarchi and Vessela Zaharieva for their assistance. We thank the Quebec Parkinson’s Network and its members (http://rpq-qpn.ca/) for their collaboration.

References


Neurobiol Aging. Author manuscript; available in PMC 2017 July 01.
• The melanoma variant *MC1R* p.R160W was suggested to be involved in Parkinson disease
• *MC1R* was sequenced in a total of 2662 individuals with PD, RBD and controls
• No *MC1R* variant, including p.R160W, was associated with PD
• The *MC1R* gene has no major role in PD
Figure 1. Cumulative carriage of MC1R variants in the different study populations
A. The carriage frequencies of one or more MC1R variants were similar among PD patients, RBD patients and controls collected at the MNI (p>0.05 for all comparisons) B. The carriage frequencies of one or more MC1R variants were similar among PD patients and controls collected at Columbia, NY (p>0.05 for all comparisons).
Figure 2. Meta-analyses of the \textit{MC1R} p.R160W variant

A. Meta-analysis of the \textit{MC1R} p.R160W in four studies under the fixed-effect model. While three studies had non-significant ORs of 0.91 – 1.28, one study alone (Tell-Marti et al.) drove the association. However, these results cannot be considered statistically significant due to the significant heterogeneity (\(p=0.048\)).

B. Meta-analysis of the \textit{MC1R} p.R160W in four studies under the random-effect model. Here too, one study introduced a significant heterogeneity to the model (Heterogeneity \(p=0.048\)).

C. Meta-analysis of the \textit{MC1R} p.R160W in three studies, excluding the one study that introduced heterogeneity, under the fixed-effect model (OR=1.11, 95\% CI 0.92-1.35, \(p=0.27\), heterogeneity \(p=0.57\)).

D. Meta-analysis of the \textit{MC1R} p.R160W in three studies, excluding the one study that introduced heterogeneity, under the random-effect model, resulting in identical OR estimates and statistics as the fixed-effect model.
Table 1

Demographic characteristics of the study populations

<table>
<thead>
<tr>
<th>Number</th>
<th>MNI Number</th>
<th>New York Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>RBD</td>
<td>Total PD + RBD</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td>Controls</td>
</tr>
<tr>
<td>551</td>
<td>351</td>
<td>902</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>346 (63.7%)</td>
<td>264 (78.6%)</td>
<td>610 (69.4%)</td>
</tr>
<tr>
<td>Age (± SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65.7 (± 9.7)</td>
<td>67.5 (± 8.7)</td>
<td>66.4 (± 9.4)</td>
</tr>
</tbody>
</table>

PD, Parkinson disease; RBD, rapid eye movement sleep behavior disorder; SD, standard deviation

\(^{a}\)MNI, Montreal Neurological Institute, Montreal, Canada, is the center where samples of European ancestry where collected through international collaborations as detailed in the methods.

\(^{b}\)Data on gender was not available for 8 PD, 15 RBD and one control from Montreal.

\(^{c}\)Data on age was not available for 14 PD, 41 RBD, 10 control from Montreal, and for one PD and 3 controls from Columbia, NY.
Table 2

Association of common *MC1R* variants with risk for PD or RBD

<table>
<thead>
<tr>
<th>Variant</th>
<th>Minor allele frequency</th>
<th>OR (95% CI), p value a</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PD MNI (n=551)</td>
<td>RBD MNI (n=351)</td>
<td>Control MNI (n=956)</td>
</tr>
<tr>
<td>p.V60L</td>
<td>0.142</td>
<td>0.121</td>
<td>0.156</td>
</tr>
<tr>
<td>p.V92M</td>
<td>0.066</td>
<td>0.068</td>
<td>0.067</td>
</tr>
<tr>
<td>p.R151C</td>
<td>0.054</td>
<td>0.064</td>
<td>0.054</td>
</tr>
<tr>
<td>p.R160W</td>
<td>0.048</td>
<td>0.037</td>
<td>0.039</td>
</tr>
<tr>
<td>p.R163Q</td>
<td>0.024</td>
<td>0.036</td>
<td>0.036</td>
</tr>
<tr>
<td>p.D294H</td>
<td>0.018</td>
<td>0.014</td>
<td>0.021</td>
</tr>
<tr>
<td>p.T314T</td>
<td>0.085</td>
<td>0.093</td>
<td>0.091</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval, PD MNI, Parkinson disease samples collected at the Montreal Neurological Institute; RBD MNI, REM sleep Behavior Disorder patients collected at the Montreal Neurological Institute, through the International RBD study group; PD NY, Parkinson disease patients collected at Columbia University, New-York; Control MNI, controls collected at the Montreal Neurological Institute; Control NY, controls collected at Columbia University, New-York. Variants were called according to NM_002386.

a Bonferroni correction for multiple comparisons set the cut-off p value for statistical significance at p<0.0071.

b p value comparing PD MNI to Control MNI using a regression model, adjusted for gender and age

c p value comparing RBD MNI to Control MNI using a regression model, adjusted for gender and age

d p value comparing PD MNI + RBD MNI to Control MNI using a regression model, adjusted for gender and age

e p value comparing PD NY to Control NY using a regression model, adjusted for gender and age


$p$ value comparing all patients (PD MNI + RBD MNI + PD NY) to all controls (Control MNI + Control NY) using a regression model, adjusted for site, gender and age
### Table 3
Populations included in meta-analysis of the *MC1R* p.R160W variant in PD.

<table>
<thead>
<tr>
<th>Study</th>
<th>population</th>
<th>Number of PD patients, (% carriers of the <em>MC1R</em> p.R160W variant)</th>
<th>Number of controls (% carriers of the <em>MC1R</em> p.R160W variant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dong et al.(^{11})</td>
<td>Non-Hispanic whites</td>
<td>777 (13.6%)</td>
<td>1550 (12.5%)</td>
</tr>
<tr>
<td>Tell-Marti et al.(^{11})</td>
<td>Caucasians from Spain</td>
<td>870 (5.0%)</td>
<td>736 (2.0%)</td>
</tr>
<tr>
<td>Current study</td>
<td>Mainly French-Canadian / French</td>
<td>551 (9.6%)</td>
<td>956 (7.8%)</td>
</tr>
<tr>
<td>Current study</td>
<td>North-American from NY</td>
<td>539 (8.9%)</td>
<td>265 (9.8%)</td>
</tr>
<tr>
<td>Current study total</td>
<td></td>
<td>1090 (9.3%)</td>
<td>1221 (8.2%)</td>
</tr>
</tbody>
</table>

\(^{2}\) Since RBD patients may convert to other synucleinopathies, such as Dementia with Lewy Bodies and Multiple System Atrophy, they were not included in the meta-analysis for the effect of the *MC1R* p.R160W variant on PD risk.