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Sleep disorders and Parkinson disease; lessons from genetics

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Running head: Genetics of sleep disorders and Parkinson disease

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Summary

Parkinson disease is a common, age-related neurodegenerative disorder, projected to afflict millions of individuals in the near future. Understanding its etiology and identifying clinical, genetic or biological markers for Parkinson disease onset and progression is therefore of major importance. Various sleep-related disorders are the most common group of non-motor symptoms in advanced Parkinson disease, but they can also occur during its prodromal phase. However, with the exception of REM sleep behavior disorder, it is unclear whether they are part of the early pathological process of Parkinson disease, or if they develop as Parkinson disease advances because of treatments and neurodegeneration progression. The advancements in genetic studies in the past two decades have generated a wealth of information, and recent genetic studies offer new insight on the association of sleep-related disorders with Parkinson disease. More specifically, comparing genetic data between Parkinson disease and sleep-related disorders can clarify their association, which may assist in determining whether they can serve as clinical markers for Parkinson disease risk or progression. In this review, we discuss the current knowledge on the genetics of sleep-related disorders in Parkinson disease context, and the potential implications on research, diagnosis, counseling and treatment.

Key words: Rapid eye movement sleep behavior disorder; RBD; Restless legs syndrome; RLS; Parkinson disease; Neurodegeneration; Genetics; Glucocerebrosidase; GBA

Glossary of terms

- **Genome-wide association study –** A case-control study that examines the frequencies of common single nucleotide polymorphisms across the human genome and compares these frequencies between patients and controls. Significant differences in frequencies, after correcting for multiple comparisons, may suggest an association between genes in the regions of these polymorphism and susceptibility to a disease.
- **Pleiotropy –** When a single genetic variant, gene or locus contribute to more than one phenotype.

Abbreviations

DLB – Dementia with Lewy bodies

EDS – Excessive daytime sleepiness

GWAS – Genome wide association study

MSA – Multiple system atrophy

OMIM - Online Mendelian Inheritance in Man

OR – odds ratio

OSA – Obstructive sleep apnea

PD – Parkinson disease

PLMS - Periodic leg movement in sleep

RBD – REM sleep behavior disorder

REM – Rapid eye movement

RLS – Restless legs syndrome

SN – Substantia nigra

Introduction

As the world's population ages, age-related disorders such as Parkinson disease (PD) threaten to become a significant financial and social burden (1), on top of the personal burden carried by the affected individuals and their families. PD is the most common neurodegenerative movement disorder, affecting 1-2% of the population older than 60 years (2-4), and the projected number of PD patients in 2030 in 15 of the most populous nations is estimated to be 8.67 million patients (5). PD is pathologically characterized by degeneration of the substantia nigra (SN) and the presence of Lewy bodies, which are aggregates of various proteins, primarily α-synuclein (6). As such, it is part of a family of disorders collectively termed synucleinopathies, mainly including PD, dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) (7). Other diseases may also have α-synuclein depositions, and while this is a shared feature, it does not imply that α-synuclein is the sole cause for these disorders.

The pathogenic process leading to PD begins many years before diagnosis, which is traditionally based on classical motor symptoms; therefore, the course of PD can be divided accordingly, to preclinical PD, prodromal PD (non-motor PD) and clinical PD, when motor symptoms appear (8). This recent division aims to distinguish between the different phases of PD, first, when neurodegeneration started but no symptoms are present (preclinical PD), then when early symptoms appear but PD is not diagnosed yet (prodromal PD), and lastly when motor symptoms present (clinical PD) (8). Clinical PD occurs when about half of the dopaminergic neurons in the SN had already been irreversibly degenerated and died, and the typical motor symptoms appear (9). One of the main challenges in PD research is identifying individuals during the prodromal phase of PD; when neuroprotective therapy is available, early diagnosis of PD will be crucial to slow or stop the degenerative process prior to motor parkinsonism.

Sleep-related disorders are, as a group, the most common non-motor features of PD. Insomnia, fragmentation of sleep, and excessive daytime sleepiness (EDS) are experienced by more than 50% of PD patients in some studies (10, 11). During the prodromal phase of PD, rapid eye movement (REM) sleep behavior disorder (RBD) (12-15), restless legs syndrome (RLS) (16) EDS(17, 18), and other sleep-related disorders may already be present. If these disorders are indeed a part of the early pathogenic process of PD, they can potentially help identify individuals at-risk for PD. While the association between RBD and PD is well established (15, 19), it is still under debate to whether people with RLS and EDS are at increased risk for clinical PD (10, 17, 20). Other sleep disorders, including periodic leg movement in sleep (PLMS), obstructive sleep apnea (OSA), insomnia and circadian sleep-wake cycle disruption also occur in PD (21). However, it is not clear if these disorders represent a part of the intrinsic pathogenic process of PD, or they simply co-occur due to other factors.

During the recent decades, the rapid development of various genetic methods have led to a wealth of genetic information on familial and sporadic PD. Mutations in genes such as GBA, LRRK2, SNCA, PARK2, PINK1, PARK7, VPS35, SMPD1 and others can lead to PD (22), and at least 45 additional risk factors in 41 genetic loci were associated with increased or decreased risk for PD in genome wide association studies (GWAS) (23, 24). Similarly, genetic studies of sleep-related disorders have identified multiple genes and loci associated with both increased and decreased risk for these disorders. For example, GWASs of RLS cohorts identified genetic loci that are associated with the risk for RLS (25), and several studies examined the genetic overlap between RLS and PD (26-29). Only recently, the first genetic studies of RBD were performed (30-32) in order to examine whether RBD and PD share a similar genetic background.

