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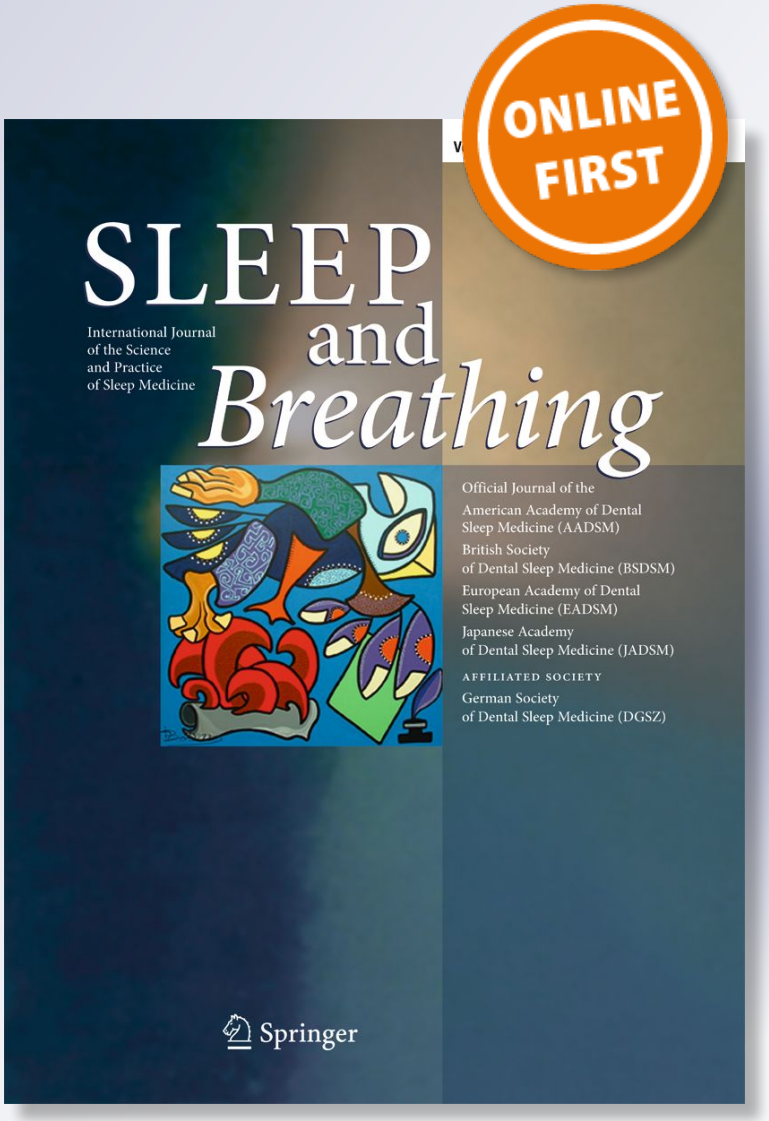

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ORIGINAL ARTICLE

Clinical and polysomnographic features of a large Turkish pedigree with restless leg syndrome and periodic limb movements

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Abstract
Purpose Restless leg syndrome (RLS) and periodic limb movements (PLMS) are common neurological diseases often associated with insomnia. A familial aggregation in RLS has been identified since it was first described; however, inheritance patterns of RLS/PLMS are poorly understood and their exact pathophysiology is not well-known. We have identified a Turkish pedigree with RLS/PLMS, which is a rare condition, in five generations of a family, including nine affected family members.
Methods A detailed clinical evaluation of the family was conducted with the help of polysomnographic recording, electrophysiological findings, and biochemical parameters.
Results The proband is a 38-year-old male member of the family who first started to show symptoms at the age of 29. All the patients from this family have been diagnosed with RLS, according to the criteria of the International RLS Study Group. Disease onset was early in all cases and even earlier in the younger generation. Three affected individuals also had PLMS on polysomnographic recordings.
Conclusion To our knowledge, this is the first Turkish family in which nine individuals in five generations are affected. We suggest an important effect of anticipation and genetic impact of the diseases and describe specific clinical features. Further investigation of clinical, genetic, and biochemical similarities between PLMS and RLS may yield important clues, adding to our understanding of the pathophysiology of these common diseases.

