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Article

# Sex differences in sleep disorders of Parkinson's disease patients associated with a genetic risk variant

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## SUMMARY

**Parkinson's disease (PD) is a neurodegenerative disorder affecting 10 million people worldwide. PD results in both motor and non-motor symptom manifestations. Notably, sleep disorders are one of the most common non-motor symptoms of PD and exhibit sex differences in frequency and severity. Although studies have identified variations in sleep disorder manifestation and genetic variants between male and female PD patients, few have examined the connection between PD sleep disorders and genetic risk factors with consideration of biological sex. To address the hypothesis that sex-specific sleep dysfunction in PD patients is associated with genetic risk variants, this study compares sleep symptom frequency and PD-associated genetic variants between males and females. The findings of this study reveal that the differential prevalence of a leucine-rich repeat kinase 2 (LRRK2) mutation (G2019S) between male and female PD patients may underlie sex differences in PD sleep disorders, including rapid eye movement (REM) behavior disorder (RBD) and insomnia. This suggests the potential of sex-specific genetic treatments in effectively managing the sleep symptoms of PD patients.**

## INTRODUCTION

Parkinson's disease (PD) is a prevalent neurodegenerative disorder that affects 0.1 to 0.2% of the population and 1% of individuals aged 60 years or older (1). There are over 10 million cases worldwide and 1 million cases in the United States (1). The annual incident rate of PD in female and male patients 40 years and older is 37.55 cases and 61.21 cases for every 100,000 people annually, respectively. For both sexes, the incident rates increase with age (2). The pathology of PD is characterized by the degeneration of dopaminergic neurons in the substantia nigra of the midbrain and the misfolding of alpha-synucleins, leading to the aggregation of protein inclusions known as Lewy bodies. PD results in motor symptoms, such as resting tremor, rigidity, and bradykinesia, and non-motor symptoms, including constipation, depression, and sleep disorders (3). The proposed mechanism of PD development involves multiple interconnected cellular processes, namely mitochondrial and proteasomal dysfunction, oxidative stress, apoptosis dysregulation, autophagy impairment, and neuroinflammatory imbalance (4). Although these mechanisms are well studied, other factors and additional mechanisms contributing to disease manifestation are still unknown.

The risk factors that cause PD are multifaceted, ranging from environmental to genetic factors (4). The genetic risk factors of PD can fall into two categories: familial and sporadic (or idiopathic). Familial PD, accounting for 5% of cases, is caused by inherited mutations that directly induce PD development (5). These mutations can be found in genes such *as SNCA, PRKN, PINK1,* and *LRRK2* (5, 6). Most cases of PD are sporadic and are associated with gene variants that increase an individual's susceptibility to PD (5). Genetic variants in sporadic PD do not directly cause the disease; rather, they interact with environmental factors to facilitate the onset of symptoms (6). Previous genome-wide association studies (GWAS) have identified several potential variants implicated in sporadic PD in the following genes: *LRRK2, SNCA, GBA, MAPT, D38, CTSB, NUPL2*, as well as others not listed (6-8).

Accumulating evidence highlights the significant impact of biological sex in PD, as the frequency, symptoms, development, and mechanism of pathogenesis of PD differ between men and women (10). The incident rates of PD in males are higher than in females, resulting in twice as many men suffering from PD than women at any given time (2-10); however, women experience higher mortality rates and faster progression of PD than men (11). Men with PD suffer greater cognitive impairment, particularly in executive function and processing speed, than women with PD (12). Women are more likely to develop tremors, anxiety, depression, involuntary muscle movement, and constipation, while men are more likely to suffer from daytime sleepiness, rigidity, and rapid eye movement (REM) behavior disorder (RBD) (10). These variations may arise from sex differences in the nigrostriatal dopaminergic pathway and hormones, as estrogen has been shown to decrease dopamine loss (10). Differences in the frequency and penetrance of certain genetic risk factors, as well as in neuroinflammatory cell activity and oxidative stress levels also contribute to sex-related differences in PD pathogenesis (11). Additionally, males and females are exposed to different types and frequencies of stressful events, such as those encountered in various occupations, which can alter the risk of developing and presenting PD (10, 11).