The purpose of this review, is first to briefly summarize the clinical associations between PD and sleep related disorders commonly affecting PD patients. This part will map possible clinical overlaps between PD and sleep related disorders, which may suggest possible shared etiology. Then, we will discuss the available genetic knowledge on PD and the various sleep disorders potentially associated with PD. By comparing the known genetic factors associated with PD and sleep disorders, we will discuss on the potential overlap in genetics, as an indicator for etiology. We will further discuss the implications of these data on our understanding of PD, its clinical course and future aspects.

Determining the temporal correlates of sleep disorders and Parkinson disease

The majority of PD patients will suffer from a sleep-related disorder, whether before or after the onset of PD (21). Defining the temporal association between these sleep-related disorders and PD is important for determining whether sleep disorders can be clinical markers for PD development and/or progression. Based upon pathoanatomical considerations, essentially all sleep-related disorders could occur during prodromal PD, yet to determine if they are pathophysiologically associated with PD or just co-occur due to other factors or to chance alone, several approaches can be taken. One approach is to examine if a certain sleep-related disorder is more common in prodromal PD compared to the general population. Since it is currently difficult to identify individuals with prodromal PD, sleep-related disorders can be determined retrospectively, which may be affected by recall bias. Examining for sleep-related disorders immediately upon the diagnosis of PD may reduce the recall bias and have more reliable results (although this is no longer in prodromal stages). Another, more reliable approach is to prospectively follow-up cohorts of individuals with sleep disorders and to examine whether they

develop PD at higher rates than the general population. These studies are more difficult to perform, and therefore less common. Based on these approaches, Table 1 summarizes the main temporal correlates between sleep-related disorders and PD, and other important clinical associations in PD.

Sleep disorders in Parkinson disease – main clinical correlates

REM sleep behavior disorder

Thus far, the only sleep related disorder that is unequivocally associated with later development of PD and other synucleinopathies is RBD. RBD is characterized by lack of atonia during REM sleep and acting out of dreams (15, 33). After the initial report on high conversion rates from RBD to synucleinopathies (14), various reports had confirmed that individuals with RBD are likely to progress to an overt synucleinopathy in a time-dependent manner (15, 19, 34-37). Figure 1 depicts the risk for conversion to a neurodegenerative disease among patients with idiopathic RBD, ranging between 8.5% and 41% at follow-up of less than 5 years, and between 52.4% and 92.5% at follow up of more than 10 years. The average time from onset of RBD to onset of synucleinopathy was estimated at 12 years (38), and the prevalence of RBD at the population level was estimated at 0.3% - 1.15% (39, 40). Similar to PD, male gender is associated with RBD, with male:female ratio between 2:1 up to 8:1 in different studies; whether this reflects a true biologic association or a presentation bias (e.g. if men tend to have more violent dreams than women, which may increase the detection rate in men compared to women) is unclear (15, 37). Among PD patients, RBD can be found in 25% - 50% (41, 42), and the presence of RBD is associated with higher and faster rates of cognitive decline and dementia in PD (43), hallucinations (44), autonomic dysfunction, color vision impairment (45) and higher doses of L-dopa needed to control motor symptoms (46). Post mortem studies of PD patients

with and without RBD suggest that RBD is associated with more diffuse spread of α-synuclein aggregation (47).

Restless legs syndrome

RLS is characterized by an unpleasant sensation in the lower limbs that typically occurs at rest in evening hours. This sensation is relieved by movement of the legs, thus disturbing sleep initiation (48). The association between RLS and PD is controversial; several studies suggested that RLS is more common among PD patients, while other studies demonstrated that the frequency or RLS among PD patients is similar to the general population (49). Although dopaminergic treatment helps both conditions, pathological and imaging data do not support a pathophysiologic association. The pathological hallmarks of PD, α-synuclein accumulation in Lewy-bodies, were absent from post-mortem studies of patients with RLS (50). Furthermore, iron levels in the SN are reduced in RLS and increased in PD (51). It was demonstrated that using sonography in PD patients, it is possible to detect increased echogenicity of the substantia nigra, likely due to the cell loss. When comparing sonographic findings among patients with RLS and PD, increased echogenicity of the substantia nigra was observed only among PD patients (52). Reduction in putamen uptake of [18 F]-dopa was observed in RLS patients, but it was not due to the loss of striatal neurons typical in PD (53). Moreover, there was no clear decrease in [18 F]-dopa uptake and [123I]-ß-CIT binding in RLS, while such decrease is also typical in PD (54, 55).

Periodic leg movement in sleep

Patients with PLMS have repetitive, stereotypical lower limb movements during sleep, typically before the onset of REM sleep, and up to 80% RLS patients may suffer from PLMS as well (56).

As in RLS, patients with PLMS respond well to dopaminergic treatment. The prevalence of PLMS among PD patients in most reports is similar to controls (57), however the occurrence of PLMS in PD has been associated with PD severity (58) and with the degree of neurodegeneration (59). In a study of PD patients with and without dopaminergic treatment, patients had slight and nonsignificant higher frequencies of PLMS than controls. Treated and non-treated PD patients had similar rates, but the groups were relatively small (60). Treating PD with deep brain stimulation (DBS) could be associated with PLMS, potentially due to the reduced intake of dopaminergic treatment in patients who underwent DBS (61).

