REVIEW

Genetic aspects of restless legs syndrome

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Restless legs syndrome (RLS), also known as Ekbom syndrome, is a common movement disorder with sensorimotor symptoms occurring during sleep and quiet wakefulness. The underlying cause for RLS is unknown but genetic influences play a strong part in the pathogenesis of RLS, particularly when the condition starts at a young age. This review explores the genetic basis of RLS and related phenotypic variations. Recently, three loci showing vulnerability to RLS have been described in French-Canadian and Italian families in chromosomes 12q, 14q and 9q, emphasising on an autosomal dominant mode of inheritance. These have been labelled RLS1, RLS2 and RLS3, respectively. However, specific causative mutations remain elusive and no linkage analysis has been identified so far in the candidate genes investigated in RLS.

Restless legs syndrome (RLS), first described by Karl Ekbom, a Swedish neurologist and neurosurgeon, is the most common movement disorder known and is characterised by an irresistible desire to move the extremities, associated with unpleasant paraesthesia or dysaesthesia. These symptoms occur predominantly at rest and worsen at night, resulting in nocturnal insomnia and chronic sleep deprivation.

In 1995, the International Restless Legs Syndrome Study Group described a set of minimal inclusion criteria for RLS, consisting of four primary features that were modified recently by a National Institutes of Health consensus statement.[1–3] The condition has a strong genetic basis and the first description of a genetic contribution to the RLS was probably noted by Oppenheim in his textbook of nervous diseases published in 1923.[4]

In white adults, prevalence of RLS and an allied syndrome, periodic limb movements in sleep (PLMS) ranges from 9% to 29%, although a figure of 7–9% is widely accepted. The prevalence seems to increase with age, although onset may occur before the age of 20 years in up to 43% of people. The precise pathophysiology of RLS remains unknown, but pharmacological and brain imaging studies suggest the involvement of dopaminergic, opiate and iron pathways in the brain and spinal cord. RLS can be primary and secondary to conditions such as iron deficiency anaemia, peripheral neuropathy and uraemia.[5]

Genetic studies in RLS can take the following patterns:

- Family aggregation studies, including anticipation
- Inheritance pattern studies
- Gene mapping and genome search for specific genetic link
- Candidate gene studies

These are summarised below.

FAMILIAL AGGREGATION STUDIES

Several groups have shown familial aggregation of RLS, and molecular genetic studies have recently suggested the presence of susceptibility genes on chromosomes 12q, 14q and 9p.[6] In an attempt to define the relationship between idiopathic and secondary RLS, and between familial and sporadic (non-familial) cases, Ondo and Jankovic[7] reported that 23 of 54 (42%) patients had a family history of RLS. In all, 92% of patients with idiopathic RLS (without neuropathy) had a family history of RLS, whereas only 13% of those with neuropathic RLS (associated with peripheral neuropathy) had a positive family history. The patients with sporadic or neuropathic RLS were older at symptom onset and tended to have a more rapid progression than those with familial or idiopathic RLS. No other major consistent differences were observed in the clinical features between the two subgroups, and levodopa and dopamine agonists were the most effective treatments.[7] In another study, Montplaisir *et al*[8] reported that 63% of first-degree relatives of 127 consecutive clinic patients with RLS also had RLS. The Night-Walkers Survey conducted by Walters *et al*[9] reported that 81% of patients with RLS with onset at <20 years had a positive family history, whereas this number was reduced to 58% in those in whom RLS occurred at >20 years. Ondo *et al*[10] also noted the phenotypic variation in genetic RLS. They reported 12 pairs of monozygotic twins in whom both members of 10 pairs had definite RLS. Despite the high concordance rate and high penetrance, the symptom descriptions and age at onset varied markedly.[10]

The phenotype of RLS is suggested to depend on the age at onset of the disorder.

INHERITANCE PATTERN STUDIES

RLS is thought to follow a mendelian autosomal dominant inheritance pattern. Several workers[11–13] have reported single families with inheritance

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Abbreviations: iRLS, idiopathic restless legs syndrome; LOD, logarithm of odds; MAO, monoamine oxidase; NTS, neurotensin; PLMS, periodic limb movements in sleep; RLS, restless legs syndrome; SCA, spinocerebellar ataxia; uRLS, secondary RLS due to uraemia

pattern suggestive of an autosomal dominant pattern. Montagna *et al*[14] have reported a large family with typical RLS over three generations, with an ''assumed'' autosomal dominant inheritance.