Sleep disorders are a major symptom in PD, with 50% to 81% of PD patients experiencing some type of sleep disorder, including insomnia, obstructive sleep apnea (OSA), restless legs syndrome (RLS), periodic limb movements, excessive daytime sleepiness (EDS), and REM sleep behavior disorder (13). Growing research suggests that there may be sex differences in prevalence of sleep symptoms (14-28), and others show no sex differences in frequency, but rather in the

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clinical expression of the disorder, wherein male PD patients experienced more fights and aggressive behavior during dreams, and female PD patients showed more disturbed sleep (29). The inconsistency in findings across studies may be attributed to the variation in ethnicities, age, and medication status among the cohorts analyzed, thus emphasizing the need for investigation with larger cohorts and more robust associations to elucidate sex-specific diagnosis and treatment of sleep disorders.

Given the prevalence of sleep disorders in PD, studies have also examined the genetic overlap between PD and sleep disorders. Mutations in the GBA and TMEM175 genes expressed in dopaminergic neurons were indicated as risk factors for RBD and PD (30-33). In contrast, variants in PD-associated genes, BST1 and LAMP3, were shown to have potentially protective effects by reducing the risk of developing RBD (33). These collective findings suggest that RBD and PD share a partial genetic overlap. Other than RBD, there remains a lack of evidence confirming the genetic overlap of RLS, OSA, excessive daytime sleepiness, or insomnia with PD (34, 35). Further investigations on the genetic connections between PD and sleep disorders are warranted.

The prevalence of PD-associated variants and their expression among PD patients differ between male and female patients, indicating the role of genetic risk factors in sex-specific PD development. For example, variants in the GBA gene, and the G2019S mutation in the *LRRK2* gene are more prevalent in female PD patients, increasing their risk for PD that is caused by these mutations (36, 37). Conversely, the prevalence of the G2385R mutation in the *LRRK2* gene has not been observed to have sex differences; however, the manifestation of PD varies between male and female carriers of the G2385R mutation, wherein females show a lower risk of autonomic dysfunction than males, suggesting that the phenotypic expressions of *LRKK2* mutations are sex-specific (38, 39). From a broader perspective, genetic sex differences extend to gene expression patterns (40). Upregulated genes in female PD patients involve signal transduction and neuronal maturation, while the genes upregulated in male PD patients involve PD-associated proteins, including PINK1 and alpha-synuclein (10, 11). Moreover, gene expression changes in protein kinase activity, proteolysis, and Wnt signaling, which regulate midbrain dopaminergic neurons, are mainly identified in women, while gene expression changes involving protein- and copper-binding activities are identified in men with PD (10, 41). Given the significant number of genetic risk factors that vary between male and female patients, there is a possibility that sex differences in PD sleep disorders may arise from these genetic variants, though this has not been investigated.

Past studies have established that the symptoms and mechanism of pathogenesis of PD differ between men and women, yet the genetic factors underlying the sex difference in sleep disorders of PD patients are still less well understood. This study hypothesized that genetic risk factors may be associated with differences in sleep disorders between males and females with PD. To examine potential genetic variants that could be a risk factor for PD sleep symptoms, we analyzed the frequency of different sleep symptoms in PD by utilizing a publicly available dataset and compared between sex and genetic variants. From the 68 variants analyzed, the results indicate that the G2019S variant on the *LRRK2* may be associated with sex differences in PD sleep disorders. This variant has been linked to RBD, sleep fragmentation, and reduced sleep quality and could be a potential therapeutic target to attenuate daily non-motor symptoms in PD patients.