Excessive daytime sleepiness

EDS is a common complaint among patients with PD. Whether EDS is associated with prodromal PD is still controversial. Two reports suggested that elderly individuals with symptoms of EDS such as napping and feeling sleepy during the day, had higher PD risk (17, 18). Of note, in these studies EDS was not assessed by an objective method, and other common causes of EDS such as OSA were not ruled out. By contrast, other reports found that in de-novo PD cohorts, the rate of EDS was similar to the general population (62, 63); if not more common in clinical PD, it is hard to imagine how it could be a prodromal feature. As the course of PD progresses, EDS becomes more common, probably due to the involvement of multiple factors (64), including dopaminergic treatment, sedative drugs, neurodegeneration of regions of the reticular activating system that subserve wakefulness, and other co-morbidities that can occur in PD such as OSA, depression, and dementia (21). Interestingly, it was demonstrated that hypocretin cells loss, which is typical in narcolepsy, may be common in PD (65), which may explain some of the narcolepsy-like sleep attacks that sometime occur during PD. These associations should be further studied in additional cohorts of PD patients.

Circadian sleep-wake cycle disruption in PD, often presenting as a combination of EDS and insomnia, may also be related to various factors that occur in, but not specific to, PD. Several PD-related symptoms have circadian presentation, including motor activity, autonomic dysfunction, gastric function, hallucinations and others (66), which may suggest that circadian control is involved. Further supporting this possibility, it was observed that melatonin and cortisol regulation, which are involved in circadian regulation, can be disrupted in PD (67).

Obstructive sleep apnea

OSA is caused by partial or complete obstruction of the upper respiratory airways during sleep, leading to multiple episodes of apnea. OSA is associated with various conditions including obesity, neurological and neuromuscular disorders, facial dysmorphism and various environmental factors. There are contradictory results regarding the occurrence of OSA in PD. Several studies suggested that among PD patients the occurrence of OSA was similar to controls or even lower (21), which was also the conclusion of a meta-analysis of five studies (68), possibly due to reduced body mass index in PD. However, other studies reported that OSA may be more common in PD patients (69), or that PD is more common among individuals with insomnia (70). Therefore the association between OSA and PD remains inconclusive.

Insomnia

Insomnia is the most prevalent sleep disorder, and is probably the most common sleep-related complaint in PD (71). The classic pattern of insomnia in PD is sleep maintenance insomnia; patients fall asleep easily but waken early (72). This may suggest a phase-advanced dysregulated circadian rhythm. However, like most of the other sleep-related symptoms, insomnia is also multifactorial and non-specific for PD. Found in up to 80% of PD patients, it

may be related to comorbid RLS, Circadian sleep-wake cycle disruption, depression, anxiety, dementia, etc. (21). Insomnia is more prevalent in advanced and more severe PD, as the parkinsonian symptoms or adverse effects to anti-parkinsonian drugs can also contribute to disturbances in initiation or maintenance of sleep (73).

Genetics of Parkinson disease – a brief overview

Once considered a purely sporadic, environmental disease, PD is known today to have a strong genetic component. Estimates of the contribution of heredity to the risk for PD range between 27% and 60% in population and familial based studies (74, 75). So far, over 40 genetic loci and genes have been linked to PD and parkinsonism, including variants that are associated with mildly increased or decreased risk for PD, variants that are strong risk factors for PD, and mutations that necessarily cause PD.(22, 24) Figure 2 details the various genes that are known or suspected to be involved in sporadic PD, autosomal dominant and autosomal recessive PD, and in atypical forms of parkinsonism.

The most common PD-associated mutations are found in GBA and LRRK2. Different mutations in these genes have variable effects on risk for PD (76-79). In some populations, including Arab-Berbers and Ashkenazi Jews, the combined frequencies of variants in these genes may reach to 30-40% of all PD cases (80, 81). In other populations, including Japanese, Chinese, French-Canadian and Spanish, they account for 10-20% of PD patients, while in others they are found in less than 10% of PD patients (76, 82, 83). GBA mutations can be divided to severe or mild mutations, and individuals with severe mutations have higher risk for PD and earlier age at onset than mild mutation carriers. As in sporadic PD, there are more men than women with

GBA-associated PD (76). Interestingly, it was demonstrated that the enzyme encoded by GBA, glucocerebrosidase, had reduced activity in brain and peripheral blood from PD patients with or without GBA mutations (84, 85). Different LRRK2 mutations, which were initially described in familial PD, also have a differential effect on the risk for PD. Some LRRK2 mutations, such as the p.G2019S, and the p.R1441C/G/H substitutions, confer higher risk for PD (82, 86), while other substitutions such as p.G2385R among Asians are associated with only mildly increased risk for PD. Unlike sporadic and GBA-associated PD, the male:female ratio in LRRK2-associated PD is 1:1.(77)

