Evidence of Syntaxin 1A Involvement in Migraine Susceptibility

A Portuguese Study

Carolina Lemos, PhD; José Pereira-Monteiro, MD, PhD; Denisa Mendonça, PhD; Eliana Marisa Ramos, BSc; José Barros, MD; Jorge Sequeiros, MD, PhD; Isabel Alonso, PhD; Alda Sousa, PhD

Objective: To confirm syntaxin 1A as a risk factor for migraine, given that syntaxin 1A interacts with several factors in migraine pathophysiology.

Design: Case-control approach.

Setting: An outpatient clinic.

Participants: In a sample of 188 migraineurs (111 without aura and 77 with aura) and 287 migraine-free controls, 3 tagging SNPs of STX1A (rs3793243, rs941298, and rs6951030) were analyzed. A backward stepwise multiple logistic regression was performed. Allelic and haplotypic frequencies were compared between cases and controls.

Results: We found that rs941298 and rs6951030 were risk factors for migraines. In particular, the TT genotype of rs941298 is associated with an increased risk of both migraine in general and migraine without aura; the GG and GT genotypes for rs6951030 are also associated with migraine, while the GT genotype of rs6951030 was found to be significant in the migraine without aura group. The single-nucleotide polymorphism rs3793243 did not show any significant association. In the haplotype-based analysis, we found an underrepresentation of the T-C-T haplotype (rs3793243-rs941298-rs6951030) in the global sample and in migraine without aura group. We found an enrichment of the G allele of rs6951030 for female migraineurs only.

Conclusions: We confirmed the involvement of syntaxin 1A in migraine susceptibility regarding rs941298. In addition, we found rs6951030 to also be associated in Portuguese migraine patients. Sex differences should be further explored to disentangle a possible sex susceptibility in syntaxin 1A.

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MIGRAINE IS A COMMON neurological disorder, affecting about 15% of the general population. Familial aggregation studies have shown that migraine is essentially caused by genetic factors, with multiple genes contributing to its liability, in addition to environmental factors. We have also confirmed the presence of a genetic component in migraine with and without aura in a Portuguese population.

Although some loci for migraine with and without aura have been proposed, the genes involved have not yet been identified. Several candidate genes have been studied, with contradictory results. Some evidence supports that the neurotransmitter system is also involved in migraine pathophysiology. Serotonin plays a role in pain modulation, and serotonin agonists are an effective therapeutic approach to migraine. The serotonin transporter is involved in serotonin reuptake and is a target for serotonin reuptake inhibitors.

Syntaxin 1A is a presynaptic plasma membrane protein of the syntaxin family that, in conjunction with other proteins, compose the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex, which is crucial for the regulation of the presynaptic release of neurotransmitters. Syntaxin 1A, encoded by the STX1A gene (OMIM 186590), is one of the regulatory proteins of the expression and subcellular localization of the serotonin transporter. Furthermore, syntaxin 1A binds to the neuronal γ-aminobutyric acid (GABA) transporter, inhibiting its reuptake. γ-Aminobutyric acid is the main inhibitory neurotransmitter in the brain, and some GABA-receptor agonists are used in migraine prophylaxis.

Nitric oxide is also involved in the formation of the SNARE complex and in the interaction of syntaxin 1A and the GABA transporter. Nitric oxide has also been as-
associated with the nociception mechanism and consequently with migraine pathophysiology.\textsuperscript{10}

The gene encoding the \( \alpha_{1A} \) subunit of a voltage-dependent calcium channel (\textit{CACNA1A}) is involved in a rare form of migraine with aura, familial hemiplegic migraine (FHM) type 1. It has been shown that the association of the SNARE proteins with presynaptic Ca\textsuperscript{2+} channels, including \textit{CACNA1A}, is essential for neurotransmitter release.\textsuperscript{11}

Recently, syntaxin 1A was proposed as a risk factor for migraine.\textsuperscript{12} The aim of this study was to confirm the involvement of syntaxin 1A in migraine’s susceptibility, using a case-control approach, given that syntaxin 1A interacts with several factors of migraine pathophysiology.

