Genomics 91 (2008) 503–507

Contents lists available at ScienceDirect

Genomics

journal homepage: www.elsevier.com/locate/ygeno

Replication study of the insulin receptor gene in migraine with aura

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ARTICLE INFO

Article history:
Received 6 March 2008
Accepted 8 March 2008
Available online 2 May 2008

Keywords:
Migraine with aura
Insulin receptor gene
INSR
Association study

ABSTRACT

We performed the first replication study for the reported association of the insulin receptor gene (*INSR*) with migraine with aura (MA). Two of 35 SNPs (rs1052371 and rs2860174) reached borderline significance (best uncorrected allelic *p* value of 0.052 for rs2860174) in stage 1 of our study (270 MA patients, 280 controls). As rs2860174 was 1 of the 5 SNPs with prior evidence of association, we also genotyped this SNP in our stage 2 sample (679 MA patients, 368 controls), and it was nonsignificant (allelic *p* value 0.478). The combined analysis of our samples showed just a nonsignificant trend for rs2860174 ($p=0.1$). However, the joint analysis of our study and the initial study reporting an association—including 1278 Caucasian MA patients and 1337 Caucasian controls altogether—displayed a significant allelic *p* value of 0.005. In conclusion, further association studies for rs2860174 with even larger numbers of individuals are required to exclude or confirm definitely a small effect of this SNP on migraine susceptibility.

Migraine is a very common and genetically complex episodic disorder. The molecular pathomechanisms of this severely disabling brain disease are largely unknown [1]. Among the different forms of migraine as classified by the criteria of the International Headache Society [2], the two most common ones are migraine without aura (MO; 70–80% of cases) and migraine with aura (MA; 20–30% of cases). Epidemiological data demonstrate that a genetic susceptibility is involved in both forms of migraine, but argue for a stronger genetic background in MA compared to MO [3].

McCarthy et al. [4] performed one of the few genetic association studies in migraine research that had reasonable statistical power and reported a significant finding, which, however, has up to now not been reanalyzed in an independent association study. In their large-scale study, 16 SNPs within the insulin receptor gene (*INSR;* OMIM *147670) were genotyped in two Caucasian samples with a total of 827 patients with MA and MO from North America and 765 control individuals. They could also replicate some of their findings in an independently collected Australian sample with 255 Caucasian patients with MO and MA and 237 controls. The strongest association was found for MA with one exonic (synonymous) and two intronic SNPs (rs1799817, rs2860172, and rs2860174, with allelic *p* values of 0.008, 0.002, and 0.007, respectively) in one of the North American samples. The only SNP that was significant gender-independently in the combined analysis of both American samples was rs2860174 (designated as SNP90). Whether this variant or any of the other *INSR* SNPs with evidence for association has a direct functional effect, e.g., on *INSR* mRNA splicing or expression levels, is currently unknown. The authors had selected the *INSR* gene for analysis due to its chromosomal localization on chromosome 19p13 near *CACNA1A,* the gene mutated in familial hemiplegic migraine type 1 (FHM1) [5], a rare autosomal dominant inherited form of MA. Indeed, in parallel with the association study, the same group published evidence for an MA susceptibility locus on chromosome 19p13 distinct from the FHM1 gene [6], and the *INSR* gene is located within the critical region between *D19S427* and *D19S592.* On the other hand, the chromosome 19p locus was later on excluded in Finnish MA families [7]. Also in a Caucasian migraine pedigree with linkage to 19p (for which *CACNA1A* mutations had been excluded) no coding mutations in the *INSR* gene were identified [8,9]. However, further plausibility of *INSR* as a putative migraine susceptibility gene comes from evidence for a comorbidity of migraine with diabetes [10] in combination with the significant association of *INSR* polymorphisms with type 2 diabetes in a recent study including 2134 Caucasian individuals [11]. Moreover, fasting is a frequent trigger factor reported by migraineurs [12–15], and there is evidence for an altered insulin metabolism in migraineurs [16].

The positive findings of the *INSR* association study for migraine have attracted much attention; however, a confirmation or rejection of the association results has not been published yet. For this reason we performed a comprehensive replication study in a large German

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doi:10.1016/j.ygeno.2008.03.006

MA case–control sample. Our study included all SNPs that were initially found to be associated with migraine (MA and/or MO) in any of the three case–control samples gender-independently. In addition, we investigated haplotype-tagging SNPs that capture the common haplotype variation in the European population at the *INSR* locus. We applied a two-stage design: our case–control sample was randomly split into two subsamples, and the selected set of SNPs was first genotyped in subsample 1. SNPs with interesting findings in subsample 1 were subsequently also genotyped in subsample 2.

Results

Single-marker analysis

Allele call rates on the Illumina platform were between 97.4 and 99.9%. Four SNPs moderately deviated from the Hardy–Weinberg equilibrium (two in the case and two in the control sample; see Table 1). These deviations were not significant after Bonferroni correction for multiple testing.