In an effort to unravel the genetic inheritance pattern of RLS, researchers at the Max Planck Institute of Psychiatry, Munich, Germany, carried out a complex segregation analysis of RLS in two groups of families to investigate the probable mode of inheritance of RLS: those with mean age at onset $\leqslant$30 years and those $>$30 years.[15] In the first group, they showed the action of a single major gene but found no evidence for a major gene in the second group. In patients in whom the syndrome appears after the age of 30 years, a combination of various genes and environmental causes is probably to blame, of which the treatable factors, such as iron deficiency, uraemia, diabetes or polyneuropathy, may induce or worsen RLS symptoms.

Winkelmann *et al*[16] assessed the frequency and characteristics of hereditary and non-hereditary RLS. They reported that 42.3% of the patients with idiopathic RLS (iRLS) and 11.7% of those with secondary RLS due to uraemia (uRLS) were classified as having definite positive hereditary RLS. Further, 12.6% of patients with iRLS and 5.8% of patients with uRLS were classified as having possible positive hereditary RLS. Patients with definite hereditary RLS were significantly younger at the age at onset than those with a negative family history (35.45 *v* 47.17 years, $p<0.05$). The clinical characteristics were similar in both groups, except that women with hereditary RLS experienced a worsening of symptoms during pregnancy (19.1% *v* 2.6%, $p<0.05$).

ANTICIPATION AND LINK WITH SPINOCEREBELLAR ATAXIA

Investigations of single families with RLS have suggested an autosomal dominant mode of inheritance with variable expression, and some families show possible anticipation and evidence for an earlier age at onset in later generations.[17 18] Anticipation has been described in several inherited neurological disorders—for example, Huntington's disease and spinocerebellar ataxia (SCA)—caused by unstable mutations in the form of expanding trinucleotide repeat sequences leading to earlier age at onset in subsequent generations. Schols *et al*[19] verified that 45% of patients with SCA3 had RLS, but it is rare in other types of autosomal dominant cerebellar ataxias (18% of patients with SCA2), and RLS is a frequent and treatable cause of disabling sleep disturbance in patients with SCA3. This study provides evidence for the expanded CAG repeat in the SCA3 gene as a molecular factor causing RLS.[19] Recent studies found that patients with SCA, SCA1, SCA2 and SCA3 are more susceptible to RLS than those without SCA (28% *v* 10%).[19 20]

GENE MAPPING AND LINKAGE STUDIES

To map a gene or genes that may have a role in the vulnerability to RLS, Desautels *et al*[21] conducted a genome-wide scan in a large French-Canadian family. They reported an important linkage chromosome 12q for RLS with a significant logarithms of odds (LOD) score of 3.59. These findings represent the first mapping of a genetic locus conferring susceptibility to RLS, and although the inheritance pattern in this family seemed to be autosomal recessive, the authors suggest a pseudodominant pattern of inheritance. Neurotensin (NTS), a strong probable candidate gene has been excluded as a candidate.

More recently, Desautels *et al*[22] carried out another study that supported the previously reported chromosome 12q linkage results. A total of 276 people from 19 families were examined using a selection of markers spanning the identified candidate interval on chromosome 12q. Two-point analyses of individual pedigrees indicated that five kindreds were consistent with linkage to chromosome 12q, and a maximum two-point LOD score of 5.67 was observed. In addition, the presence of heterogeneity in RLS suggested as linkage was formally excluded across the region in six pedigrees. The results supported the presence of a major RLS-susceptibility locus on chromosome 12q, which is designated as *RLS1*, and suggest that at least one additional locus may be responsible for the origin of this prevalent condition.

Table 1 Candidate genes investigated in restless legs syndrome and linkage analysis identified so far

Candidate gene	Linkage
1. DA receptor genes	
D_1–D_5 receptors	Nil
DAT	Nil
TH	Nil
Dopamine β hydroxylase	Nil
2. GTP cyclohydrolase	Nil
3. GABA A receptor subunits (α1–6, β1–3, χ1–3, p1–2)	Nil
4. α-1 subunit of the glycine receptor (chromosome 5q31)	Nil
5. MAO-A	Nil
6. MAO	Nil
7. Neurotensin	Nil

DA, dopamine; DAT, dopamine transporter; GABA, γ-amonibutyric acid; GTP, guanosine triphosphate; MAO, monoamine oxidase; TH, tryosine hydroxylase.