**METHODS**

**SUBJECTS**

One hundred eighty-eight unrelated patients with migraine (111 without aura, 77 with aura), from the neurology outpatient clinic, at Hospital de Santo António, Porto, Portugal, were sequentially enrolled in this study. Patients with FHM were excluded; migraineurs with cooccurrence of migraine with and without aura were included in the group with aura. Control subjects (n=287), with no history of migraine, were ascertained among healthy blood donors and from the obstetrics and gynecology department of Hospital de Santo António. Women with menstrual headaches were excluded from the control group. Controls were from the same ethnic and geographical origin as the cases (northern region of the country) and were age-matched.

A diagnostic interview was performed in cases and controls, based on the operational criteria of the International Headache Society, using the same structured questionnaire. The first edition of the International Headache Society criteria\textsuperscript{13} was used before 2004; when revising the diagnosis using the second edition,\textsuperscript{14} we found no differences in patients’ diagnosis (data not shown). Participants gave their written informed consent, and the ethics committee of the Hospital de Santo António approved the project.

**SELECTION OF SNPs AND GENOTYPING**

Genomic DNA was isolated from peripheral blood, using a standard salting out method\textsuperscript{15} or from saliva, using ORAGENE kits according to the manufacturer’s instructions (DNA Genotek Inc.). Single-nucleotide polymorphisms (SNPs) were selected based on a data registry from the International HapMap Project; tagging SNPs were selected using haplowlivew 4.1, at an \( r^2 \) threshold of 0.80, with a minor allele frequency greater than 0.10, by an aggressive tagging approach.\textsuperscript{16} Tagging SNPs included rs3793243 (located in chromosome 7: 72 759 293), rs941298 (72 763 199), and rs6951030 (72 771 177, according to the Ensembl database).

In the first stage, allelic discrimination was performed using molecular beacons and real-time polymerase chain reactions (PCRs) (IQ5 Real-Time PCR Detection System, Bio-Rad Laboratories). A few discrepancies were found, however, after sequencing (to confirm uncertain genotypes): real-time PCR did not prove to be a reliable method for allelic discrimination with these SNPs. Therefore, we chose to sequence all samples for rs3793243 and rs941298, while for rs6951030 we used a restriction-enzyme analysis. Therefore, we chose to sequence all samples for rs3793243 and rs941298, while for rs6951030 we used a restriction-enzyme analysis.

All SNPs were PCR-amplified using HotStar Taq Master Mix Kit (Qiagen) according to the manufacturer’s instructions (primer sequences are available from the authors on request). Sequencing was performed using the Big Dye Terminator Cycle Sequencing, version 1.1, Ready Reaction (Applied Biosystems), according to the manufacturer’s instructions, and samples were loaded in an ABI-PRISM 3130 XL genetic analyzer (Applied Biosystems). Restriction enzyme analysis was performed with Bsr after PCR amplification, and electrophoresis was performed on digestion products in a 2% agarose gel, stained with ethidium bromide.

**STATISTICAL ANALYSIS**

Power estimations were performed using the Genetic Power Calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/). Analysis of Hardy-Weinberg equilibrium was also performed.\textsuperscript{17} Demographic data of patients and controls were compared using a \( \chi^2 \) test for categorical variables. To compare SNP allele frequencies between cases and controls, the \( \chi^2 \) test was used, and odds ratios (ORs) were estimated with 95% confidence intervals (CIs). Significance was set at \( p < 0.05 \).

A backward stepwise multiple logistic regression was performed (with the most frequent homozygote as the reference category) to evaluate the association between the SNPs’ genotypes and the occurrence of migraine, by including the 3 SNPs and sex in the initial model. We also evaluated the role of STX1A in the migraine subtypes. All analyses were performed in the total sample, as well as in the subsets of migraine with and without aura. Significance was set at \( p < 0.016 \) (considering 3 logistic regressions) using a Bonferroni correction to correct for multiple comparisons.

