



## Genetic variants IL1B +3954C>T and -511C>T associated with incapacity and allodynia in migraine

Aline Vitali da Silva<sup>1</sup> , Barbara Ferreira Khoury<sup>1</sup> , Debora Villas Boas Rezende<sup>1</sup> ,  
Ana Paula Gallina Pezzini<sup>1</sup> , Beatriz Rabello Espinosa<sup>1</sup> , Tainah Mendes Ahrens<sup>1</sup> ,  
Adriano Torres Antonucci<sup>1</sup> , Valéria Aparecida Bello<sup>1</sup> , Regina Célia Poli Frederico<sup>1</sup> ,  
Carlos Eduardo Coral<sup>2</sup> , Edna Maria Vissoci Reiche<sup>2</sup> , Andrea Name Colado Simão<sup>2</sup> 

<sup>1</sup>Pontifical Catholic University of Paraná, Curitiba, Paraná, Brazil.

<sup>2</sup>State University of Londrina, Londrina, Paraná, Brazil.

### Introduction

The main mechanisms in the pathophysiology of migraine are cortical spreading depression and trigeminal activation with the release of CGRP. Neurogenic inflammation and neuroinflammation can exert an influence over both these mechanisms, but there are still a number of gaps in our understanding. Interleukin (IL)-1 $\beta$  is a pro-inflammatory cytokine whose levels of plasma increase during the attack phase of migraine. Thus far, its genetic variants have not been well studied.

### Objective

To investigate the association between the genetic variants IL1B +3954C>T (rs1143634) and -511C>T (rs16944) and susceptibility to migraine and its clinical characteristics.

### Subjects and Methods

Case control study comprising 307 participants, of whom 152 had a diagnosis of migraine and 155 were healthy controls, paired by sex, age, ethnicity and BMI. The clinical and demographic data were evaluated. The patients with migraine were interviewed using a structured form containing information about the type of migraine (with or without aura, episodic or chronic), age at onset of the disease, frequency of attacks, accompanying symptoms that triggered headaches. The patients also answered validated questionnaires to evaluate incapacity (Migraine Disability Assessment - MIDAS) and impact (Headache Impact Test - HIT-6) for migraine, the presence of allodynia (ASC-12), as well as symptoms of anxiety (State Anxiety Inventory - STAI 1 and 2), depression (Beck Depression Inventory) and a hyperacusis scale.

The genetic variants IL1B +3954C>T (rs1143634) and -511C>T (rs16944) were identified using polymerase chain reaction (PCR) and the fluorescence levels of PCR products were evaluated using a Step One thermocycler (Applied Biosystems). The analyses were conducted using the dominant, codominant, recessive and over-dominant genetic models. Categorical data were evaluated via the chi-squared test or Fisher's exact test, and continuous data were evaluated using the Mann-Whitney test. Binary logistic regression was used to determine association when  $p < 0.1$  in the univariate analyses. A significant statistical difference was considered when  $p < 0.05$ .

### Results

The participants in the study were mostly female (76.8% and 81.6%,  $p = 0.23$ ), young adults (median of 31 to 36 years,  $p = 0.30$ ), Caucasian (76.8% and 82.2%,  $p = 0.21$ ) and BMI with a median of 24.6 and 25.3 Kg/m<sup>2</sup> in the control and migraine groups, respectively ( $p = 0.41$ ).

55.6% of participants with migraine were classified as episodic while 44.4% were classified as chronic. Aura was present in 36.2%. Prophylactic medication was used in 44.7%, and 34.1% made excessive use of painkillers.

The +3954CT genotype was associated with a higher chance of severe incapacity compared to the +3954CC genotype in the codominant model (OR = 2.14 with 95% CI 1.05-4.36;  $p = 0.035$ ), and also when compared to the CC+TT genotypes in the over-dominant model (OR = 2.26 with 95% CI 1.11-4.57;  $p = 0.024$ ). The CT + TT genotypes of the variant -511C>T were associated with a substantial or severe impact on migraine (OR = 3.03 with 95% CI (1.11-8.29);  $p = 0.031$ ), in the dominant model.

Mild-to-severe allodynia was associated with the -511CT genotype in the codominant and over-dominant models (OR = 2.65 with 95% CI 1.05-6.67;  $p = 0.039$  and OR = 2.38 with 95% CI 1.01-5.59;  $p = 0.047$ , respectively). Phonophobia was associated with the CT+TT genotype of the variant -511C>T (OR = 2.55 with 95% CI 1.11-5.90;  $p = 0.028$ ).

No association was found in the variants IL1B +3954C>T and -511C>T with susceptibility to migraine, chronification, presence of aura, accompanying symptoms, prodrome, postdrome, age at onset, hyperacusis, anxiety or depression in all the genetic models analyzed.

### Conclusion

IL-1 $\beta$  is a cytokine that has been widely studied with regard to migraine. Its production in the trigeminal ganglion has been demonstrated in experimental studies, as well as increased plasma levels in the first few hours of pain. An earlier study identified an association of the variant +3954C>T with susceptibility to migraine, a finding that was not, however, replicated in the present study. This discrepancy may be due to the smaller sample size (163) in the earlier study. However, although not exerting an effect on susceptibility, the variant +3954C>T did influence the form of presentation of the migraine, with a higher chance of severe incapacity. The genetic variant -511C>T, not previously studied with regard to migraine, was associated with the impact of migraine, allodynia and phonophobia.

The variants IL1B +3954C>T (rs1143634) and -511C>T (rs16944) did not have an effect on susceptibility to migraine, however they did have an influence on the form that the disease presented.

**Keywords:** Migraine. Cytokines. IL-1 $\beta$ .