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Discussion

MAOA: susceptibility locus for the severity of RLS phenotype?☆

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1. Objective

The objective of this study is to investigate the role of the monoamine oxidase (MAO) A and MAOB genes (two distinct genes on chromosome Xp11) in association with the restless legs syndrome (RLS) phenotype.

2. Study design

The study is a population-based, case-control association study on the French-Canadian population.

3. Methods

A total of 96 RLS patients and 200 aged-matched controls all of French-Canadian origin were investigated. Diagnosis was based on the International Restless Legs Syndrome Study Group Criteria. Additionally, nocturnal polysomnogram recording (PSG) and a suggested immobilization test (SIT) were performed in all patients. The periodic leg movements in sleep (PLMS) index, sleep latency and leg movement during the SIT (total number of leg movements divided by the duration of the SIT in minutes) were calculated. Clinical features such as age at onset of the disease and a positive family history were considered.

In all subjects DNA was extracted from peripheral lymphocytes. First, a functional variable number of tandem repeat (VNTR) polymorphisms in the MAOA gene promoter region were genotyped. Patients and controls were compared after categorizing each subject into one of two groups based on the functional characterization of the respective alleles: a low (= short allele) and a high (= long allele) activity allele group. (This was done because previous studies demonstrated that the short allele displays a lower transcriptional efficiency and activity compared to those with longer repeats [1].) Second, a variant in a dinucleotide repeat located within the second intron of the MAOB gene was studied.

The relationships between variations of these loci and several clinical features were also investigated.

4. Results

When studying the MAOA and MAOB gene polymorphisms, no difference in allelic distribution was found between patients and controls. However, after stratifying by sex, RLS-affected females were found to carry a higher proportion of the high transcription activity alleles of MAOA compared to controls. Furthermore, females carrying the high transcription alleles showed a longer sleep onset latency and a higher movement index during the SIT. In contrast, there was no association of sleep parameters and MAOA gene polymorphisms in males. For the MAOB, no association between the gene polymorphisms and RLS patients could be identified.

5. Conclusions

Affected females with the high activity alleles of the MAOA gene, resulting in an elevated MAOA activity, had a greater risk of being affected by RLS than females carrying the low activity alleles. The authors concluded that an elevated MAOA activity would lead to an increased dopaminergic catabolism and consequently reduced synaptic levels of this neurotransmitter. Because this functional polymorphism seems to influence the movement index during the SIT and the sleep latency, the authors concluded that the MAOA gene plays a modulating role in the RLS phenotype. A high activity allele of the MAOA gene may represent a modifying factor of the severity of RLS manifestations in females. Concerning the sex effect, the authors speculated

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that the exclusive impact of MAOA for females might result from the interaction of estrogens and dopamine. Most of the participating women were postmenopausal, with consequent decline of serum levels of estrogens and, therefore, alteration of the dopaminergic transmission, which might result in different vulnerability to RLS. However, the authors mentioned that a direct relationship between MAOA and estrogens has thus far not been demonstrated, and speculated that estrogens might interact with specific MAOA alleles. Interestingly, the low activity allele was observed more commonly in females than males, both within the control population and in comparison to other populations. In conclusion, the authors stated that their results need further investigations and should be confirmed by independent studies.

6. Comment

This is the first study, conducted by a group of scientists with experience in the genetics of RL, indicating a gene with a possible modulating role for the dopaminergic metabolism in RLS. This group, moreover, has access to an interesting population of French-Canadians suspected of having possible founder effects for RLS. The rationale for investigating MAOA and MAOB genes is obvious; these genes encode enzymes involved in the metabolism of dopaminergic and catecholaminergic neurotransmitters. The activity or inactivity of these enzymes therefore has a consequence on the synaptic levels of dopamine. Furthermore, several treatment and pharmacological studies have suggested an involvement of these neurotransmitters in the pathophysiology of RLS [2,3]. It can therefore be hypothesized that enzymes modifying the dopaminergic transmission also modify the phenotype and/or severity of RLS patients. In light of the fact that gender differences of MAOA in connection with dopaminergic neurotransmission have thus far not been shown, further investigation is needed concerning the exclusive influence of the allelic frequencies within the MAOA gene for female RLS patients. The MAOA and MAOB genes are located on the X chromosome, and one could therefore speculate that the MAO alleles might have a higher vulnerability, and consequently a higher impact, on the phenotype for men having no compensatory X chromosome. Other influences on the respective phenotype depending on MAOA alleles have been reported in association with affective and movement disorders. A study of children, using a linkage transmission/disequilibrium test to investigate the association of attention deficit/hyperactivity disorder (ADHD) with MAOA and MAOB genes, revealed that ADHD was in linkage with the MAOA locus [4]. The authors suggested that MAOA might be a susceptibility factor for ADHD. Interestingly, an association of ADHD with periodic limb movement disorder (PLMD) has been reported. PLMD and/or RLS seem to occur more frequently in children with ADHD than in controls [5]. Symptoms of RLS frequently appear in parents of ADHD children [6], and it was suggested that there is a common genetic basis for both diseases. However, MAO inhibitors have been shown to be effective in the treatment of ADHD, and whether these drugs also have an impact on RLS, or at least some characteristic features in sleep, remains to be investigated.

The authors did not perform a PSG study for any of the controls. Nor do they indicate whether or not the controls were scrutinized for possible RLS symptoms; we may assume not. According to the higher prevalence of RLS in the general population [7], and possibly even higher prevalence in the French-Canadian population [8], at least 10% of the controls were no doubt also affected by RLS. Consequently, the difference between controls and patients would be even higher and *P* values even more powerful. However, whether or not a direct correlation of prolonged sleep latency and increased movement index to MAOA alleles can be drawn remains to be investigated. Increased sleep latency is one, but not the most characteristic, feature of sleep disturbance in RLS patients and may be rather nonspecific. The authors themselves carefully discussed this; besides further investigations of RLS populations, patients with PLMD should be investigated in respect of their allelic frequencies within the MAOA gene.

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