These analyses were performed using SPSS, version 16.0. Haplotype frequencies were compared between cases and controls, using Haploview 4.1 with all parameters set at the default values.\textsuperscript{16} Haplotypes were estimated, using an accelerated expectation-maximization algorithm similar to the partition-ligation expectation-maximization algorithm described by Qin et al,\textsuperscript{18} and case-control counts were obtained by summing the fractional likelihoods of each individual for each haplotype.\textsuperscript{16} Frequencies of analyzed haplotypes were above 1%, according to the Haplovlew threshold; to correct for multiple comparisons, regarding estimation of allelic and haplotype frequencies, we used 10 000 permutations. In the pooled sample, a \( \chi^2 \) and OR were estimated, assuming \( p < 0.05 \), to compare allelic and genotypic frequencies between cases and controls.

We analyzed a sample of 188 unrelated migraineurs and 287 age-matched controls (case to control ratio of 1:1.5). With this sample, we had a power of 64% to detect association (for a nominal \( p = 0.05 \), assuming a high-risk allele frequency of 0.1, a relative risk for AA genotype of 2.25, and 1.5 for Aa genotype. A migraine prevalence of 16% had been previously estimated in a Portuguese population.\textsuperscript{19,20}

Demographic and clinical data can be found in Table 1. A family history of migraine was present in 87% of the cases. No significant differences were found regarding sex between patients and controls (\( p > 0.05 \)). Both case and control groups were in Hardy-Weinberg equilibrium for the 3 SNPs studied. The correlation between the 3 SNPs was small, denoting the weak linkage disequilibrium (LD) between them according to the LD plot (Figure). In our sample, the 3 SNPs were also in weak LD (data not shown).
Regarding allele frequencies (Table 2), we found an enrichment of the G allele of rs6951030 among migraineurs (OR, 1.52; 95% CI, 1.12-2.06) as well as in the group without and the group with aura (without aura, OR, 1.48; 95% CI, 1.04-2.12; with aura, OR, 1.58; 95% CI, 1.06-2.36); however, after permutation-based correction, the result for migraine without aura and aura did not reach significance. We found an enrichment of the T allele for rs941298 in patients with migraine without aura than in controls, suggesting a possible protective role of the T allele of this SNP in the other groups. There were no significant differences in the allele frequencies between cases and controls, regarding rs3793243, for any of the groups.

Additionally, we stratified these data by sex and found an enrichment of the G allele of rs6951030 only in female migraineurs (OR, 1.56; 95% CI, 1.11-2.20), but this was not significant after permutation-based correction. In men, no significant results were found (not shown).

Genotypic frequencies of the SNPs are shown in Table 3. Results from the backward stepwise multiple logistic regression, with the 3 SNPs and sex included in the initial model, are shown in Table 4. Values for each SNP were adjusted for the remaining significant variables in the model. For the migraine sample, the TT genotype of rs941298 showed an increased risk in patients with migraine (OR, 2.22; 95% CI, 1.19-4.12), significant after Bonferroni correction; the GT and GG genotypes of rs6951030 were also associated with an increased risk of migraine (GT, OR, 1.68; 95% CI, 1.13-2.51; GG, OR, 3.27; 95% CI, 1.35-7.88), also significant after Bonferroni correction. Interestingly, the TT genotype of rs941298 also showed an increased risk of migraine without aura (OR, 3.11; 95% CI, 1.52-6.33); and heterozygosity for rs6951030 was associated with an increased risk of migraine without aura (OR, 1.85; 95% CI, 1.14-2.99), withstanding Bonferroni correction. An OR higher than 2 (OR, 3.01; 95% CI, 1.05-8.64) was found for the GG genotype, which may indicate that this genotype is also a risk factor for migraine without aura (though not statistically significant after Bonferroni correction), similar to what was found in the sample of migraine with aura (OR, 3.20; 95% CI, 1.14-8.92). The SNP rs3793243 did not show any significant association.

In a haplotype-based analysis (Table 5), C-C-G was more frequent in migraineurs than in controls (OR, 1.40, but it did not withstand permutation-based correction). Also, T-C-T was less frequent in migraineurs and in patients with migraine without aura than in controls, suggesting a possible protective role of the T allele of rs941298 (nonsignificant after multiple-testing correction). In men, we did not find any differences in haplotype frequencies between cases and controls (data not shown).