## RESULTS

This study investigated the genetic risk factors associated with sex differences in sleep symptoms in PD patients. To determine sleep symptoms with sex differences, we obtained a daytime sleepiness dataset from the Mendeley repository that evaluated sleep symptoms in PD patients (42). We also extracted datasets from the Parkinson's Progression Markers Initiative (PPMI - see Acknowledgments), including their RBD questionnaires that likewise assessed the presence of sleep symptoms in a PD cohort longitudinally. We analyzed data from the RBD dataset from the years 2011 to 2015, which includes the first five years of the study. Additionally, we evaluated data from 2021 to examine the persistence of the symptoms. We performed chi-square tests for independence between male and female patients in the daytime sleepiness and PPMI RBD dataset to determine sleep symptoms with significant sex differences in frequencies.

To find the genetic risk factors potentially associated with the differences in frequencies between male and female PD patients, we analyzed an additional PPMI dataset containing the allelic status of PD-associated variants among the patients that were also assessed by PPMI's RBD questionnaires. We performed chi-square tests for independence between the male and female PD patients to determine sex differences in the frequency of variants between males and females.

The daytime sleepiness dataset included 150 PD patients in Albany, New York, of which 63% were male and 27% were female. The ages of the patients range from 37 to 84 years old. Our chi-square analysis revealed significant differences between male and female PD patients in periodic leg movement of sleep (PLMS) and RBD, where males have increased incidence in both conditions. In contrast, there

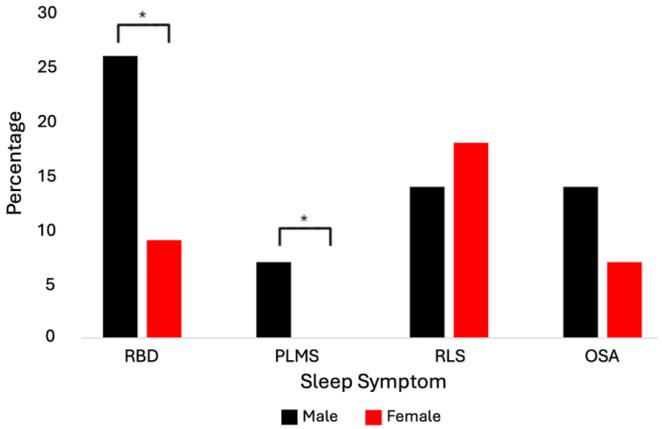


**Figure 1: Prevalence of sleep symptoms among male and female PD patients in daytime sleepiness dataset.** For each sleep symptom, percentages were calculated from male patients with the symptom/total male patients and female patients with the symptom/total female patients using data obtained from the daytime sleepiness dataset. *p-value < 0.05. P-values were calculated by chi-square test of independence and represent the significance of the difference in frequencies of sleep symptoms between male and female groups.

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were no significant differences between males and females in OSA and RLS ($p$-value < 0.05, **Figure 1**).

Since the previous analysis suggested a sex-specific phenotype for sleep symptoms in PD, we proceeded with analyzing PPMI's RBD dataset. For the PPMI RBD questionnaire results collected in 2011, 299 PD patients were evaluated, of which 64% and 26% were male and female, respectively. Our analysis revealed significant differences between male and female PD patients in moving arms/legs during sleep and hurting bed partners, both with higher frequency among male PD patients than female PD patients ($p$-value < 0.05, **Figure 2A**).

In 2012, 547 PD patients were evaluated, of which 64% and 26% were male and female, respectively. There were significant differences between male and female PD patients in moving arms/legs during sleep, hurting bed partners, sudden limb movements, and depression. Male PD patients had a higher frequency of moving arms/legs during sleep, hurting bed partners, and sudden limb movements, but female PD patients had a higher frequency of depression ($p$-value< 0.05, **Figure 2B**).

In 2013, 629 PD patients were evaluated, of which 64% and 26% were male and female, respectively. There were significant differences between male and female PD patients in moving arms/legs during sleep, hurting bed partners, sudden limb movements, aggressive dreams, remembering dreams, and depression, all with higher frequency among male PD patients than female PD patients ($p$-value < 0.05, **Figure 2C**).