Keywords Restless leg syndrome (RLS) · Periodic limb movements (PLMS) · Genetics · Polysomnography · Turkey

G. Babacan-Yildiz · E. Gürsoy · M. Kolukisa · A. Celebi
Department of Neurology, Bezmialem Vakif University,
School of Medicine,
Istanbul, Turkey

F. Karaköse · E. M. Akkoyunlu
Department of Chest Diseases, Bezmialem Vakif University,
School of Medicine,
Istanbul, Turkey

E. Lohmann (✉)
Department of Neurology, Istanbul Medical School,
Istanbul University,
30390, Istanbul, Turkey
e-mail: ebbalohmann@gmx.net

Introduction

Periodic limb movements (PLMS), previously known as nocturnal myoclonus, are characterized by brief, repetitive, and stereotypical periodic flexions of the extremities, mostly of the lower limbs. They are generally associated with the extension of the big toe and result in poor quality of sleep and insomnia. Movements are typically bilateral but may predominate in one limb or alternate between them. PLMS can also occur during waking hours showing the same clinical picture but with a greater intensity and speed [1]. The diagnosis is established according to the American Academy of Sleep Medicine (AASM) criteria [2] by using polysomnography (PSG) and including recording of the surface electromyographic activity in the affected muscles [3]. Each movement lasts 0.5 to 5 s and occurs at intervals of approximately 4 to 90 s [3]. A PLM index (number of movements per hour of sleep) greater than 5 in children and greater than 15 in adults is considered as abnormal [1] and defined as periodic limb movement disorder (PLMD) by the International Classification of Sleep Disorders [2, 4].

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In comparison to PLMD, restless leg syndrome (RLS) is a purely clinical diagnosis. This common neurological disorder is characterized by an irresistible urge to move the legs, especially during rest or inactivity, and occasionally also affects the upper extremities [5]. RLS can cause sleep disruption resulting in daytime fatigue [6]. The current findings in the RLS field are summarized in a recently published review by Yeh et al. [7]. For the purpose of clinical diagnosis, four cardinal criteria were established and revised by the International RLS Study Group [5]: (a) an irresistible urge to move the legs, usually associated or caused by unpleasant and uncomfortable sensations, that (b) begins or worsens during periods of rest, (c) is relieved by movement, and (d) occurs or worsens in the evening or at night. A relatively strong genetic contribution has been demonstrated for RLS: Genome-wide association studies in RLS cases from Germany and Iceland have identified variants at four loci encompassing the genes MEIS1, BTBD9, MAP2K5/SKOR1, and PTPRD [8–10]. Interestingly, BTBD9 is a likely genetic determinant of PLMS. In one of these studies, the presence of a single allele resulted in doubling the risk for RLS, while a double allele resulted in increasing the risk by fourfold [10].

Even if RLS and PLMS are defined as separate clinical syndromes, it is suggested that they are related: PLMS are more common in asymptomatic family members of patients with RLS compared to the general population [10]. Thus, PLMS may serve as an end phenotype for RLS. However, not all patients with RLS have PLMS, and the majority of individuals with PLMS do not have waking symptoms of RLS [8]. Although both syndromes are closely associated, currently, their pathophysiology has not been well-defined [11]. We herein describe a five-generation Turkish RLS family including four reported affected family members and five family members who meet the criteria at examination for diagnosis of RLS [5].

Methods

Proband and family description

The proband, a 38-year-old right-handed man, was self-referred to Bezmialem Vakif University, School of Medicine, Neurology outpatient clinic for differential diagnosis of insomnia. The patient complained of RLS and repetitive short-lasting lower limb movements occurring during sleep and disturbing his sleep. His wife also reported that his feet and leg periodically moved when he was asleep. Additional medical history and neurological examination were unremarkable, but in the detailed questionnaire, daytime fatigue, mild lower back pain, and depressive moods were noted. The patient showed a dramatic improvement of symptoms after treatment with pramipexole (0.250 mg/day). Family history revealed that his father, his paternal grandfather, his brother, and also his son suffered from RLS symptoms (Fig. 1). The family originated from Kastamonu, a Black Sea province in Turkey. Parental consanguinity was known for the parents of individual IV2 and IV5 and parents of individual II5 are known to be first cousins. In addition to this, as all family members originated from the same village, it was presumed that there were multiple consanguinities. In order to determine patients with RLS in the family, the standardized International Restless Legs Syndrome—Rating Scale (IRLS-RS) questionnaire was administered to all 37 participating family members.

