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Familial aggregation of restless legs syndrome: A case report of four affected relatives in a Colombian family, with a narrative review

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Abstract

Introduction: Restless legs syndrome (RLS) is a neurological sensorimotor disorder with both sporadic and familial forms, the latter frequently associated with a genetic basis.

Materials and methods: Four members of a family from Yarumal, Antioquia, with symptoms suggestive of restless legs syndrome, underwent a neurological evaluation, including a workup for secondary causes. The diagnosis was established by applying the clinical criteria proposed by the *International Classification of Sleep Disorders, Third Edition, Text Revision* (ICSD-3-TR), thereby ensuring greater diagnostic certainty. Additionally, a narrative review was conducted using Medline to explore the genetic component of restless legs syndrome.

Results: Genetic studies, including genome-wide association studies (GWAS) and whole-exome sequencing (WES), have identified several risk variants associated with restless legs syndrome. In vivo mouse and zebrafish models have elucidated the role of some variants in the neurobiology of this syndrome.

Conclusion: This is the first case report of a Colombian family with four documented members and two deceased members affected by restless legs syndrome across three generations. The family exhibits an autosomal dominant inheritance pattern, although with significant clinical variability. Despite its complexity, restless legs syndrome demonstrates a significant genetic component contributing to its familial aggregation.

Keywords: Restless legs syndrome, Genetics, Sleep disorders, Inheritance pattern, Pedigree, Colombia.

Agregación familiar del síndrome de piernas inquietas: reporte de caso de cuatro miembros afectados en una familia colombiana, con una revisión narrativa

Resumen

Introducción: el síndrome de piernas inquietas (RLS, por sus siglas en inglés) es un trastorno neurológico sensoriomotor que puede presentarse en forma esporádica o familiar, esta última frecuentemente asociada con una etiología genética.

Materiales y métodos: a cuatro miembros de una familia de Yarumal, Antioquia, con síntomas sugestivos de síndrome de piernas inquietas, se les realizó una evaluación neurológica que incluyó la investigación de posibles etiologías secundarias. El diagnóstico se estableció aplicando los criterios clínicos propuestos por la *International Classification of Sleep Disorders, Third Edition, Text Revision* (ICSD-3-TR), permitiendo así una mayor certeza diagnóstica. Adicionalmente, se realizó una revisión narrativa de la información disponible en Medline acerca del componente genético del síndrome de piernas inquietas.

Resultados: los estudios genéticos, incluidos los estudios de asociación del genoma completo (GWAS) y de secuenciación del exoma completo (WES), han identificado múltiples variantes de riesgo asociadas con el síndrome de piernas inquietas, y los modelos in vivo han dilucidado el rol de algunas variantes implicadas en la neurobiología del síndrome.

Conclusión: este es el primer reporte de una familia colombiana con cuatro miembros documentados y dos fallecidos afectados por el síndrome de piernas inquietas a lo largo de tres generaciones. La familia presenta un patrón de herencia autosómico dominante, aunque con una variabilidad clínica significativa entre los sujetos. A pesar de su complejidad, el síndrome de piernas inquietas muestra un componente genético importante que contribuye a su agregación familiar.

Palabras clave: síndrome de piernas inquietas, genética, trastornos del sueño, patrón de herencia, genealogía, Colombia.

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Introduction

Restless legs syndrome (RLS) is classified among sleep-related movement disorders and is characterized by sensory-motor symptoms, often described by patients as an urgent or uncontrollable need to move one or both legs (1,2). This syndrome can occur sporadically or exhibit familial aggregation (3–5). It is reported that approximately 60% of individuals with RLS have a family history of the condition, and a higher frequency of first-degree relatives with RLS is seen in those with early-onset symptoms (onset before 45 years of age), suggesting an autosomal dominant (AD) pattern of inheritance (5). This article aims to review the available information on the genetic component of RLS by discussing a clinical case of a family from Yarumal, Antioquia, with four affected members across three generations.

Methods

A neurological evaluation was conducted on four members of the same family from Yarumal, Antioquia, who presented with symptoms suggestive of restless legs syndrome (RLS). A comprehensive diagnostic approach was taken, including an investigation for secondary causes. Following the identification of this family, a literature review was performed using the Medline database to explore the genetic component of RLS, employing search terms such as "Restless Legs Syndrome," "Genetics," and "Family Aggregation".