In 2014, 742 PD patients were evaluated, of which 61% and 29% were male and female, respectively. There were significant differences between male and female PD patients in moving arms/legs during sleep, hurting bed partners, sudden limb movements, complex movements, awakening movements, stroke, and depression, all with higher frequency among male PD patients than female PD patients ($p$-value < 0.05, **Figure 2D**).

In 2015, 786 PD patients were evaluated, of which 59% and 31% were male and female, respectively. There were significant differences between male and female PD patients in moving arms/legs during sleep, hurting bed partners, aggressive dreams, nocturnal behavior, sudden limb movement, complex movements, awakening movements, stroke, and depression, all with higher frequency among male PD patients, except for depression, which had a higher frequency among female PD patients ($p$-value < 0.05, **Figure 2E**).

Notably, the frequencies of arm/leg movement and hurting bed partner consistently showed significant differences between males and females from 2011 to 2015, with a higher prevalence in males than females for both symptoms (**Figure 3**). Moreover, the percentage of females reporting arm/leg movements slightly increased from 2011 to 2015, while the percentage of males who had the symptom remained relatively stagnant (**Figure 3A**). However, the percentages for both females and males who hurt their bed partner increased over time (**Figure 3B**).

For the PPMI RBD questionnaire results collected in 2021, a total of 898 PD patients were evaluated, of which 54% and 36% were male and female, respectively. Our analysis revealed significant differences between male and female PD patients in moving arms/legs during sleep, hurting bed

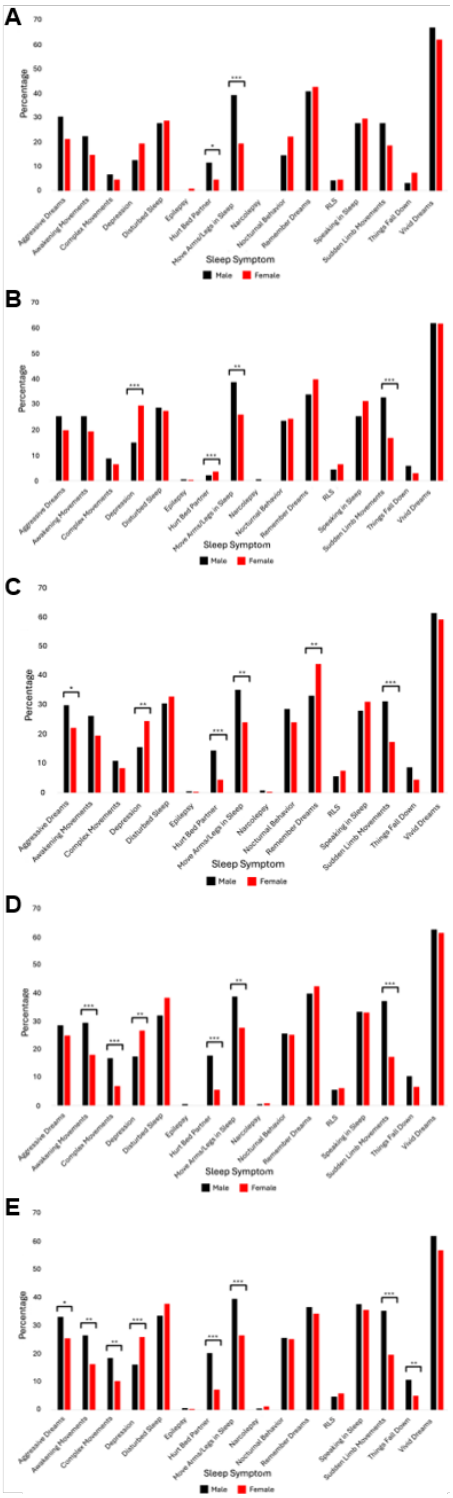


**Figure 2: Prevalence of sleep symptoms among male and female PD patients in 2011 – 2015 REM sleep behavior questionnaires from PPMI.** A) 2011 B) 2012 C) 2013 D) 2014 E) 2015. For each sleep symptom, percentages were calculated from male patients with the symptom/total male patients and female patients with the symptom/total female patients using data obtained from the PPMI RBD questionnaire dataset. *p-value < 0.05, **p-value < 0.01, ***p-value < 0.001. P-values were calculated by chi-square test of independence and represent the significance of the difference in frequencies of sleep symptoms between male and female groups in each year.