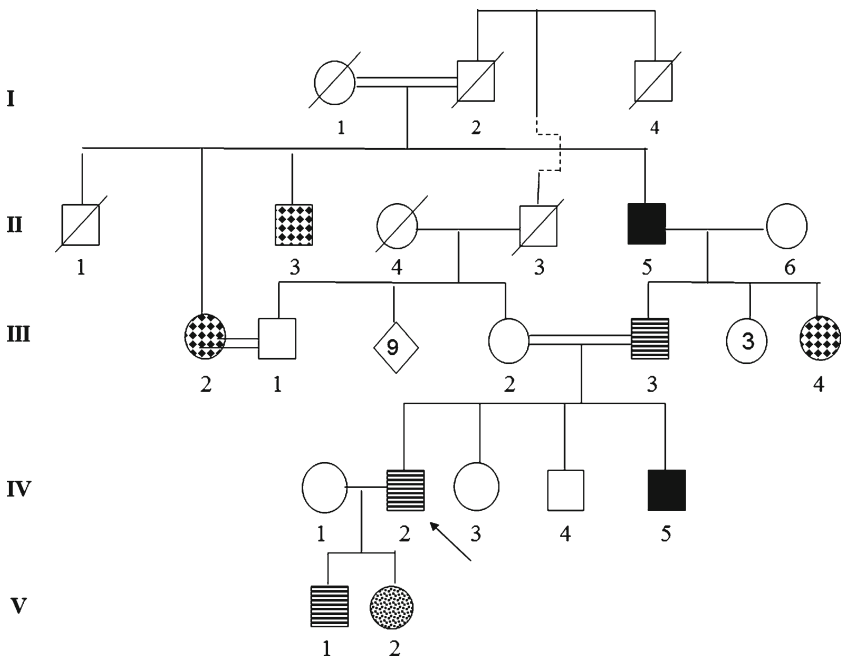

Fig. 1 Pedigree of the Turkish RLS/PLMS family. *Black symbol* RLS, *belted symbol* RLS + PLMS, *dotted symbol* possible RLS, *checkered symbol* reported to be affected

Clinical, biochemical ascertainment, and polysomnography

A detailed clinical evaluation was conducted of all family members who reported RLS complaints and/or limb movements occurring during sleep time and who had IRLS-RS higher than 10/40. This included a physical and neurological examination, electromyography (EMG), sympathetic skin responses, heart rate variability, blink reflex and nerve conduction studies, full blood count, glucose, iron, ferritin, transferring levels, and PSG recordings. Because of their young age (7 and 12 years), the individual V1's and IV2's assessments were also obtained by asking his parents about the patient's difficulty initiating sleep, excessive daytime sleepiness, and leg movements when asleep. Sleep was recorded and scored according to Rechtschaffen and Kales' method [12], using 30-s epochs to objectify the complaints. PSG included an electroencephalographic recording (C3/A2, C4/A1, according to the 10–20 international electrode placement system), a right and left electrooculogram, and a chin electromyogram. In order to detect apneas or hypopneas, recording of oral and nasal airflow, thoracic and abdominal movements, and oximetry was performed. Surface EMG of the right and left anterior tibialis muscles were recorded so as to quantify leg movements. Electrocardiogram was recorded with a standard D2 lead. PLMS during sleep were recorded and scored according to standard criteria, that is, leg movements lasting 0.5 to 5 s, separated by intervals of 4 to 90 s, and occurring in a series of at least four consecutive movements. Percentages of rapid eye movement (REM) sleep atonia and of phasic chin EMG activity during REM sleep were measured, according to the method described by Lapierre and Montplaisir [13]. Furthermore, to better assess motor activity during REM sleep, phasic EMG activity of the lower limbs was also recorded in both tibialis muscles. Lower limb phasic activity was obtained by averaging the values of the activity recorded in both tibialis muscles. Diagnoses of RLS and PLMS were established following the IRLS Study Group [11] and AASM criteria [2], respectively. The study was approved by the Bezmialem Vakif University Medical School Ethics Committee and was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from each participant.