Clinical cases

Clinical characteristics of the four documented members will be presented. Table 1 provides a summary and additional data about other family members.

Patient II.1

A 70-year-old male patient reported experiencing motor restlessness in both lower limbs since the age of 50. This symptom occurred daily, predominantly in the late afternoon and during the night, preventing him from falling asleep. Walking for 30 minutes provided relief. He attributed worsening symptoms to a SARS-CoV-2 infection in 2020, which prompted a neurology consultation. He also reported increasing anxiety over the past three months related to sleep difficulties, for which he is under psychiatric care. His medical history includes hypertension, dyslipidemia, and generalized anxiety disorder. Family history revealed similar symptoms in his mother and three siblings (Figure 1). Physical and neurological examinations were unremarkable; body mass index (BMI) was 30.8. Laboratory tests during follow-up were normal, including serum iron, ferritin, and total iron-binding capacity. Polysomnography showed severe sleep architecture disruption, increased sleep latency, and an elevated apnea-hypopnea index without periodic leg movement. The patient reported partial improvement of symptoms with the current regimen. Pregabalin and pramipexole were continued for RLS symptoms, while melatonin was used to improve sleep onset. Based on PSG findings, CPAP titration was also considered.

Table 1. Family members' characteristics

Patient	I.1	II.1	II.2	II.3	II.4	III.3
Gender	F	M	M	F	F	F
Age at examination (years)	-	70	-	67	63	45
RLS onset (years)	Unknown	50	Unknown	30	37	35
Medical history	Unknown	HBP DL Anxiety	AMI	HBP DL	HBP DL	Hypothyroidism
Toxic exposure	Caffeine Alcohol	No	Alcohol	No	Caffeine Alcohol	Caffeine

Note. Empty spaces are for data that could not be collected.

Abbreviatures: HBP: High blood pressure; AMI: Acute myocardial infarction; DL: Dyslipidemia.

Source: Own elaboration.

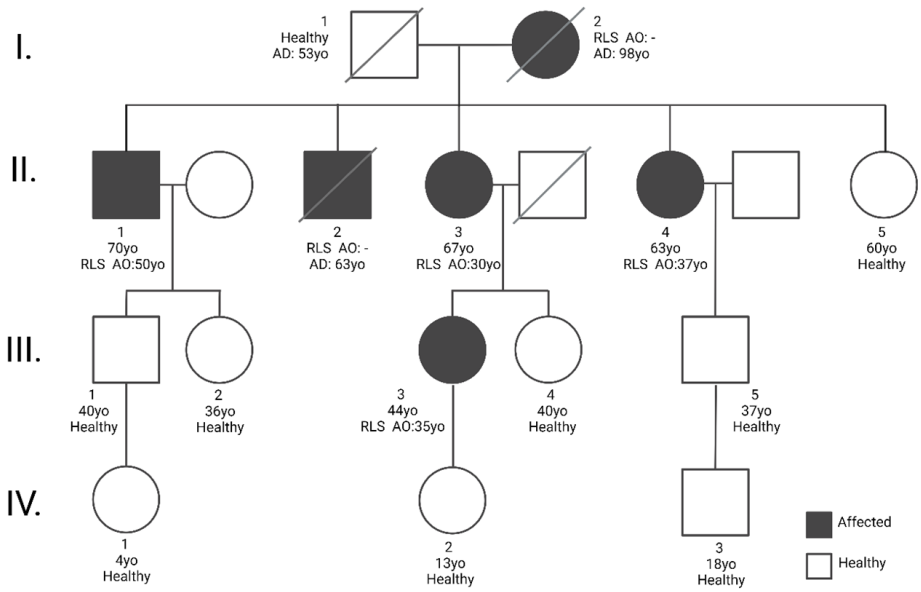

Figure 1. Family pedigree

Note. The figure shows the pedigree of a family with six members affected by restless legs syndrome across three generations. Black-filled symbols represent clinically affected individuals; those with a diagonal line are deceased. The distribution of cases and vertical transmission in both sexes are consistent with an autosomal dominant inheritance pattern. Abbreviatures: RLS: Restless legs syndrome; AD: Age at the time of death; AO: Age of onset.

Source: Own elaboration.