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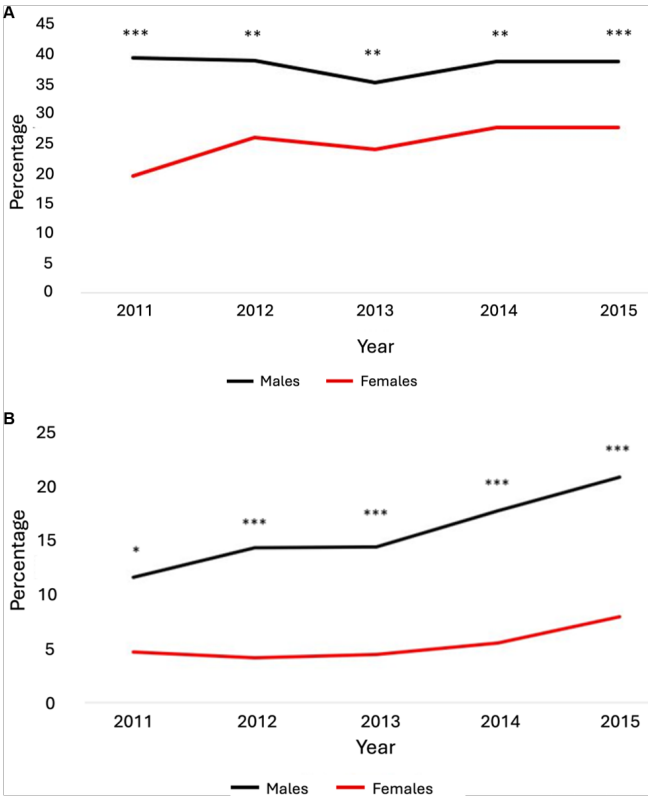


**Figure 3: Prevalence of arm/leg movements and hurting bed partner among male and female PD patients from PPMI from 2011 – 2015.** A) Percentages were calculated from male patients with arm/leg movements/total male patients and female patients with arm/leg movements/total female patients for each year using data obtained from the PPMI RBD questionnaire dataset. Percentages were calculated from male patients who hurt their bed partner/total male patients and female patients who hurt their bed partner/total female patients for each year using data obtained from the PPMI RBD questionnaire dataset. B) *p-value < 0.05, **p-value < 0.01, ***p-value < 0.001. P-values were calculated by chi-square test of independence and represent the significance of the difference in frequencies of arm/leg movements (A) or hurting bed partners (B) between male and female groups in each year.

partners, aggressive dreams, nocturnal behavior, sudden limb movement, complex movements, awakening movements, and parkinsonism (motor impairment), all with higher frequency among male PD patients, except for depression, which had a higher frequency among female PD patients (*p*-value < 0.05, **Figure 4**).

Given the data showing a consistent trend relating to sex and frequency of various sleep symptoms in PD patients, we analyzed an additional PPMI dataset containing the allelic status of PD-associated variants for these patients. Whole-exome sequencing of these patients was performed in 2011 at the start of the study to look at allelic status for known PD genetic risk variants. We performed chi-square tests on 68 genetic variants to determine sex differences in frequency of a variant between males and females. The chi-square test revealed significant differences in frequences between male and female PD patients for the variants rs34637584, rs33939927, rs14235, rs4444903, and rs104893877 (*p*-value < 0.05). To account for multiple comparisons, Bonferroni correction was applied. Variant rs34637584 showed significant differences in frequencies between males and females after the correction, with a higher prevalence of the mutation in females (adjusted *p*-value < 0.05, **Figure 5**). This variant is responsible for the G2019S mutation in the *LRRK2* gene and has been shown to impair cellular processes, including kinase and GTPase activity and endoplasmic reticulum $Ca^{2+}$ homeostasis, resulting in cell death and neurodegeneration (45, 46).