Patients with cooccurrence of migraines with and without aura were first included in the sample with aura. In a further analysis, we decided to exclude these patients from the analysis, and the results we found were similar regarding the involvement of the 3 SNPs in migraine with aura (data not shown).

Additionally, we performed a pooled analysis of our data and those published by Corominas et al,12 excluding the Catalan patients with hemiplegic migraine. We found a significant association between rs941298 and the total sample and the group with migraine without aura (not shown). With allele frequencies of rs941298 pooled together, risk was significantly increased for the migraine sample and in patients with migraine without aura who have the T allele (not shown). For rs6951030, we did not find any significant results after pooling.

We performed a PupaSuite database search21 to assess a putative functional role of these SNPs: (1) rs6951030 is located in a conserved region, which may indicate it

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With Migraine</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=188)</td>
<td>(n=287)</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Migraine without aura</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>Sex, F/M</td>
<td>153/35</td>
<td>217/70</td>
</tr>
<tr>
<td>Age at observation, mean (SD), y</td>
<td>36.14 (12.84)</td>
<td>36.42 (12.35)</td>
</tr>
<tr>
<td>Age at onset, mean (SD), y</td>
<td>17.67 (8.15)</td>
<td></td>
</tr>
<tr>
<td>Family history of migraine, %</td>
<td>87</td>
<td></td>
</tr>
</tbody>
</table>

Figure. Linkage disequilibrium plot of single-nucleotide polymorphisms within STX1A (HaploView 4.1); $r^2$ values are given within each square. kb indicates kilobases.
is important for gene regulation; and (2) rs941298 is located in a triplex sequence and may affect its structure formation, altering regulation. Additionally, we assessed if there were any regulatory SNPs in LD with rs6951030 and rs941298. The SNP rs6951030 is not in LD with any other SNP genotyped in the HapMap project. We found that rs867500 (in LD with rs941298) is located in an exonic-splicing enhancer motif.

We analyzed the role of STX1A in migraine susceptibility and, more specifically, in migraine subtypes with and without aura. Our findings confirm the involvement of STX1A as a risk factor for migraine. The intronic variants rs941298 and rs6951030 may play a role on migraine and, particularly, in migraine without aura. Additionally, we cannot exclude the effect of rs6951030 in migraine with aura, because the homozygous state of GG results in an OR above 2; however, the result was not significant after Bonferroni correction.

The haplotype analysis also supports the involvement of the rs6951030 G allele in migraine susceptibility and a protective role for the T allele both for migraine and migraine without aura. With this we also confirmed the increased risk conferred by the rs941298 T allele. Comparing allele frequencies, we found an association of rs6951030 with migraine and migraine subtypes, while for rs941298 only an association with migraine without aura was found; results for rs3793243 were not significant.

We found a sex-related effect in rs6951030, because only the female group showed enrichment of the G allele. This may be due to hormonal effects mediated by epigenetic modifications.22 We cannot exclude, however, that the nonincreased risk in men is due to its small size in our sample. It would be important to explore this in larger samples to disentangle a possible sex susceptibility regarding syntaxin 1A.

In the recent study from Catalonia, Spain,12 significant differences were found between cases and controls, both in allele and genotype frequencies of rs941298. The T allele was overrepresented in cases, either with or without aura. In our study, we also found an effect of the TT genotype in the global sample and in the subset of migraine without aura. In contrast to our results, no association with rs6951030 was found in the Catalonian study.

Although our study replicates the involvement of STX1A in migraine susceptibility, different variants were associated. Our data suggest a stronger effect of this gene in migraine without aura regarding rs6951030 and rs941298. The difference between our results and those from Catalonia12 regarding rs6951030 may be due to allele fre-
frequency variation across populations; it may be more marked owing to gene
and gene environment interactions.23 This emphasizes the importance of repli-
cating association studies in several populations.