Results

According to the IRLS group criteria [11], five family members (II5, III3, IV2, IV5, and V1) suffered from RLS; three also met the AASM criteria for PLMS (III3, IV2, and V1; Fig. 1). All affected family members were examined in more detail. V2 also complained of mild RLS symptoms and some brief, repetitive movements of the legs, but following IRLS-RS and AASM criteria RLS and/or PLMS, a definitive diagnosis could not be established. All affected family members were nonsmokers and did not use selective serotonin reuptake inhibitors. None of the subjects were affected with any other condition known to cause non-idiopathic RLS or with any other neurologic or sleep disorder, including sleep apnea syndrome, rapid eye movement sleep behavior disorders, and narcolepsy. In addition, none of the subjects reported the use of medication known to affect sleep, sensory, or motor functions. Clinical symptoms and additional findings including demographic data, biochemical analysis, and electrophysiological examination are shown in Table 1. Two patients (II5 and III3) were found to suffer

Table 1 Clinical, biochemical, and electrophysiological findings of the affected patients

Patient	II5	III3	IV2	IV5	V1
Gender	M	M	M	M	M
Age at examination (years)	77	56	36	30	12
RLS onset (years)	70	54	29	25	9
PLMS onset (years)	–	NA	31	–	6
Medical history	DM	DM	Depression	None	None
Glucose (70–100 mg/dl)	132	122	107	88	113
Iron (28–134 μg/dl)	60	60	77	70	27
Ferritin (7–14 ng/dl)	44	119	60	56	20
Hg (11–16 g/dl)	15	16	15	14	13
Hct (40–53 %)	40	44	42	41	38
Transferrin (180–380 mg/dl)	276	229	230	242	348
EMG	PNP	PNP	Normal	Normal	Normal
SSRs	Abnormal	Abnormal	Normal	Normal	Normal
HRV	Abnormal	Normal	Normal	Normal	Normal
Blink reflex	Normal	Normal	Normal	Normal	Normal

RLS restless leg syndrome, *PLMS* periodic leg movements, *Hg* hemoglobin, *Hct* hematocrit, *EMG* electromyogram, *SSRs* sympathetic skin responses, *DM* diabetes mellitus, *HRV* heart rate variability, *PNP* polyneuropathy, *NA* not available

from sensorial axonal diabetic neuropathy (Table 1), and patient II5 had permanent painful dysesthesia.

Cranial magnetic resonance imaging (MRI) was normal in all affected family members except in patient II5; his cranial MRI showed generalized mild cerebral atrophy, but clinical and neurological examinations were normal. Individuals II2, II3, and III4 were also reported to suffer from RLS symptoms, but the patients were unfortunately not available for any more detailed information and examination. Additional biochemical and iron tests as well as complete blood were normal in all affected members (Table 1). PSG characteristics are shown in Table 2. Total sleep time was reduced in three patients (II5, III3, and V1), with low sleep efficiency in only one patient (II5) due to prolonged periods of wakefulness after sleep onset. The same variables were normal in patients IV2 and IV5. Percentage of slow wave sleep was elevated in patients IV5 and V1. Sleep spindle and K complex were significantly increased in patients II5, III3, and IV2. None of the patients were found to have apnea (AHI <5) and oxyemoglobin saturation was always higher than 90 % in all patients through the night. PLMS were not observed in patients II5 and IV5. Patients III3 and III1 showed PLMS almost exclusively during non-rapid eye movement (NREM) sleep. Individual V1 presented PLMS during NREM and REM sleep. Besides PLMS, no other motor behaviors were observed during sleep in these patients.