Patient II.3

A 67-year-old female patient reported experiencing motor restlessness in both lower limbs since the age of 30. This symptom occurred daily, predominantly at night, and worsened on days with increased physical activity. She noted that the motor symptoms disrupted her sleep, waking her around 23:00, and that she walks to alleviate them, typically resuming sleep around 02:00. She denied experiencing daytime sleepiness. Her medical history includes hypertension and dyslipidemia, both managed with medication. She denied toxic exposures. At the time of consultation, she mentioned being treated with pregabalin for symptom control. Physical examination revealed a BMI of 32 and bilateral grade III oedema with a fovea in the lower limbs; however, capillary refill was less than 2 seconds, with no nail abnormalities or trophic changes suggestive of a vascular etiology. Neurological evaluation showed no abnormalities. The management plan included continuing pregabalin and initiating pramipexole for motor symptom management, along with trazodone for the sleep disorder. The patient reported partial control of symptoms with the current therapy.

Patient II.4

A 63-year-old female patient reported occasional motor restlessness in both lower limbs, occurring approximately 3 to 4 times a month since the age of 38. She did not feel that these symptoms significantly affected her sleep. She noted that symptoms improved with walking and occasionally self-medicated with paracetamol. She did not identify any specific triggers for symptom exacerbation. Her medical history includes hypertension and dyslipidemia. She reported regular consumption of four cups of coffee and one to two glasses of wine daily but denied any other toxic exposures. Physical and neurological examinations revealed no significant abnormalities, and laboratory tests, including iron tests, were normal. The management plan included initia-

ting daily pramipexole and implementing non-pharmacological measures such as reducing alcohol and coffee consumption.

Patient III.3

A 45-year-old female patient presented with a 10-year history of intermittent motor restlessness in both lower limbs. These episodes occurred sporadically, lasting up to 10 days at a time. The symptoms were primarily nocturnal and most pronounced when the patient was supine. Notably, the symptoms improved after approximately 10 minutes of walking and occasionally disrupted her sleep. The patient did not identify any triggering factors. Her medical history is significant for well-controlled hypothyroidism since the age of 20. She denied a history of anemia and reported no similar symptoms during pregnancy. The patient consumes four cups of coffee per day. Both physical and neurological examinations were unremarkable; BMI was 31.14. Laboratory tests yielded normal results, including iron tests. Given that the symptoms do not significantly impact her quality of life, the treatment plan consists of non-pharmacological management only.

Results

This is the first report of a Colombian family with 6 members affected by restless leg syndrome across three generations. Due to the death of 2 members, clinical evaluation was conducted just on 4 members. Although the clinical details of the 2 deceased members are not available, we find it appropriate to include in the table some descriptions provided by their relatives.

Overview of RLS

Restless legs syndrome (RLS) is a neurological sensorimotor disorder in which patients experience uncomfortable sensations, typically in the lower limbs, often accompanied by an irresistible urge to move. These symptoms emerge during periods of rest, worsen in the evening or at night, and are relieved by movement (3–5). The syndrome can be classified as primary (idiopathic) or secondary and may occur sporadically or with a familial aggregation (4).

Initially, RLS was considered rare; however, population studies have revealed that its prevalence is significant and varies due to clinical variability. The highest rates are found in Europe and North America (5–10% of adults, with only 2–3% experiencing moderate to severe symptoms), whereas Asia and Africa report lower rates (1–4%) (6). In Latin America, prevalence estimates range from 0.8% to 3%, varying by country (6). In Colombia, a 2006 study in Sabaneta, Antioquia, found a prevalence of 7.3%, although the sample was not representative (7). Other Colombian studies evaluate the prevalence of RLS in the context of other diseases (8).

The prevalence of RLS in women is approximately twice that in men, and symptom severity is greater in women. The age of onset exhibits a biphasic distribution, with peaks observed in the second and fifth decades of life (9). As evidenced in this group, the three affected women of generation II (II.3 and II.4) reported an early onset of symptoms, with differences of 20 (II.3), 13 (II.4), and 15 years (III.3), respectively, compared to the age of onset of member II.1. Early onset is mostly associated with family history and a slower progression of the disease (9).

Regarding RLS etiology, a genetic factor is proposed for the primary form, while the secondary form is associated with various clinical conditions such as terminal renal failure, iron deficiency, and pregnancy, particularly in the third trimester (10,11). Although the three affected women had no symptoms during pregnancy, the literature describes the presence of symptoms during pregnancy as a risk factor for developing RLS later (3,11,12). Other contributing factors include inflammatory processes, autoimmune diseases, obesity, neurological conditions, and exposure to certain medications and alcohol (10). Members II.1 and II.3, who are the most affected, also present obesity according to anthropometric parameters, but member III.3, who also presents obesity, does not report severe symptoms. Although members II.4 and III.3 were the only patients with a history of exposure to toxins, they presented mild symptoms.