Additionally, when pooling both samples, we found a significant effect of the T allele of rs941298 in mi-
graineurs; this was expected, as the Catalonian study found significant results for this SNP and we saw an in-
creased risk with the TT genotype in our sample. These results show that this SNP may be involved in suscepti-
bility to migraine in both populations. More impor-
tantly, we found an increased risk with the G allele of rs6951030 in Portuguese migraineurs, which was not pres-
ent in the pooled sample; we can postulate that the as-
sociation with rs6951030 is specific to our population.

In FHM, glutamate release, facilitated by the mu-
tated voltage-dependent calcium channel α1A subunit, re-
results in cortical spreading depression (CSD), a slowly propa-
gating wave of neuronal and glial depolarization, that moves through the cortex.24 Cortical spreading de-
pression is the underlying mechanism implicated in the visual, sensory, or motor aura observed in migraine with aura, during which several neurotransmitters are re-
leased.25 In migraine without aura, imaging studies sug-
gest that CSD may occur in silent brain areas, leading to

Table 4. Results From the Backward Stepwise Multiple Logistic Regression

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Migraine</th>
<th>Migraine Without Aura</th>
<th>Migraine With Aura</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>rs3793243</td>
<td></td>
<td>.25</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>1 [Reference]</td>
<td></td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>CT</td>
<td>0.66 (0.39-1.11)</td>
<td>.12</td>
<td>0.62 (0.32-1.19)</td>
</tr>
<tr>
<td>TT</td>
<td>0.86 (0.38-1.94)</td>
<td>.71</td>
<td>0.88 (0.33-2.34)</td>
</tr>
<tr>
<td>rs941298</td>
<td></td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>1 [Reference]</td>
<td></td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>CT</td>
<td>1.16 (0.77-1.75)</td>
<td>.48</td>
<td>1.32 (0.80-2.18)</td>
</tr>
<tr>
<td>TT</td>
<td>2.22 (1.19-4.12)</td>
<td>.01b</td>
<td>3.11 (1.52-6.33)</td>
</tr>
<tr>
<td>rs6951030</td>
<td></td>
<td>.004b</td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>1 [Reference]</td>
<td></td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>GT</td>
<td>1.68 (1.13-2.51)</td>
<td>.01b</td>
<td>1.85 (1.14-2.99)</td>
</tr>
<tr>
<td>GG</td>
<td>3.27 (1.35-7.88)</td>
<td>.008b</td>
<td>3.01 (1.05-8.64)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.

a After Bonferroni correction, significance level was set at α=.016.

b Significant value.

Table 5. Results From the Haplotype Analysis

| Haplotypea | Cases | | | | | Controls | | | | | | | | | |
|------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|            | Carriers | Noncarriers | Carriers | Noncarriers | OR (95% CI) | χ² | P Valueb | After Permutation | |
| All patients | | | | | | | | | | | | | | | | | | | |
| C-C-G      | 89.9 | 286.1 | 105.4 | 468.6 | 1.40 (1.02-1.92) | 4.28 | .04c | .17 |
| T-C-T      | 30.8 | 345.2 | 81.7 | 492.3 | 0.54 (0.35-0.83) | 7.94 | .005c | .03c |
| Patients with migraine without aura | | | | | | | | | | | | | | | | | | | |
| T-C-T      | 14.9 | 207.1 | 81.7 | 492.3 | 0.43 (0.24-0.77) | 8.49 | .004c | .02c |
| T-T-T      | 74.1 | 147.9 | 147.9 | 426.1 | 1.44 (1.03-2.02) | 4.61 | .03c | .15 |

Abbreviations: CI, confidence interval; OR, odds ratio.

a rs3793243-rs941298-rs6951030.

b Only haplotypes with any significant result are shown.

c Nominal and corrected; significant value.

Although no functional role has yet been described for any of these intronic SNPs, it would be important to further evaluate that possibility. We found that both rs941298 and rs6951030, but also rs867500 (which is in LD with rs941298), are located in regions that are po-
tentially important for regulation. Further analyses are needed to evaluate a potential functional role of these SNPs and understand their effect on syntaxin 1A.