Discussion

Here, we reported a large Turkish family with RLS symptoms, observed in nine individuals over the five generations (Fig. 1). In addition to RLS, three individuals (III3, IV2, and V1) were also found to suffer from PLMS. Their diagnosis was confirmed by PSG. Approximately 80 % of RLS patients experience PLMS [14, 15]. The lack of PLMS findings in the other affected family members might be related to the very short examination time (one night), but a great PLMS variability over multiple nights has been shown before [16]. Additionally, PLMS can occur without the associated EEG micro-arousals and with the absence of sleep complaints or of daytime symptoms. As we did not perform PSG in clinically very mild or non-affected family members and the age of PLMS onset can differ between the family members, the possibility of additional family members suffering from PLMS cannot be excluded. Global RLS prevalence ranges from 0.01 % in Africa to 18.3 % in Europe and has been suggested to rise with increasing latitude [17], nevertheless familial aggregation first described by Ekbom [18] is well-known in RLS. In most studies, autosomal-dominant heritance has been suggested, although autosomal-recessive and bilinear inheritances were also observed. Desautels et al. performed linkage analysis using an autosomal-recessive model on a large family of French Canadian origin [19]. The authors noted that autosomal-dominant inheritance is suggested clinically in RLS but also stated that their LOD scores were higher under a recessive model. Possible reasons included pseudo-dominant inheritance or ascertainment bias. Transmission in our family is an important subject for discussion: autosomal-dominant or pseudo-dominant inheritance can be suggested; there is an important effect of anticipation over the three generations (more than 20 years) that has been related to this transmission type before [11, 20, 21], but which has not found in autosomal-recessive-related pedigrees [21]. On the other

Table 2 Polysomnographic findings of affected family members

Patient	II5	III3	IV2	IV5	V1	Normal reference
Age at examination (years)	77	56	36	30	12	–
Time in bed (min)	416.2	401.0	481.2	471.5	462.4	–
Total sleep time (min)	180.5	354.5	474.5	454.0	458.5	Adult, 420 min Child, 730 min
Sleep onset latency (min)	64.5	13.0	3.0	3.5	1.5	<20 min
Sleep efficiency	45.8 %	90.7 %	98.6 %	96.8 %	99.7 %	85–90 %
REM sleep (%)	6.4 %	12.4 %	21.9 %	17.2 %	14.5 %	20–25 %
No. of awakenings	8	2	0	5	0	–
Wake time (min)	179.5	32.5	0	13.5	0	–
Stage 1	7.5 %	1.7 %	0.4 %	2.3 %	0	2–5 %
Stage 2	77.3	76.3 %	62.3 %	47.1 %	41.2 %	45–55 %
Stage 3	8.9	9.6 %	15.4 %	33.4 %	44.7 %	5–15 %
IRLS-RS (0–40)	35	20	22	15	17	<10
PLMS index	0	12.2	15	0	8.4	<5 in children, <15 in adults

Sleep efficiency: the number of minutes of sleep divided by the number of minutes in bed. PLMS index: number of movements per hour of sleep
REM rapid eye movement, *IRLS-RS* International Restless Legs Syndrome Study Group Rating Scale

hand, parents of individuals IV2 and IV5 are known to be consanguineous and parents of individual II5 are known to be first cousins. Additionally, it is suggested that there is multiple consanguinity within the family as all family members originated from the same village: rates of consanguinity are found to rise up to 40 % in some regions of Turkey [22]. Because of this, there is strong evidence for a genetic background in the disease related patho-mechanism, but the type of inheritance is highly debatable and needs to be explored in further studies. There are some worth mentioning features in the clinical presentation of our family compared to those previously reported also including PLMS in their phenotype [21, 23, 24]: PLMS are known to be more frequent in the elderly [25, 26]. In our family, PLMS were not found in the older generation, but interestingly, patient V1 already suffered of PLMS at the age of 6 years, a very rare finding in childhood [27]. In addition, attention deficit/hyperactivity disorder (ADHD), also frequently reported in association with juvenile PLMS [28], was not reported for this patient (V1) or any other member of the family. It is also interesting to note that PLMS preceded or followed the RLS onset (patients V1 and IV2) in our family, which lead us to the suggestion that they result from either independent or equal reciprocal effects. Early studies strongly reported a direct relationship between sympathetic hyperactivity and RLS, and especially PLMS [29, 30]. In the present study, the rise in sympathetic activity detected by frequency domain heart rate variability analysis (II5) and sympathetic skin responses (II5 and III3) was noted. We only found two patients with increased sympathetic activity (II5 and III3) and it is not clear whether in those cases the dysautonomic function was related to diabetic neuropathy [31] or a positive correlation between sympathetic activation and the RLS. However, age might also be an influence, as the three patients with normal sympathetic activity were young at time of examination (36, 30, and 12 years). Polysomnographic evaluation in the affected members was performed to confirm the presence of the disease. The recordings show increased sleep onset latency, caused by a painful dysesthesia in the legs, and increased arousal (II5, III3, and IV5) and poor sleep efficiency (II5), caused by leg movements during the night, compared to normal values described by Carskadon and Dement [32]. The percentage of each sleep stage varies with age, with decreasing amounts of REM and deep sleep (stage 3) in older people, but all affected family members had a clearly altered pattern of non-REM sleep stages (Table 2) and all but one (IV2) had, independently from their age at examination, decreased REM sleep time.