These findings support the clinical variability of RLS reported in the literature and do not establish a causal relationship. Many hypotheses have been described about the pathophysiological mechanism of RLS. It is recognized as a complex phenomenon in which genetic, environmental, and individual factors may be involved (10).

The first mechanism is related to iron deficiency. Since Ekbom's description, iron deficiency has been

associated with RLS, and replacement therapy has been shown to improve symptoms (5,13). Despite this, only 31% of patients with iron deficiency anemia have RLS (14), suggesting that the deficiency might be at the central nervous system (CNS) level. Different studies have revealed that RLS patients have lower ferritin and higher iron and transferrin levels in cerebrospinal fluid (CSF) compared to controls. However, taking into account the higher levels of transferrin, iron concentrations in RLS patients were considered reduced (15). MRI studies revealed higher R2' values in the basal nuclei of RLS controls, particularly the substantia nigra and putamen, indicating greater iron levels compared to patients. This measure correlated inversely with symptom severity (16). Post-mortem analysis found decreased iron staining in neuromelanin cells of the substantia nigra of RLS patients and changes in the concentration of proteins implicated in iron metabolism (17,18).

The second mechanism proposes dopamine dysfunction. Dopamine agonists (DA) alleviate motor symptoms in RLS, suggesting a dopaminergic deficiency (3,5). However, studies have shown that RLS patients may also exhibit hyperdopaminergic states, evidenced by increased tyrosine hydroxylase activity, elevated dopamine at the synaptic cleft, and decreased dopamine transporter and D2 receptor (DR2) levels (3,19). Animal studies, CSF analysis, and PET scans have shown that dopamine production and D2R expression follow a circadian rhythm, reaching their nadir in the late afternoon when symptoms typically begin (3,20,21). Dopamine agonists may correct the relative deficiency caused by circadian variation, but they can induce augmentation syndrome, an effect of high DA doses, where the patient's dopaminergic activity is altered, increasing their susceptibility. While the exact initial change in the dopaminergic pathway is unclear, the interplay of these processes leads to a broader compromise (21). Additionally, iron deficiency affects dopaminergic function by altering tyrosine hydroxylase and dopamine receptor expression (3).

Other mechanisms described include hyper-glutamatergic state and downregulation of adenosine. The improvement of sleep-related symptoms by alpha-2-delta ligands supports this hypothesis (4,22,23). The last mechanism involves genetic risk factors, which will be described in the next section.

The diagnosis of RLS is clinical, based on the presence of the five diagnostic criteria established by the *International Classification of Sleep Disorders, Third Edition, Text Revision* (ICSD-3-TR) (Table 2) (5). The criterion B emphasizes the importance of considering differential diagnoses that can explain the symptomatology, such as leg cramps, positional discomfort, akathisia, polyneuropathy, and venous disorders. History and physical examination are crucial for identifying alternative diagnoses and potential triggers, like certain medications (4,5,24).

Diagnostic aids should include measuring serum ferritin levels and transferrin saturation levels to determine the need for iron replacement therapy (5). Polysomnography may be requested, although it is not mandatory for diagnosis. Findings can include increased sleep latency, sleep fragmentation, and periodic limb movements in sleep (PLMS) in 60% of patients (3,5).

Table 2. ICSD-3-TR diagnostic criteria for restless legs syndrome

International Classification of Sleep Disorders, Third Edition, Text Revision diagnostic criteria (must be all criteria)
A) An urge to move the legs, usually accompanied by or thought to be caused by uncomfortable and unpleasant sensations in the legs. The symptoms must:
1. Begin or worsen with rest or inactivity such as lying down or sitting
2. Be partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues, and
3. Occur exclusively or predominantly in the evening or night rather than during the day
B) The symptoms listed above are not solely accounted for by a condition that mimics restless legs syndrome (eg, leg cramps, positional discomfort, myalgia, venous stasis, edema, arthritis, habitual foot tapping).
C) The symptoms cause concern, distress, sleep disturbance, or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning.

Source: Taken from (5).