## DISCUSSION

The objective of this study was to determine potential genetic risk factors associated with sex differences in PD sleep disorders. Before identifying genetic risk factors, we performed a chi-square analysis to identify PD sleep symptoms that displayed significant sex differences in frequency between males and females. An initial analysis from a dataset of 150 PD patients revealed significant sex differences in PLMS and RBD with higher prevalences in males, but not for OSA and RLS.

Specifically, our results suggested that men are more likely to experience RBD, which is consistent with previous research indicating an association between RBD and the male sex (18, 19). Additionally, there was a higher prevalence of PLMS among men. However, this may not be a sex difference in PD sleep symptom manifestation because the association of PLMS with PD is uncertain (43, 44).

Our results were also consistent with several studies showing no significant difference in the prevalence of RLS or OSA between male and female PD patients (24, 25). This suggests that males and females with PD share similar predisposition to RLS and OSA. However, some studies have reported notable differences in RLS among their cohorts (22, 23), indicating potential sex differences dependent on additional factors such as environmental exposures.

Our findings supported Bjørnarå et al.'s observation that male PD patients were more likely to experience aggressive

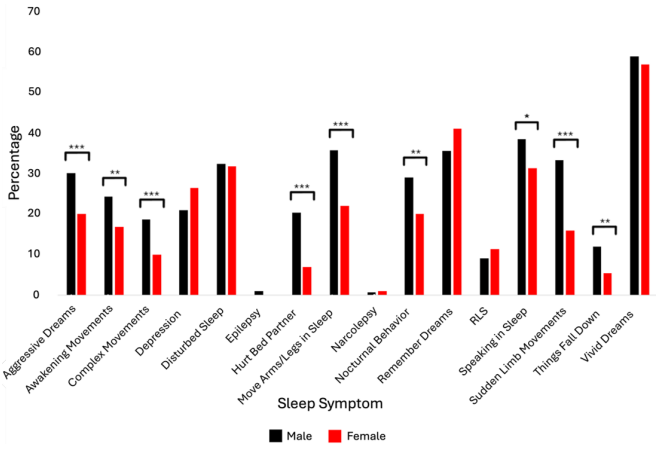


**Figure 4: Prevalence of sleep symptoms among male and female PD patients in 2021 REM sleep behavior questionnaire from PPMI.** For each sleep symptom, percentages were calculated from male patients with the symptom/total male patients and female patients with the symptom/total female patients using data obtained from the PPMI RBD questionnaire dataset. *p-value < 0.05, **p-value < 0.01, ***p-value < 0.001. P-values were calculated by chi-square test of independence and represent the significance of the difference in frequencies of sleep symptoms between male and female groups in each year.

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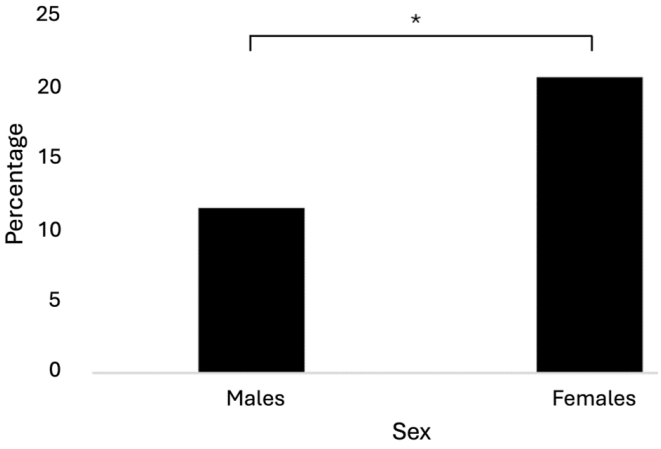


**Figure 5: Prevalence of the rs34637584 genetic variant in male and female PD patients from PPMI.** Percentages were calculated from male patients with the genetic variant/total male patients and female patients with the genetic variant/total female patients. The frequency of rs34637584 was significantly different between male and female PD patients using chi-square test of independence and Bonferroni correction. *Adjusted p-value < 0.05

dreams and awakening of their movements (30). The same study also reported that men had higher rates of fights and violent behavior. Our results showed that male patients were more likely to have movement during sleep and hurt their bed partner in comparison to female patients. Frequency of these two symptoms identified in 2011 at the beginning of the study persisted and remained significant over time until the last study timepoint.