Mutations and copy number variations in other genes are scarce and are probably responsible for less than 2% of all PD cases (22). Mutations in only few genes are known to cause PD in an autosomal dominant manner, the first to be discovered are in SNCA (87), encoding α-synuclein, the protein that accumulates in Lewy bodies. Point mutations, duplications and triplications of SNCA were described in autosomal dominant, mostly early-onset PD (88). VPS35 mutations are the only other well-validated cause for autosomal dominant, typical PD, and they are very rare, probably accounting for less than 0.5% of PD patients (89). While there is some compelling evidence that mutations in CHCHD2 (90), DNAJC13 (91), TMEM230 (92) and RIC3 (93) may also lead to autosomal dominant PD, more studies are necessary to fully accept these genes as PD-causing. In the cases of CHCHD2 and GCH1, only a few studies demonstrate this association, therefore additional case-control or familial studies are necessary to determine their role in PD. In the cases of DNAJC13 and TMEM230, the main evidence for association of these genes with PD comes from the same large family, therefore additional case-control and familial studies are necessary to determine which of them is associated with PD, if at all. Heterozygous carriage of specific SMPD1 mutations were also

suggested to strongly increase the risk for PD (94, 95), but more case-control and familial studies in additional populations, as well as functional studies on its potential mechanism, are needed to demonstrate the association between SMPD1 and PD, and to better understand the role of SMPD1 in PD.

The most common cause of autosomal recessive PD are mutations in PARK2 (Parkin), leading to early-onset, often juvenile PD, which account for 8.6% of PD with age at onset < 50 years (96). Homozygous and compound heterozygous mutations in PINK1 and PARK7 (DJ1) are other well validated causes of autosomal recessive, early onset PD or PD-like disease (96). Heterozygous mutations in PARK2 (97), PINK1 (98) and PARK7 (99) may be risk factors for typical, late or early onset disease, but this needs to be confirmed in additional studies. Other genes that are often cited as autosomal recessive PD-causing genes are in fact leading to atypical forms of parkinsonism (Figure 1) and their role in typical PD is still not clear.

A recent PD GWAS included data from a total of 19,061 PD patients and 100,833 controls, and identified 24 loci that likely increase or decrease the risk for PD, and a more recent GWAS with a total of >25,000 patients and >400,000 controls identified 17 additional loci (Figure 2) (23, 24). These loci include genes that were already associated with familial and sporadic PD such as GBA, LRRK2, SNCA, and GCH1 (although rare GCH1 mutations in sporadic PD were reported in only one study (100), which requires replications in additional case control studies of sporadic PD), and genes with mutations that had not yet been described in PD. Recently, mutations in VPS13C, one of the genes implicated in the GWAS, were identified in autosomal recessive, severe and rapidly progressive parkinsonism (101). The loci of other genes that cause typical or atypical parkinsonism, including PARK2, PINK1, PARK7 and ATP13A2 (22), were not identified in the GWAS meta-analysis (23, 24). It is important to note that

although the calculated effects on PD risk associated with these GWAS markers are small, with odds ratios (OR) typically ranging between 0.75-1.80 (23, 24), each loci can harbor genetic variants with either minor, medium, or major effect of the risk for PD.

Genetic overlap between RBD and PD

Although the association between RBD and PD was initially reported 2 decades ago, only recently genetic studies that specifically focus on RBD have been performed. The strongest genetic association reported thus far, is with mutations in GBA (32, 102). Clinically, GBA-associated PD and RBD-associated PD have many similarities. Both GBA and RBD are associated with rapid motor progression (103, 104) and the postural-instability-gait-dysfunction phenotype (105, 106), autonomic dysfunction (45, 103), cognitive decline and faster progression to dementia (43, 103, 107). Moreover, both GBA and RBD are associated with DLB (15, 37, 108) and MSA (37, 109). Therefore, it is no surprise to find that GBA mutations were associated with RBD in cohorts of idiopathic RBD patients (32, 102). Moreover, this association was even stronger than the association with PD in a similar population (110), suggesting that GBA mutations are more specifically associated with the RBD subtype of PD. Furthermore, in clinical PD patients screened with an RBD questionnaire, GBA mutations were associated with probable RBD (32). It was further demonstrated that among biallelic GBA mutation carriers, as well as among heterozygous carriers who did not have PD, RBD scores were significantly worse than controls (111). From a pathological point of view, both RBD-associated PD and GBA-associated PD probably have a more diffused spread of α-synuclein accumulation (47, 112). These are suggestive leads, but more studies are needed to confirm the association between GBA and RBD.

While GBA- and RBD-associated PD are clinically similar, LRRK2-associated PD typically has a more benign course, with less rapid cognitive decline (113), less hyposmia (reduced sense of

smell) and less autonomic dysfunction than sporadic PD (114). Therefore, it was not surprising that LRRK2 mutations were not associated with idiopathic RBD (30) nor with probable RBD in a clinical PD cohort (115). In two studies that examined PD patients and controls with LRRK2 mutations, RBD was less common in LRRK2 mutation carriers (116, 117). Our unpublished data confirms the lack of association between LRRK2 and RBD (Gan-Or et al., unpublished data). The differences between male : female ratios in LRRK2-associated PD, in which there is equal (1:1) ratio (77), and RBD, in which male gender strongly predominates (118), provide further support for the lack of association between LRRK2 mutations and RBD.

In an initial screening of 9 loci that were previously associated with PD, an association between markers at the SCARB2 and MAPT loci as found in idiopathic RBD patients, and additional markers at the GAK and SNCA loci demonstrated a marginal association (31). An additional study, in a smaller population, also suggested that MAPT may be associated with RBD (119). However, this association need to be confirmed in larger studies. The association with SCARB2 is of special interest to the RBD/GBA association, since this gene encodes the transporter responsible for glucocerebrosidase transport, from the endoplasmic reticulum and the lysosome (120). Recently, it was demonstrated that the DLB-associated gene, APOE, is not associated with RBD (121). However, larger scale GWASs are needed to examine whether other PD-associated loci are specifically associated with RBD or whether RBD might have unique genetic risk factors that were not detected in unselected PD GWASs. Whether RBD is associated with other genes that cause familial PD remains undetermined, however various studies reported RBD in patients with mutations in SNCA (122) and PARK2 (123).