Management measures include non-pharmacological options and pharmacological options. In patients with ferritin values <75 ug/L and transferrin saturation <20%, iron replacement therapy is indicated, initially administered orally. In cases of intolerance or ineffectiveness, intravenous administration is recommended (5). Non-pharmacological options include avoiding strenuous physical activity, reducing consumption of coffee, tobacco, or alcohol, and replacing drugs that may act as potential triggers (3).

Regarding pharmacological measures, the first-line options are dopaminergic agonists and alpha-2-delta ligands. Among dopaminergic agonists, pramipexole and rotigotine are the most appropriate due to their greater affinity for the D3 receptor, allowing adequate control of motor symptoms. However, their use is associated with augmentation syndrome and impulse control disorders (3,5,25). In fact, the most recent clinical practice guideline from the American Academy of Sleep Medicine recommends against the use of pramipexole as a first-line treatment due to these safety concerns, favoring the use of alpha-2-delta ligands when possible (25).

Among alpha-2-delta ligands, pregabalin and gabapentin are preferred. They primarily control sleep disorders and have less effect on the motor component. In the event of therapeutic failure, it is indicated to switch the pharmacological group or combine both groups. An alternative in case of non-response to these measures is the addition of opioids; however, their potential for abuse and other risks should be carefully considered. Screening for substance use disorder is advised (3,5).

A recent study by Petramfar and Jankovic (26) showed that a younger age at disease onset, longer symptom duration, initial use of dopamine agonists, and a positive family history among first-degree relatives increase the likelihood of developing refractory RLS. Based on these findings, the authors advise against the use of dopamine agonists, particularly in young patients with a family history. Patient II.1 shares several of these risk factors—long-standing symptoms, use of dopamine agonists early in the disease course, and a strong family history—which may place him at higher risk for treatment resistance. Although not currently refractory, his clinical profile highlights the importance of individualized therapeutic strategies and long-term monitoring in familial RLS.

Familial aggregation and genetic component of RLS

Family aggregation is a well-documented feature of RLS, indicating a potential genetic etiology. Approximately 60% of individuals with RLS are reported to have an affected first-degree relative (5). In this family, this component is evidenced, with six affected members across three generations.

Concerning data reported in familial studies, Xiong et al. (27) followed 192 subjects for 15 years and assessed 479 affected relatives, revealing a family aggregation rate of 77% with significant phenotypic variability. Siblings of the subjects showed a relative risk of 3.6 (95% CI, 2.8-4.4), while offspring presented a relative risk of 1.8 (95% CI, 1.0-2.7). Among the subjects, 43% had between two and five affected relatives, and 6.3% had ten or more affected relatives (27).

Regarding the pattern of inheritance, most studies support an AD pattern with variable expressivity (1,28,29). In this family, as shown in Figure 1, the inheritance pattern is compatible with AD inheritance. In the first generation, only member I.2 (Mother) is affected, and the disease is transmitted to the offspring, affecting four of the five members (80%) of the second generation and one member of the third generation. In Xiong's study, 90% of pedigrees exhibited this pattern, although a small percentage (2.8%) also demonstrated bilineal inheritance, in which both parents were affected or had a family history (27). The finding of differential patterns to AD, despite their low frequency, coupled with the high clinical variability of RLS, limits the certainty of establishing an AD pattern with confidence. For example, Winkelmann et al. observed differences in inheritance patterns between families with early-onset symptoms (<30 years) and those with late-onset symptoms (>30 years), showing clear evidence of AD inheritance in the former group, while the Mendelian pattern was not evident in the latter group (28).

Studies in twins have demonstrated high concordance rates among monozygotic twins (83%, 61%, and 53.75%) (30–32), which significantly surpass those observed in dizygotic twins (45% and 15.4%) (31,32). Despite this high concordance, phenotypic variability and concordance below 100% among monozygotic twins suggest the influence of indi-

vidual epigenetic factors on the expression of RLS (1,33).

In large families, studies have also identified a phenomenon known as genetic anticipation, where the onset of symptoms occurs at a younger age in successive generations, sometimes accompanied by increased symptom severity (3). In a study of a large German family, a decrease in the age of symptom onset was observed across generations II-IV, with the average age dropping from 51.5 years in the second generation to 19.8 years in the fourth generation (10).