Bonati *et al*[23] reported a major evidence of linkage to a new locus for RLS on chromosome 14q13–21 in a 30-member, three-generation Italian family with RLS and PLMS. This was the second RLS locus identified, and the first locus consistent with an autosomal dominant inheritance pattern. The accurate clinical evaluation of family members with and without RLS allowed for the configuration of RLS as a phenotypic spectrum ranging from PLMS to RLS.

Levchenko *et al*[24] aimed to replicate this finding and determine the importance of this locus in the French-Canadian population. The results supported the existence of the 14q locus, and indicated that this locus may also be responsible for RLS in a small fraction of French-Canadian patients. However, absence of linkage in most of the relations suggests that the genetic cause of RLS in the French-Canadian population is largely distinct from that in the Italian population.

Most recently, Chen *et al*[25] characterised 15 large and extended multiplex pedigrees consisting of 453 people, of whom 134 had RLS. A weighted average correlation of 0.17 was obtained between first-degree relatives, and heritability was estimated to be 0.60 for all types of relative pairs, indicating that the disorder was highly heritable in this cohort. Model-free linkage analysis identified a major novel RLS-susceptibility locus on 9p24–p22, with a multipoint non-parametric linkage score of 3.22. Suggestive evidence of linkage indicated by non-parametric linkage scores between 2 and 3 were found on chromosomes 3, 4, 5 and 6. Model-based linkage analysis, with the assumption of an autosomal dominant mode of inheritance, validated the linkage of RLS to 9p24–p22 in two families (two-point LOD score 3.77; multipoint LOD score 3.91). Chen *et al*[25] also suggested an indirect confirmation of an RLS gene on chromosome 12q22–q23.

Thus, identification of three genetic loci for RLS on three different chromosomes, 12q22–23,[21] 14q13–21,[23] and 9p24–22,[25] suggests that RLS is a genetically highly heterogeneous disorder.

CANDIDATE GENES

Impairment in the central dopaminergic system has been consistently suggested as an aetiological factor in RLS, and

thus genes associated with dopaminergic neurotransmissions have been studied. In 96 unrelated patients, Desautels *et al*[26] found that women with the high-activity allele of the monoamine oxidase A (MAO-A) gene promoter polymorphism had lower levels of synaptic dopamine and a greater risk (odds ratio 2) of having RLS than those carrying the low-activity allele (three repeats). The association was not observed in men, and there were no differences between either group regarding the *MAO-B* gene. They concluded that the *MAO-A* gene may represent a modifying factor associated with the severity of RLS manifestations in women.

Desautels *et al*[27] further evaluated NTS for mutational analysis, as NTS is transcribed by one of the genes in the region of chromosome 12q, an RLS-susceptibility locus identified recently. NTS is an important modulator of the dopaminergic transmission, and a strong functional and positional candidate in the context of RLS. None of the observed variants cosegregated with RLS, and no disease-associated polymorphisms were detected in any of the analysed families. On the basis of these results, it is unlikely that the *NTS* gene is responsible for RLS in chromosome 12-linked families.

On the basis of our knowledge of the pathology, pathophysiology or pharmacology of the disease, other candidate genes can be hypothesised to be associated with the aetiology of the inherited disease. Dichgans *et al*[28] studied polymorphic markers surrounding 22 candidate genes. Linkage analysis using markers either within or surrounding the genes was carried out for tyrosine hydroxylase, guanosine triphosphate cyclohydrolase, dopamine transporter, D_1–D_5 dopamine receptors, γ-aminobutyric acid A receptor subunits (α1–6, β1–3, χ1–3, p1–2) and the α-1 subunit of the glycine receptor (chromosome 5q31) (table 1). No evidence of linkage could be found for any of these chromosomal regions in the investigated family.[26] However, determining a genetic linkage has many difficulties. Genetic studies are based on an accurate assumption of the mode of inheritance and penetrance, and the rate of phenocopies of the disease. Currently, these issues remain unclear in RLS.