Hexanucleotide expansions of C9orf72, which causes amyotrophic lateral sclerosis and fronto-temporal dementia, have a minor or no role in PD (124). However, one report identified

two C9orf72 expansion carriers in 2 RBD patients (125). To determine this was a random finding or whether a true association exists, studies in additional populations are necessary. Another gene that was suggested to be involved in PD, but was later refuted, is the melanoma-associated gene MC1R (126, 127). It was recently shown that variants in this gene are also not associated with RBD(128).

Overall, it seems that the genetic background of RBD and PD overlap considerably, but perhaps not fully, suggesting that RBD-associated PD has its own genetic background. It is possible that some markers seen in GWASs of PD are particularly markers of RBD-associated PD that become significant due to the high frequency of RBD in PD cohorts. If so, selecting specifically RBD patients (or patients with other markers of disease subtype) may increase the power of GWAS to find important associations. To map the genetic risk loci in RBD, two approaches can be taken: 1) performing GWAS on RBD cohorts and 2) re-analyzing data from the PD GWASs only in PD patients who also have RBD.

Preliminary data suggested that some genetic factors may affect the rate of progression from RBD to the defined synucleinopathy diseases (31). This issue should be studied in larger cohorts, since it may have important implications for future clinical trials. If genetic factors can predict the rate of progression from RBD to synucleinopathies, RBD patients who carry specific variants that are associated with more rapid progression could be prioritized for clinical trials of drugs that aim to stop the progression of the disease.

Restless legs syndrome, periodic leg movements during sleep and Parkinson disease genetics

The largest published RLS GWAS included 922 cases and 1,526 controls in the discovery phase and 3,935 cases and 5,754 controls in the replication phase.(25) While this is not as large as the PD GWASs (24), it is large enough to provide reliable results. Thus far, six genes and genetic loci were associated with RLS in GWASs: MEIS1, BTBD9, PTPRD, MAP2K5/SKOR1, TOX3 and the intergenic rs6747972 on chromosome 2 (25). Given the strong clinical overlap between RLS and PLMS, it is not surprising that five of the GWAS loci associated with RLS, were also associated with PLMS (129). None of these loci were associated with PD, and none of the 24 PD GWAS loci were associated with RLS (24). When examining the online database PDgene (www.pdgene.org), which provides meta-analyzed results from various GWASs, five of the six RLS markers, rs2300478 (MEIS1), rs9357271 (BTBD9), rs1975197 (PTPRD), rs12593813 (MAP2K5/SKOR1) and rs6747972 (intergenic), have a meta-analysis *p*-value>0.05, demonstrating that these markers are not associated with PD. However, one RLS marker in the TOX3 locus, rs3104767, had an OR of 1.07 (95% confidence interval [CI] 1.04-1.10, $p=5.03 \times 10^{-5}$) in a meta-analysis of 15 PD studies (PDgene). In the largest RLS GWAS it had an OR of 1.35, 95% CI 1.27-1.43, $p=9.40 \times 10^{-19}$ (25). Of note, this marker is not significant in the PD GWAS meta-analysis after correction for multiple comparisons, so it requires further study. Two studies specifically examined the RLS GWAS markers in PD case-control cohorts, and no evidence for association with PD was found (26, 29).

Several studies of familial RLS have found genetic loci that may be involved in autosomal dominant or recessive RLS. Table 2 details these loci as well as those identified in the RLS GWAS. Some of these familial loci, which received the aliases of RLS1 – RLS8 (OMIM.org), include genes that were implicated in RLS GWAS (RLS3 includes PTPRD, RLS6 includes BTBD9, and RLS7 includes MEIS1), while the other loci were not associated with a

specific gene. It remains undetermined whether these loci indeed represent true genetic determinants of RLS, since most were replicated a few times at most, or not at all (130). When comparing these loci to known PD loci, there is very little evidence for any potential overlap between these RLS loci and PD loci and known genes. The PD-associated gene LRRK2 is found within the RLS1 locus, however this locus includes more than half of the long arm of chromosome 12 (OMIM.org), which contains a few hundred genes. RLS2, RLS3, RLS4, RLS5, RLS7 and RLS8 do not include PD-associated genes. RLS6 contains the HLA genes, some of which were associated PD (24), but it also includes BTBD9 (131). Additional candidate gene studies in RLS suggested the involvement of MAOA (132) and NOS1 (133), and while these genes are awaiting replication studies, they are also not associated with PD (PDgene) (24).

Other studies specifically examined PD-associated genes or genetic markers in RLS. There was no association between one of the strongest risk factors for PD, the MAPT associated SNP rs1052553, and RLS in a case-control study (28). Studies of families that presented both with PD and RLS also provided no evidence for genetic overlap between PD and RLS. PARK2 mutations did not segregate with RLS and did not affect the phenotype of RLS in two families with PARK2-associated PD (134). The Rep1 allele of SNCA which is more frequent in PD than controls, was in fact less frequent in RLS, demonstrating opposite directionality of effect in PD and RLS (27). Therefore, there appears to be no evidence of a true overlap between PD- and RLS-associated genes and genetic loci.