In this family group, it is not possible to determine whether an anticipatory phenomenon occurred due to the unknown age of symptom onset in member I.2, but among members II.3 and III.3 the onset ages are similar. Notably, only one affected member is recognized in the third generation, despite all members being 37 years old or older, which exceeds the youngest age of onset reported by other family members. This highlights the importance of considering clinical variability and the wide spectrum of severity observed in other families, which may complicate the diagnosis but can be partially addressed through active questioning. Although anticipation has been reported in additional studies (34), other authors such as Babacan et al. found this phenomenon in only 2 of the 5 pedigrees evaluated, which could suggest that it is not a constant effect (29).

To understand the genetic basis of RLS, multiple studies have been conducted. On the one hand, genome-wide association studies (GWAS) have identified 23 risk variants at 22 loci, involving genes such as *MEIS1, BTBD9, PTPRD, CCDC148, MAP2K5, MYT1, RANPB17, MICALL2,* and *LMO1* (3,35,36). The study by Didriksen et al. confirmed 19 of the 20 variants previously reported by Schormair et al. (35) and identified five new variants, three of which exceeded the threshold of statistical significance (36). Genes reported in Schormair's study are implicated in neurogenesis, synaptogenesis, locomotor behavior and DNA repair processes (35). Additionally, Didriksen et al. found that 11 of the 23 variants affect the expression of 17 genes through cis-eQTL mechanisms (36).

On the other hand, whole-exome sequencing (WES) studies have been developed to investigate the disease. Unlike the variants reported by GWAS, WES allows the identification of rare variants in the coding regions of the genome, which have a greater effect and explain aspects of the genetic risk in complex diseases such as RLS (37). So far, four studies have addressed this aspect, three of which have been reported by Jiménez-Jiménez et al. and are associated with genes such as *PCDHA3, BTBD9,* and *TRAPPC6B* (1,38-41). Despite the advantages of this technique, research on rare variants is still scarce (37). Other approaches, such as transcriptome-wide association studies (TWAS), have also identified additional variants, helping to elucidate new susceptibility genes (42,43).

Although multiple findings have been reported, the variant rs113851554 in MEIS1 showed the strongest association with RLS among GWAS studies, with an OR of 2.03 (95% CI, 1.99-2.07) in the combined analysis (36). *MEIS1* encodes a protein belonging to the TALE (three-amino-acid loop extension) family of homeobox proteins, which plays crucial roles in neurogenesis, cell differentiation, and synaptogenesis (1,36). In vitro studies using human cell cultures under conditions of iron deficiency have shown a significant decrease in *MEIS1* expression levels, indicating a potential link between this gene and iron metabolism (44).

Furthermore, the impact of the *MEIS1* gene on RLS has been assessed through in vivo models (1,2). Spieler et al. analyzed highly conserved non-coding regions in zebrafish and mouse models. In mouse models, risk alleles were found to diminish the gene's enhancer activity in embryonic ganglionic eminences, which give rise to structures like the Globus pallidus and striatum during embryonic development (45). Additionally, heterozygous mouse models for *MEIS1* have highlighted the effects of reduced gene expression, including motor alterations such as hyperactivity (45).

These studies and models of the RLS collectively underscore the association between risk variants and key aspects of RLS pathophysiological mechanisms, supporting the evidence of the genetic factor in the etiology of this syndrome.

Conclusion

This is the first documented case of a Colombian family with four confirmed members and two deceased members affected by RLS across three generations. The family exhibits an AD inheritance pattern; however, they show significant variability in age of onset, symptom severity, and impact on quality of life, consistent with findings from other studies of large

families. Reconstruction of the genealogy played a pivotal role in identifying this inheritance pattern. Continued longitudinal follow-up is crucial to identify new cases within the family and to recognize any changes in the clinical pattern of affected members. Despite its complexity, RLS demonstrates a significant genetic component contributing to its familial aggregation.

Authors' contribution. Jonathan Ruiz-Triviño: conceptualization, formal analysis, investigation, writing-original draft; Omar Buriticá: investigation, writing-review & editing, supervision; David Aguillón: conceptualization, funding acquisition, resources, supervision, writing-review & editing; Francisco Lopera: funding acquisition, resources, writing-review & editing; Margarita Giraldo: conceptualization, formal analysis, investigation, methodology, supervision, writing-review & editing.

Ethical implications. Before clinical evaluation, participants provided written informed consent, which was approved by the Bioethics Committee of the Grupo de Neurociencias de Antioquia. The consent process included authorization for the storage and use of their clinical data for research purposes. Participants were also informed of their rights as research subjects, including the right to confidentiality and the right to withdraw from the study at any time without consequences.

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