Given that the frequencies of several sleep disorders and symptoms significantly differed between sexes, we proceeded to look at a PPMI dataset containing the allelic status of PD-associated genetic variants. Following Bonferroni corrections, only variant rs34637584 showed significant sex differences in frequencies.

The rs34637584 SNP is a missense mutation in the LRRK2 gene, leading to the G2019S protein change. The LRRK2 G2019S mutation is one of the most common mutations in both familial and sporadic PD and has been implicated in PD development through multiple mechanisms. For example, the mutation was demonstrated to impair kinase and GTPase activity in mice as well as disrupt endoplasmic reticulum $Ca^{2+}$ homeostasis, leading to mitochondria dysfunction and neurodegeneration (45, 46). Consistent with other studies, the results of our study reveal a significantly higher prevalence of the LRRK2 G2109S mutation in female PD patients compared to male PD patients (37, 47). Moreover, PD patients carrying the LRRK2 G2019S variant were shown to have a lower risk and severity of RBD compared to PD patients without the variant (32). Given that the mutation may have protective effects against RBD, the higher prevalence of the mutation in females may underlie the lower prevalence of RBD in female PD patients compared to male PD patients, portraying a protective effect in females (38).

Besides RBD, the G2019S mutation was shown to increase sleep fragmentation and reduce sleep quality in mice by altering sleep spindle expression implicated in sleep regulation (48). Additionally, G2019S mice were demonstrated to have elevated glutamatergic synapse activity, which excites thalamocortical circuits and ultimately disrupts sleep (48, 49). As such, the higher prevalence of the G2019S mutation in females may explain the higher rates of insomnia and disturbed sleep reported by female PD patients than male PD patients (14-16). While mice models demonstrate the biological mechanism of the mutation to sleep fragmentation, clinical observations of LRRK2-PD patients carrying the mutation also generally align with an increased frequency of sleep disturbances (50). Thus, the differential prevalence of the G2019S mutation between male and female patients may contribute to sex differences observed in sleep disorders of PD.

A limitation of this study is that it cannot confirm a causal association between mutations, particularly the LRRK2 G2019S mutation, and the sex biases observed in sleep disorders of PD patients. Confounding motor and mood symptoms, as well as environmental factors, may also underlie sex differences in sleep disorder manifestation. The prevalence of the mutation may not be the sole determinant of how sleep disorders manifest differently between male and female patients. Future studies should focus on larger and more diverse samples to establish sex-specific symptoms and their associations with the LRRK2 G2019S mutation in male and female PD patients. Moreover, the genetic testing was performed solely at the beginning of the PPMI study, whereas sleep symptom reports were ongoing until 2021. This large temporal difference between the genetic variants and RBD data may influence the associations found in this study. Moreover, changes by environmental and epigenetic factors may accumulate over time, which can significantly influence gene expression and manifestation of sleep symptoms. As such, future investigations should determine the genetic status and sleep symptoms of PD patients in proximal timeframes for more reliable analysis.

Collectively, our work suggested that the differential prevalence of the LRRK2 G2019S mutation may be a genetic risk factor underlying sex differences in sleep disorders of PD patients, including RBD and insomnia. Among the cohorts analyzed, significant sex differences in sleep disorder symptoms include RBD, PLMS, aggressive dreams, sleep movement, sudden limb movement, awakening of own movement, and violence towards bed partners, all with higher frequency in males. These findings contribute to the growing literature on sex differences in PD and emphasize the importance of considering sex as a factor in the diagnosis and treatment of PD, particularly when addressing sleep disorders. Moreover, the identification of sex-specific genetic risk factors highlights the potential for tailored genetic therapeutic approaches that can effectively manage sleep-related issues in PD patients. With more targeted and personalized interventions, the quality of life for male and female PD patients experiencing sleep disturbances can ultimately improve.