Obstructive sleep apnea genetics and Parkinson disease

Studying the genetics of OSA is complicated by comorbidities that can predispose to OSA and are also heritable. These comorbidities can be divided into four major groups: 1) obesity and metabolic disturbances 2) craniofacial and upper airway morphology 3) ventilation control and 4) sleep and circadian rhythm control. It is also likely that other genes unrelated to these conditions may also be risk factors for OSA. For example, family studies that demonstrated that first-degree relatives of OSA patients were more likely to have OSA after adjusting for body mass index (135).

OSA is a common condition often with familial aggregation, and although there are still not enough genetic studies, in recent years more progress has been made. Various candidate gene studies have highlighted genes including LPAR1, PLEK, PTGER3, (136) TNF (137), CRP (138), GDNF (139), HTR2A (140), PPARGC1B (141), NRG1 (142), FTO (143), TRABD2B (144), SLC6A4 (145) and LEPR (146), most of which have not been replicated; therefore at this point they should be considered with caution. Possible exceptions are TNF, LEPR and HTR2A, which has some evidence for association with OSA in more than one study. A meta-analysis demonstrated an association between a variant in the promoter of TNF and risk for OSA (137), and another meta-analysis suggested that variants in LEPR are associated with a reduced risk for OSA (146). Interestingly, it was demonstrated that a TNF polymorphism was associated with increased TNF-α levels in children with OSA, and significant increase in excessive daytime sleepiness symptoms was observed in association with this polymorphism (147). Therefore, the association with TNF may be explained by increased sleepiness which makes them more likely to present. Meta-analysis of HTR2A variants suggested association with OSA only in men (140). However, none of these genes were replicated in a recent, large GWAS meta-analysis that included a total of 12,558 participants of Hispanic origin (144). Another GWAS-level significant

locus for OSA was suggested in this study, around the GPR83 gene (144). However, this study did not include a replication population, and these associations should be considered with caution. None of these genes or genetic loci were implicated in PD (PDgene) (24), suggesting that the genetic background of the two conditions is probably distinct. However, since more genetic studies are necessary in OSA, it cannot be determined with certainty that there is no true genetic overlap.

Circadian sleep-wake cycle disruption genetics and Parkinson disease

Many of the genes and proteins regulating the circadian clock are well characterize, including PER1, PER2, PER3, CRY1, CRY2, CLOCK, ARNTL, ARNTL2, CSNK1D, CSNK1E, TIMELESS, NPAS2, NR1D1, DBP, FBXL3, BHLHE40, BHLHE41 and others that were thoroughly reviewed (148-150). It important to note that most of the knowledge on the function of these genes and proteins is derived from animal studies (151), therefore the role of human genetic variations in these genes and their potential effects on sleep patterns require more study. However, variants in some of these genes were suggested to be involved in circadian clock patterns or related disorders. However, often they were not replicated in additional studies, and none of these genes and variants were also associated with risk for PD (24). For example, one of the most studied genetic variants is a SNP in the CLOCK 3' untranslated region, which was associated with diurnal preference (152), but this association was not replicated (153). This variant was also suggested to be involved in sleep regulation in various psychiatric disorders, but also with inconsistent results.(154, 155) Like all variants in the CLOCK locus, this variant is not associated with PD in the meta-analysis of PD GWASs (PDgene) (24). Similarly, other variants in these genes that were suggested to have effects on the circadian cycle or sleep related

measures, such as PER1 rs2735611 (156), PER2 rs2304672, PER3 rs228697 and ARTNL2 rs922270 (157), are also not associated with PD in this meta-analysis (p>0.05 for all SNPs). Similar observations, i.e., possible association with circadian sleep cycle and lack of association with PD, are true for other variants in these genes (158, 159). Since some variants in these genes may also be associated with affective disorders, their potential effect on common psychiatric symptoms in PD such as depression and anxiety should be further studied.

Recently, three large GWASs examined the association of genetic markers with chronotype, with substantial genetic overlap. A total of 9 genes (RGS16, PER2, FBXL13, AK5, HCRTR2, HTR6, TNRC6B, APH1A and ERC2) were identified in two or three of the studies, thus well validated (160-162). As the other genes associated with the circadian sleep-wake cycle, these two are not associated with PD.

Genetics of insomnia and excessive daytime sleepiness

Genetic studies of both insomnia and EDS are complicated by the various factors that are associated with these two conditions. Therefore, identifying genes and variants specifically associated with insomnia and EDS is challenging, which may explain the relatively low number of genetic studies of these conditions (163). Since EDS can be related to circadian sleep-wake cycle disruption, PLMS and other sleep disorders that were reviewed here, the same genes involved in these disorders can also be involved in EDS (164). Several twin studies suggested that heritability is indeed a contributing factor for insomnia (165, 166), but most of these studies did not control for the heritability of comorbidities that may cause secondary insomnia. Two GWASs(167, 168) and several candidate gene case-control studies were performed in attempt to identify genetic markers of insomnia. While several candidate genes were suggested, including ROR1, PLCB1 (167), CACNA1C (168), CLOCK (169), SLC6A4 (170) and GABRB3 (171),

they are still awaiting proper replication studies in order to determine their role in insomnia. None of these genes was previously associated with PD.