This family report adds to the growing literature describing the clinical and polysomnographic features of both RLS and PLMS. We suggest an important effect of anticipation and genetic impact of the diseases and describe some particularities in the clinical feature that are not always in line with previous studies. Further investigation of clinical, genetic, and biochemical similarities between PLMS and RLS may yield important clues to the still unknown pathophysiology of these common diseases.

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References

1. Natarajan R (2010) Review of periodic limb movement and restless leg syndrome. J Postgrad Med 56:157–162
2. American Academy of Sleep Medicine (2005) International classification of sleep disorders, 2nd ed. Diagnostic and coding manual. Westchester
3. Pollmächer T, Schulz H (1993) Periodic leg movements (PLM): their relationship to sleep stages. Sleep 16:572–577
4. Coleman RM, Pollak CP, Weitzman ED (1980) Periodic movements in sleep (nocturnal myoclonus): relation to sleep disorders. Ann Neurol 8:416–421
5. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J (2003) Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 4:101–119
6. Hornyak M, Feige B, Voderholzer U, Philipsen A, Riemann D (2007) Polysomnography findings in patients with restless legs syndrome and in healthy controls: a comparative observational study. Sleep 30:861–865
7. Yeh P, Walters AS, Tsuang JW (2012) Restless legs syndrome: a comprehensive overview on its epidemiology, risk factors, and treatment. Sleep Breath. doi:10.1007/s11325-011-0606-x
8. Winkelmann J, Schormair B, Lichtner P, Ripke S, Xiong L, Jalilzadeh S, Fulda S, Pütz B, Eckstein G, Hauk S, Trenkwalder C, Zimprich A, Stiasny-Kolster K, Oertel W, Bachmann CG, Paulus W, Peglau I, Eisensehr I, Montplaisir J, Turecki G, Rouleau G, Gieger C, Illig T, Wichmann HE, Holsboer F, Müller-Myhsok B, Meitinger T (2007) Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. Nat Genet 39:1000–1006
9. Schormair B, Kemlink D, Roeske D, Eckstein G, Xiong L, Lichtner P, Ripke S, Trenkwalder C, Zimprich A, Stiasny-Kolster K, Oertel W, Bachmann CG, Paulus W, Högl B, Frauscher B, Gschliesser V, Poewe W, Peglau I, Vodicka P, Vávrová J, Sonka K, Nevsimalova S, Montplaisir J, Turecki G, Rouleau G, Gieger C, Illig T, Wichmann HE, Holsboer F, Müller-Myhsok B, Meitinger T, Winkelmann J (2008) PTPRD (protein tyrosine phosphatase receptor type delta) is associated with restless legs syndrome. Nat Genet 40:946–948
10. Stefansson H, Rye DB, Hicks A, Petursson H, Ingason A, Thorgeirsson TE, Palsson S, Sigmundsson T, Sigurdsson AP, Eiriksdottir I, Soebech E, Bliwise D, Beck JM, Rosen A, Waddy S, Trotti LM, Iranzo A, Thambisetty M, Hardarson GA, Kristjansson K, Gudmundsson LJ, Thorsteinsdottir U, Kong A, Gulcher JR, Gudbjartsson D, Stefansson K (2007) A genetic risk factor for periodic limb movements in sleep. N Engl J Med 357:639–647
11. Trenkwalder C, Paulus W (2010) Restless legs syndrome: pathophysiology, clinical presentation and management. Nat Rev Neurol 6:337–346
12. Rechtschaffen A, Kales A (1968) A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. University of California, Brain Information Service/Brain Research Institute, Los Angeles

