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# Prothrombotic genetic risk factors in chronic daily headache

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**Abstract** The aetiology of chronic daily or near-daily headache (CDH) is unknown. We evaluated prothrombotic genetic risk factors (factor V G1691A, factor II 20210 G/A, methylenetetrahydrofolate reductase mutations and plasminogen activator inhibitor-1 4G/5G polymorphism) in 100 patients with CDH, and in 73 healthy controls. Patients did not differ from controls for the studied prothrombotic polymorphisms. These findings suggest that prothrombotic genetic risk factors do not play a role in the development of CDH.

**Key words** Chronic daily headache • Hemostasis • Genetic risk factors

## Introduction

Chronic daily headache (CDH) is a neurologic disorder characterized by daily or near-daily headache (occurring 15 or more days per month). Primary CDH can be subclassified into disorders of short duration (< 4 h/attack) and disorders of long duration (> 4 h/attack). Primary CDH includes chronic daily migraine (previously called transformed migraine), chronic tension-type headache, hemicrania continua and new daily persistent headache [1]. Population-based studies suggest that approximately 4%–5% of the general population have primary CDH [2, 3]. Because primary CDH is a worldwide medical problem, it is important to detect risk factors for this disorder. Recently, we have emphasized that prothrombotic abnormalities of coagulation had a role in patients suffering from secondary CDH with isolated intracranial hypertension and cerebral venous thrombosis [4]. It is therefore possible that unrecognized inherited thrombophilia may occur in primary CDH patients. To test this hypothesis we investigated polymorphisms of the genes involved in abnormalities of the coagulation system in patients with CDH, in order to evaluate the role of genetic risk factors for developing CDH.

## Materials and methods

### Patients and controls

We studied 100 patients (10 men and 90 women; mean age, 39 years; SD, 10) with CDH. CDH was diagnosed according to the criteria of Silberstein et al. [5]. Patients were enrolled if CDH lasted at least six months. All the patients had normal results upon magnetic resonance imaging (MRI) and MR venography of the brain.

The control group consisted of 73 consecutively enrolled subjects (8 men and 65 women; mean age 38.5 years; SD 9) matched to the patients with CDH according to sex, age, and geographic origin. None of the controls suffered from CDH or migraine.

### Genotyping

The transition from G to A at nucleotide 1691 of the factor V gene (factor V Leiden, FVL), the G to A transition at nucleotide 20210 of the prothrombin gene (FII), the C677T substitution of the methylenetetrahydrofolate reductase (MTHFR) gene and the plasminogen-activator inhibitor-1 (PAI-1) 4G/5G polymorphism were evaluated [6–9].

## Results

The characteristics of the 100 patients are summarized in Table 1. Table 2 shows the genotype distribution of the studied polymorphisms in cases and controls. The FVL mutation was found in a heterozygous state in 6 of the 100 CDH patients (6%) and in 4 (5.5%) control subjects (not significant). Two patients had the G20210A mutation of FII in a heterozygous state, and the frequency of the MTHFR mutation was similar between case patients and controls. Additionally, we did not detect differences in genotype distribution of the PAI-1 polymorphism when comparing patients and control subjects.

## Discussion

In this study, we found that the prevalence of the studied genetic variations did not significantly differ between patients with CDH and controls. Consistent with our observations, others authors have demonstrated that the inherited thrombophilia risk factors did not play a role in the development of migraine [10]. Higher prevalence of the factor V Leiden mutation was found in migraine with aura in one study [11], but this was not confirmed in another study [12]. Some authors reported that genetic abnormalities of the protein C system increased the probability of having thrombotic stroke in patients with migraine with aura, especially young patients [13]. However, others did not find a G to A transition at position 20210 in the prothrombin gene and excluded this mutation as a major risk factor for migrainous infarction [14]. Thus, there is no

**Table 1** Demographics and clinical profiles of 100 patients with CDH

| | | |
|---|---|---|
| Males, n | 10 | |
| Mean age, years (SD) | 39 | (10) |
| Body mass index, mean (SD) | 26 | (5) |
| Headache history (no. of patients) | | |
| 7–12 months | 3 | |
| 13–60 months | 9 | |
| > 60 months | 88 | |
| Headaches profile (no. of patients) | | |
| Severe headache | 58 | |
| Marked functional impairment | 31 | |
| Pulsating headaches | 50 | |
| Unilateral headaches | 23 | |
| Head pain aggravated by postural change or physical activity | 48 | |
| Exacerbation during menses | 6 | |
| Aura | 9 | |
| Chronic daily headaches (no. of patients) | | |
| Chronic daily migraine | 63 | |
| Chronic tension-type headache | 37 | |
| Overuse of analgesics (no. of patients) | 31 | |

**Table 2** Prothrombotic genotype frequencies (%) of 100 patients and 73 controls

| | FVL | | | FII | | | MTHFR | | | PAI-1 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | + + | + – | – – | + + | + – | – – | + + | + – | – – | + + | + – | – – |
| CDH patients | 0 | 6 | 94 | 0 | 2 | 98 | 20 | 50 | 30 | 26 | 39 | 35 |
| Controls | 0 | 4 | 96 | 0 | 1 | 99 | 19 | 55 | 26 | 26 | 43 | 31 |

*FVL*, factor V Leiden; *FII,* factor II; *MTHFR*, methylene tetrahydrofolate reductase; *PAI-1*, plasminogen-activator inhibitor-1

conclusive evidence that either migraine with aura or migraine stroke are statistically associated with prothrombotic genetic risk factors.

In conclusion, our study provides evidence that polymorphisms of the genes involved in the coagulation system do not represent genetic risk factors for developing CDH.

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