In another study, Desautels *et al*[29] conducted a large, population-based case–control study focusing on the French-Canadian population, investigating eight candidate genes associated with dopaminergic transmission (D_1–D_5 receptors, dopamine transporter, tyrosine hydroxylase and dopamine β hydroxylase). On comparing the allele and genotype frequencies between patients and controls, it was found that these loci have no major effect on the vulnerability to RLS.

FUTURE RESEARCH

Channelopathy is being investigated as an underlying aetiology for RLS. High-throughput mutation research projects are under way in Canada for screening of ion-channel genes in familial neurological disorders, including epilepsy, Tourette's syndrome and RLS. Researchers in this project propose to identify the genetic factors responsible for the aforementioned diseases by screening for mutations in ion channel genes. Genetic basis of RLS is also being further explored by twin studies. New research on 1937 pairs of identical and non-identical twins carried out at the Twin Research Unit, St Thomas' Hospital, London, UK, indicates that genetic factors make a substantial contribution to common sleep disorders. Heritability was estimated to be 52% for disruptive snoring, 48% for daytime sleepiness, 54% for restless legs and 60% for legs jerking or PLMS.[30] Iceland has a homogeneous population, providing an ideal base for genetic studies. A large population-based study investigating the genetic basis of RLS in the Icelandic population has also started under the stewardship of Rye *et al*. Abnormalities of iron metabolism in the brain are being increasingly regarded as an underlying causative factor for RLS. Further research is likely to concentrate on iron-regulatory protein genes in RLS.

The identification of susceptibility loci in RLS provides us with new insight into the pathophysiology of the disease. Owing to the problems in genetic linkages studies on people with RLS, future studies need to be more detailed in relation to the clinical picture of RLS to clearly define the exact phenotype of the disease. This would improve the phenotype–genotype links and correlation. However, with the emergence of newer genetic technology, it is conceivable that gene or genes for RLS will be unearthed in the near future.

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WEB TRAWL

Malaria on the internet

Malaria is endemic in many parts of the world and remains one of the world's biggest killers. Healthcare professionals, patients and those travelling to affected areas (who clearly wish to avoid becoming patients!) all have need of reputable, up to date information about the disease. So what does the internet have to offer? Typing ''malaria'' into a search engine produces over 25 000 000 results, although it is easy to refine your search, depending on the type of information you are looking for. The World Health Organization has a specific section on its website devoted to malaria (**http://www.who.int/malaria**). This provides detailed information and fact sheets on a variety of topics; much is specifically for those who are working in affected areas, with subjects including diagnosis and treatment, dealing with epidemics and treating malaria in the HIV-positive patient. For the traveller, there are several very useful pages detailing the types of malaria prevention and the situations where they should be used, along with a map showing the countries where malaria is endemic. There is the facility to download a high-resolution version of the map and also an Excel spreadsheet listing the affected countries. This would be useful to take travelling, but it is dated 2004 and it would be prudent to check whether there have been any major changes since that time, before deciding to rely on it completely. The American Centers for Disease Control and Prevention (CDC) also provides detailed information about malaria on its website (**http://www.cdc.gov/Malaria**). Again there is information for doctors and other healthcare professionals working in malaria affected areas, as well as advice on diagnosis and treatment (last updated August 2005), although the latter is designed specifically for American doctors treating travellers returning to the US. Likewise, there is information for US travellers (last updated June 2006). There is some variation in the recommendations for prevention of malaria and in the availability of preventive drugs, but travellers from other countries may find this of interest. The sections on counterfeit drugs and cautionary tales from travellers affected by malaria would be of universal interest. For the UK traveller, the malaria section on the TravelDoctor website should provide all the necessary information. This is accessed at **http://www.traveldoctor.co.uk/malaria.htm** and provides detailed, clearly laid out advice on which prophylaxis is required for which country. Finally, health professionals everywhere with an interest in malaria may wish to visit **http://www.malariajournal.com**. It is an online, peer reviewed, open access journal that is updated regularly (the most recent update at the time of writing was three days prior). It publishes articles on all aspects of the disease and sets out to be of interest to health professionals and to scientists working in this field. Overall, there is a wealth of reliable information about malaria available on the internet, produced by a variety of reputable organisations. This selection of websites alone could well provide all the information you and your patients require.

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