13. Lapierre O, Montplaisir J (1992) Polysomnographic features of REM sleep behavior disorder: development of a scoring method. Neurology 42:1371–1374
14. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lespérance P (1997) Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord 12:61–65
15. Picchietti DL, Walters AS (1999) Moderate to severe periodic limb movement disorder in childhood and adolescence. Sleep 22:297–300
16. Trotti LM, Bliwise DL, Greer SA, Sigurdsson AP, Gudmundsdóttir GB, Wessel T, Organisak LM, Sigthorsson T, Kristjansson K, Sigmundsson T, Rye DB (2009) Correlates of PLMs variability over multiple nights and impact upon RLS diagnosis. Sleep Med 10:668–671
17. Koo BB (2012) Restless legs syndrome: relationship between prevalence and latitude. Sleep Breath. doi:10.1007/s11325-011-0640-8
18. Ekbom KA (1945) Restless legs: a clinical study. Acta Med Scand 158:1–123
19. Desautels A, Turecki G, Montplaisir J, Xiong L, Walters AS, Ehrenberg BL, Brisebois K, Desautels AK, Gingras Y, Johnson WG, Lugaresi E, Coccagna G, Picchietti DL, Lazzarini A, Rouleau GA (2005) Restless legs syndrome: confirmation of linkage to chromosome 12q, genetic heterogeneity, and evidence of complexity. Arch Neurol 62:591–596
20. Lazzarini A, Walters AS, Hickey K, Coccagna G, Lugaresi E, Ehrenberg BL, Picchietti DL, Brin MF, Stenroos ES, Verrico T, Johnson WG (1999) Studies of penetrance and anticipation in five autosomal-dominant restless legs syndrome pedigrees. Mov Disord 14:111–116
21. Esteves AM, Pedrazzoli M, Bagnato M, Moreira F, de Mello MT, Tufik S (2008) Two pedigrees with restless legs syndrome in Brazil. Braz J Med Biol Res 41:106–109
22. Koc I (2008) Prevalence and sociodemographic correlates of consanguineous marriages in Turkey. J Biosoc Sci 40:137–148
23. Trenkwalder C, Seidel VC, Gasser T, Oertel WH (1996) Clinical symptoms and possible anticipation in a large kindred of familial restless legs syndrome. Mov Disord 11:389–394
24. Birinyi PV, Allen RP, Hening W, Washburn T, Lesage S, Earley CJ (2006) Undiagnosed individuals with first-degree relatives with restless legs syndrome have increased periodic limb movements. Sleep Med 7:480–485
25. Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O (1991) Periodic limb movements in sleep in community-dwelling elderly. Sleep 14:496–500
26. Youngstedt SD, Kripke DF, Klauber MR, Sepulveda RS, Mason WJ (1998) Periodic leg movements during sleep and sleep disturbances in elders. J Gerontol A Biol Sci Med Sci 53:391–394
27. Kirk VG, Bohn S (2004) Periodic limb movements in children: prevalence in a referred population. Sleep 27:313–315
28. Picchietti DL, Underwood DJ, Farris WA, Walters AS, Shah MM, Dahl RE, Trubnick LJ, Bertocci MA, Wagner M, Hening WA (1999) Further studies on periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. Mov Disord 14:1000–1007
29. Sforza E, Pichot V, Barthelemy JC, Haba-Rubio J, Roche F (2005) Cardiovascular variability during periodic leg movements: a spectral analysis approach. Clin Neurophysiol 116:1096–1104
30. Guggisberg AG, Hess CW, Mathis J (2007) The significance of the sympathetic nervous system in the pathophysiology of periodic leg movements in sleep. Sleep 30:755–766
31. Nazhel B, Yetkin I, Irkeç C, Koçer B (2002) Sympathetic skin response in diabetic neuropathy. Electromyogr Clin Neurophysiol 42:181–185
32. Carskadon MA, Dement WC (1994) Normal human sleep: an overview. In: Principles and practice of sleep medicine. Saunders, Philadelphia, pp. 16–25