## MATERIALS AND METHODS

### Data description

A dataset that evaluated daytime sleepiness in 150 PD patients was obtained from the Mendeley Data Repository (42). Information for patient's demographics, medical history, medications, the Unified Parkinson Disease Rating Scale, Schwab and England scale, Hoehn and Yahr scale, the Montreal Cognitive Assessment, the modified Epworth Sleepiness Scale, the Parkinson Disease Sleep Scale version

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2, and the Mayo Sleep questionnaire were included (42).

Two additional datasets from Parkinson's Progression Markers Initiative (PPMI) were extracted from the Image and Data Archive (IDA). Data used in the preparation of this article were obtained June 15, 2023, from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/access-data-specimens/download-data), RRID:SCR 006431. For up-to-date information on the study, visit www.ppmi-info.org. PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners (see Acknowledgments).

The specific datasets used in this study were the REM sleep behavior disorder questionnaire and the genetic variant dataset. This analysis used data openly available from PPMI. All investigators complied with the PPMI Data Use Agreement. The REM sleep behavior disorder questionnaire includes "yes" or "no" observations of 21 mood and sleep-related symptoms experienced by each patient. The number identifiers of each participant are listed in the "PATNO" column, which is universal across PPMI datasets. The column "EVENT_ID" identifies when measurements are taken on the patient, with unique codes to indicate the patient's initial and subsequent visits. The study continually enrolls new patients each year. Measurements for patients were taken from the years 2011 (n=299), 2012 (n=547), 2013 (n=629), 2014 (n=742), 2015 (n=786), and 2021 (n=898). Answers to the questionnaire were reported by patients or their caregivers. Patients who had or did not have a symptom are designated a value "1" and "0," respectively.

The PPMI genetic variants dataset contains the allelic status of PD-associated variants in patients (n = 960) using whole-genome sequencing (WGS) data of PPMI samples (hg38 aligned data) performed in 2011 (51). Specific procedures regarding the preparation of the dataset are outlined by PPMI (51). The "PATNO" column lists subjects' number identifiers, and all other columns show the number of copies of an allele (0 to 2) of each variant in each patient. Variants are identified by their reference SNP cluster ID (rsID). Information regarding the variant's chromosome number, base pair position, and reference and alternate allele are also included. For the purpose of our analysis, we only considered 68 genetic variants that were present in at least one of the patients.

### Code for data analysis

We used R programming to conduct data analysis. Please refer to the following link for the full code: https://github.com/AlbertZhang2006/Analysis-of-Sleep-Symptoms-in-Parkinson-s-Patients.git

### Statistical analysis

All datasets were imported into R programming for analysis. Chi-square tests of independence were performed for each sleep-related symptom on the daytime sleepiness dataset to determine significant differences in sleep symptoms between male and female PD patients. Chi-square tests was selected as the most suitable for the non-continuous categorical nature of the data and was used to test for independence between male and female and the presence or absence of a particular sleep symptom. Expected values were calculated based on a contingency table created under the assumption of the null hypothesis, which states that there is no association between the sleep symptom frequency and sex.

Additional separate chi-square tests of independence were performed on the PPMI REM sleep behavior disorder questionnaire to determine significant associations of sex and prevalence of each RBD symptom prompted in the questionnaire. For the RBD sleep behavior disorder questionnaire, data was analyzed by year given that patients were evaluated across multiple years, with the selection of the years 2011 – 2015, as well as the following years until 2021. Participants with multiple entries in the same year were excluded. Finally, chi-square tests of independence were performed on the PPMI PD genetic variants dataset (n = 961) to determine variants that appear significantly different between males and females. To enhance the rigor of our analysis in pinpointing the associated variant, we opted for a Bonferroni correction, considering the total number of genetic variants tested.

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