Although our sample is not very large, we had spe-
cial concern in obtaining a high case to control ra-
tio—to increase power. Also, cases and controls were matched for age at observation and sex and were from the same geographic region (several studies, using mark-
ers sensitive to population stratification as lineage mark-
ers, have shown that there is no population substruc-
ture among the Portuguese population). Also, we used corrections for multiple testing to prevent type I errors (Bonferroni and permutation-based corrections). We used logistic regression analyses to examine the SNPs’ effects altogether.

In conclusion, our study favors and brings new insight into the involvement of syntaxin 1A in susceptibility to migraine and strengthens the role of neurotransmitter release in its pathophysiology. We can thus confirm the association between syntaxin 1A and migraine found in Catalan patients. Additional studies with larger samples in other populations will be important to disentangle the role of this gene in migraine subtypes.

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Correspondence: Alda Sousa, PhD, Department of Population Studies, Instituto Ciências Biomédicas Abel Salazar, University of Porto, 4099-003 Porto, Portugal (absousa@icbas.up.pt).

Author Contributions: The principal author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Lemos, Alonso, and Sousa. Acquisition of data: Lemos, Pereira-Monteiro, Ramos, Barros, and Alonso. Analysis and interpretation of data: Lemos, Mendonça, Sequeiros, and Sousa. Drafting of the manuscript: Lemos. Critical revision of the manuscript for important intellectual content: Pereira-Monteiro, Mendonça, Ramos, Barros, Sequeiros, Alonso, and Sousa. Statistical analysis: Lemos, Mendonça, and Sousa. Obtained funding: Lemos, Pereira-Monteiro, and Sequeiros. Administrative, technical, and material support: Alonso. Study supervision: Pereira-Monteiro, Sequeiros, Alonso, and Sousa.

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REFERENCES

To date, CSF analyses have not been a routine component of assessment and care for patients with cognitive impairments and suspected AD in the United States. There is now ample evidence that these measurements have value; physicians need to formulate when and how to incorporate CSF measurements into their practice. We strongly recommend CSF analyses of Aβ1-42, T-tau, and P-tau in circumstances where having a definitive diagnosis of AD is important for counseling patients about such concerns as work, driving, and making other lifestyle changes. The CSF biomarkers will also improve accuracy for determining treatment in clinical situations where other conditions, such as normal-pressure hydrocephalus, depression, or vascular ischemic changes, figure in the differential diagnosis. There is already ample evidence that the AD CSF signature has a place in predicting which individuals with MCI are at risk to progress to dementia, and it may even have value in predicting the rate of cognitive decline. The CSF analyses of Aβ, T-tau, and P-tau should have a central place in experimental clinical trials to increase the likelihood that participants have AD and eliminate other diagnoses that might dilute treatment effects. Gazing into the future when there are neuroprotective medications for AD, we can envision a recommendation that CSF analyses be implemented as a screening test to identify clinically healthy individuals at risk for MCI and AD. The information gained would enable early application of treatments to delay onset of symptoms or slow progression of cognitive impairments.

A. Zara Herskovits, MD, PhD
John H. Growdon, MD

Author Affiliations: Department of Pathology, Brigham and Women’s Hospital (Dr Herskovits) and Department of Neurology, Massachusetts General Hospital (Dr Growdon), Boston, Massachusetts.

Correspondence: Dr Growdon, Department of Neurol-

ogistry, Massachusetts General Hospital, Wang Ambulatory Care Center 729, Boston, MA 02114 (jgrowdon@partners.org).

Financial Disclosure: None reported.

REFERENCES


Correction

Errors in Table. In the article “Evidence of Syntaxin 1A Involvement in Migraine Susceptibility: A Portuguese Study,” published in the April issue of the Archives (2010; 67[4]:422-427), there were a few errors in Table 3. In the rs941298 section of the table, the CC and TT genotype cells in the “All Patients With Migraine” column should be switched. The number and frequency for the TT genotype should be 28 (14.9%) and for the CC genotype, 86 (45.7%). The CC and TT genotype cells should also be switched in the “Controls” column: the number and frequency for the TT genotype should be 28 (14.9%) and for the CC genotype, 142 (49.3%).