Conclusions

Generally, the genetic study of sleep related disorders still lags behind other medical fields, although in recent years some progress has been made. Only a few GWASs have been performed in sleep disorders, and while basic genetic twin and familial studies had been performed in the past, there are very few studies that applied next generation sequencing technologies on families with sleep-related disorders. So far, there is no evidence for overlap in genetic predisposition for PD and either insomnia, EDS, OSA or circadian sleep-wake cycle disruption. In addition, there is no known overlap between RLS/PLMS genetic markers and PD, although this should be further studied.

In contrast, there is convincing evidence that the genetic basis of PD and RBD overlap, at least partially. Since we now know that the vast majority of cases of RBD have in fact a synucleinopathy in progress, this is not surprising. Of note, although not surprising, these observations linking some PD genetic markers and RBD may have importance for future studies and clinical trials. For instance, when asymptomatic carriers of GBA mutations are being followed up, screening for RBD should be considered for early detection of conversion to a synucleinopathy. Such population of GBA mutation carriers with RBD could be ideal for future clinical trials, since they are highly likely to convert to PD or another synucleinopathy. More genetic studies on RBD are required to identify additional genetic factors that are either shared with PD or unique to RBD, which will allow better characterization of this population.

Practice points

1. Little is known about the genetics of most sleep-related disorders, especially those with multiple comorbidities such as insomnia, EDS and OSA. Identification of genetic markers that specifically affect these disorders is challenging, and adjusting for factors that affect the predisposition for these disorders (for example, controlling for BMI in genetic studies of OSA) is necessary in order to identify such genetic markers.
2. While sleep-related disturbances are probably the most common non-motor symptoms in PD, the genetic evidence, as well as most of the clinical, imaging and pathological evidence suggest that only RBD is specifically associated with PD. Although it is possible that RLS and EDS occur more in PD, it is most likely not due to shared genetic predisposition.
3. RBD is manifesting as a sleep disorder, but in most cases it is in fact a neurodegenerative synucleinopathy in early stages, and should be considered as such by sleep specialists.

Research agenda

1. More genetic studies are needed in sleep-related disorders, whether candidate-gene or GWAS approaches in case-control cohorts, or studies of familial cases with next generation sequencing. Large collaborations will be needed to overcome the difficulties arising from the multiple comorbidities involved in most of these disorders.
2. Although the current genetic evidence support lack of pleiotropy between RLS and PD, more studies are needed, specifically of the TOX3 locus but also others, to conclusively elucidate this possibility.
3. To better understand the progression from RBD to the different synucleinopathies, large and preferably prospective genetic studies that examine how genetic variants are associated with RBD progression are needed. Such studies should examine both the rate of progression, and to which synucleinopathy RBD progresses into, and if there are genetic markers that are specific to RBD and were not detected in PD studies.
4. Future clinical trials focusing on RBD patients should be among the leading strategies to identify drugs for PD. Such studies can be stratified by the genetic status of the patients. For example, studying drugs that aim to modify the enzymatic activity of the enzyme encoded by GBA would ideally be performed on RBD patients with GBA mutations.

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Figure legends.

Figure 1. Risk for progression from REM sleep behavior disorder to synucleinopathies according to follow-up time.

Studies that examined the risk for progression from REM sleep behavior disorder to synucleinopathies are depicted, with follow-up time divided to < 5 years (blue bars), between 5 and 10 years (orange bars) and above 10 years (green bars). In all studies follow-up-dependent increase in risk is observed, with risk >80% in most studies that calculated the risk in follow-up > 10 years. Postuma et al. 2015a refers to ref (19), and Postuma et al. 2015b refers to ref (36).

Figure 2. Summary of Parkinson disease genetics.

Genes that are known or suspected to be involved in typical or atypical Parkinson disease (PD) are depicted, according to the level of confidence in their involvement, and according to the type Parkinsonism they are associated with: sporadic PD, autosomal dominant PD, autosomal recessive PD, and syndromes that include atypical parkinsonism.

Table 1

Summary of temporal and clinical correlates of sleep related disorders and Parkinson's disease

Sleep disorder	Prodromal PD	Motor PD	Other clinical correlates in PD
REM sleep behavior disorder	- More than 80% of RBD patients will develop a synucleinopathy in a time dependent manner. - Dream enactment and RBD are common in newly diagnosed PD patients.	- RBD can occur after the onset of PD, and the rates of PD patients with RBD increases with disease duration. - 25%-50% of PD patients have RBD. - Possibly associated with faster motor progression and higher doses of levodopa. - REM sleep without atonia, which does not fulfil all criteria for RBD, is also more common in PD than in controls.	- Associated with cognitive decline, dementia and hallucinations. - Associated with autonomic dysfunction.
Restless legs syndrome	- No evidence that individuals with longstanding RLS develop PD at higher rates than individuals without RLS. - Late-onset RLS possibly may be prodromal sign of PD. - Contradictory results in newly diagnosed PD.	- Contradictory results, some studies suggest higher rates of RLS in PD, while others demonstrate similar rates to controls. - Estimates may be confounded by non-specific motor symptoms - When PD and RLS co-occur, PD symptoms usually precede RLS symptoms.	- RLS was associated with depression in PD. - associated with DBS, possibly due to reduction of dopaminergic treatment. - Duration of antiparkinson therapy may strongly contributes to of RLS in PD, could be related to "wearing off". - Patients with RLS did not have α-synuclein pathology. - RLS patients did not have increased echogenicity of the substantia nigra on sonography, a finding that is typical of PD. - Other imaging studies in RLS patients did not support overlap with PD
Periodic leg movement in sleep	- No evidence that PLMS precede PD, and similar PLMS index in newly diagnosed PD patients vs. controls.	- Similar frequency of PLMS in PD patients and controls. - Can occur after reduction in dopaminergic treatment following deep brain stimulation surgery. -Possibly associated with striatal	- PLMS associated with severity of PD symptom, sleep disturbance, and decreased quality of life.

		dopaminergic nerve loss.	
Obstructive sleep apnea	- OSA can mimic RBD symptoms, but no evidence for increased rate of progression to PD. - No increased OSA in newly diagnosed PD.	- Most studies did not show an association between OSA and PD. - A meta-analysis of 5 studies suggested that PD patients have reduced risk for OSA. - Other studies suggested that PD is more common among individuals with insomnia.	- Even coincidental OSA, if present, can still be cause of somnolence and may warrant treatment.
Excessive daytime sleepiness and sleep attacks	- Contradictory results regarding the involvement of EDS in prodromal PD. - Case control studies of newly diagnosed PD demonstrated similar frequencies of EDS in patients and controls. - Other studies suggested that EDS may precede PD.	- EDS and sudden onset of sleep are common in PD, in some studies more than 50% of patients. - Frequency of EDS increases with disease progression, severity of PD symptoms and levodopa dosage. - Increased hypocretin loss was observed with advanced PD.	- All dopaminergic agents can cause somnolence. Some studies suggest that dopamine agonist treatment may be particularly associated with EDS in PD, while others did not. - Associated with dementia.
Insomnia	- Insomnia is not common in newly diagnosed PD patients. - Possible slight increase in insomnia in prodromal PD.	- Some studies suggested that the frequency of insomnia increases with PD progression. - Other studies demonstrated that the frequency of insomnia remains stable through follow up, and may fluctuate during the course of PD.	- Insomnia is associated with depression in PD, but significance of association is unclear, since insomnia is often a component of depression in general.
Circadian sleep-wake cycle disruption	- Analysis of newly diagnosed PD patients suggested that disruption of the circadian sleep-wake cycle may occur early in the disease. It was not clear if this disruption precedes the motor symptoms of PD.	- Circadian melatonin levels had lower amplitude in PD patients compared to control. - The lower melatonin levels were not associated with disease duration, levodopa doses and UPDRS scores. - However a previous study suggested that melatonin levels were affected by dopaminergic treatment.	- Hallucinations in PD are associated with altered rest-activity rhythm.

Table 2.

Genetic loci and genes associated with restless legs syndrome

Locus name (OMIM)	Chromosomal region	Implicated genes	Comments
RLS OMIM loci			
RLS1	12q12-q21	Yet to be identified.	Large locus that includes more than half of the large arm of chromosome 12. The PD-associated gene LRRK2 is in this locus, but there is no evidence that it has a role in RLS.
RLS2	14q13-q21	Yet to be identified.	This locus represents about one quarter of the long arm of chromosome 14, and it includes dozens of genes, none of which was associated with PD.
RLS3	9p24-p22	PTPRD	This locus encompasses about half of the short arm of chromosome 9, and it includes the PTPRD gene, which is a well validated GWAS marker. There is no evidence that in the families in which this locus was identified there are mutations in PTPRD that can explain the association.
RLS4	2q33	Yet to be identified.	This locus includes dozens of genes, none of which was specifically associated with RLS
RLS5	20p13	Yet to be identified.	This locus represents about a fifth of the short arm of chromosome 20, and includes dozens of genes, none of which was specifically associated with RLS
RLS6	6p21	BTBD9	This locus was identified in a genome wide association study, with variants around the BTBD9 gene. This region contains the HLA genes that may be involved in PD. However, since it is very likely that BTBD9 is responsible for RLS in this region, there is no suggested genetic pleiotropy in this locus between RLS and PD.
RLS7	2p14-p13	MEIS1	This locus is was identified in case-control studies and GWAS, and includes the strongest genetic risk factor for RLS detected to date.
RLS8	5q31	PCDHA3, WWC2, ATRN, FAT2	While the most plausible candidate in this region was reported to be PCDHA3, it is still possible that any of the other genes is associated with RLS in this locus, and additional studies are required to determine the association of this locus with RLS.
Genome-wide association study loci			
NA	Chromosome 2	MEIS1	The GWAS associated marker was rs2300478, and the minor allele was associated with

			an increased risk for RLS (OR 1.68). Also called RLS7.
NA	Chromosome 2	Intergenic region	The GWAS associated marker was rs6747972, and the minor allele was associated with an increased risk for RLS (OR 1.23).
NA	Chromosome 6	BTBD9	The GWAS associated marker was rs9357271, and the major allele was associated with an increased risk for RLS (OR 1.47). Also called RLS6.
NA	Chromosome 9	PTPRD	The GWAS associated marker was rs1975197, and the minor allele was associated with an increased risk for RLS (OR 1.29). Found in the RLS3 locus.
NA	Chromosome 15	MAP2K5, SKOR1	The GWAS associated marker was rs12593813, and the major allele was associated with an increased risk for RLS (OR 1.41).
NA	Chromosome 16	TOX3	The GWAS associated marker was rs3104767, and the major allele was associated with an increased risk for RLS (OR 1.35).

OMIM, Online Mendelian Inheritance in Man; RLS, restless legs syndrome; GWAS, genome-wide association study; OR, odds ratio.