Two of the altogether 35 SNPs genotyped in our stage 1 sample comprising 270 patients with MA (77 male/193 female) and 273 control individuals (82 male/191 female) displayed borderline significant ($p = 0.05$) allelic association with MA (Fig. 1 and Tables 1 and 2): rs1052371 and rs2860174. After permutation-based correction for the number of tests performed, the allelic p values of these SNPs increased to 0.73 and 0.74, respectively. However, among the five *INSR* SNPs that were previously reported to be associated with migraine [4], rs2860174 reached borderline significance also in our uncorrected single-marker analysis. As this was hence the SNP with the best a priori evidence for association (it was the only significant marker in the combined analysis of both North American samples in the original study), we subsequently genotyped rs2860174 in our stage 2 sample 2 [679 patients with MA (128 male/551 female) and 368 control individuals (77 male/291 female)]. No significant allele frequency differences could be observed in this subsample (allelic p value of 0.478; Table 2). However, a combined analysis for rs2860174 including our stage 1 and 2 samples showed a nonsignificant trend ($p = 0.1$; odds ratio = 1.17; Table 2). As also observed in the prior study, the minor allele (T allele) of rs2860174 was more common in the patient sample.

Haplotype analysis

We also performed a haplotype-based comparison of case–control genotypes in our stage 1 sample, starting with the markers that were associated with migraine in the original study (rs1051690, rs1799817, rs2860172, rs2860174, and rs2860183) or that showed uncorrected association in our stage 1 sample (rs1052371, rs2860174). We evaluated all possible SNP combinations of these six polymorphisms, yet, for none of the 63 SNP combinations was the p value obtained for the global haplotype smaller than those obtained for the two borderline-associated SNPs alone (data not shown). However, nominally significant differences on the same order of magnitude were found for some individual haplotypes. The A-T haplotype over the two SNPs rs1052371 and rs2860174 displayed an estimated frequency of 8.3% in

Table 1
Genotyping results and statistical analysis in subsample 1

SNP rs ID	Distance (bp)	Allele 1/2 (strand)	Deviation from HWE (p value)		Minor allele frequency in%		Allelic p value	OR (95% CI)
			Controls	Cases	Controls	Cases		
rs1052371		A/G (+)	0.06	0.22	12.8 (A)	17.1 (A)	**0.05**	0.71 (0.51–1.00)
rs3745550	2,980	A/G (−)	0.50	0.30	17.8 (A)	15.9 (A)	0.39	1.15 (0.84–1.58)
rs1051690 (=*SNP279*)	1,390	A/G (−)	**0.05**	0.44	19.1 (A)	18.4 (A)	0.76	1.05 (0.77–1.42)
rs2288404	8,023	A/G (−)	0.23	0.13	49.3 (G)	48.3 (A)	0.43	0.91 (0.72–1.15)
rs1799817 (=*SNP274*)	311	A/G (+)	0.28	0.95	16.5 (A)	20.1 (A)	0.13	0.79 (0.58–1.08)
rs2860172 (=*SNP84*)	2,078	A/C (−)	0.31	0.95	16.4 (A)	20.1 (A)	0.11	1.28 (0.94–1.75)
rs2860174 (=*SNP90*)	3,343	A/T (+)	0.47	0.94	15.8 (T)	20.4 (T)	**0.05**	1.37 (1.00–1.87)
rs6510950	5,771	A/G (−)	0.37	0.39	5.1 (G)	5.0 (G)	0.94	1.02 (0.59–1.76)
rs8103483	8,885	A/G (−)	0.35	**0.02**	47.8 (G)	48.1 (G)	0.91	0.99 (0.78–1.25)
rs2252673	5,044	C/G (−)	0.87	**0.03**	16.7 (G)	14.3 (G)	0.27	1.20 (0.86–1.67)
rs8106126	11,186	A/G (+)	0.09	0.14	38.6 (A)	42.7 (A)	0.17	1.19 (0.93–1.51)
rs7258741	1,461	A/G (+)	0.24	0.74	5.9 (A)	5.2 (A)	0.64	0.88 (0.52–1.49)
rs2245649	149	A/G (−)	0.75	0.24	7.8 (G)	6.7 (G)	0.51	1.17 (0.73–1.85)
rs2059807	2,895	A/G (+)	0.15	0.24	40.6 (A)	45.5 (A)	0.10	1.22 (0.96–1.56)
rs1366234	1,708	A/C (+)	0.72	0.46	23.5 (A)	21.9 (A)	0.53	0.91 (0.69–1.21)
rs11671975	9,463	A/G (+)	0.92	0.40	23.7 (G)	22.5 (G)	0.63	0.93 (0.70–1.24)
rs8112883	2,040	A/C (−)	0.92	0.57	27.6 (A)	25.8 (A)	0.50	0.91 (0.70–1.19)
rs891087	5,198	A/G (+)	0.93	0.65	8.8 (A)	7.5 (A)	0.42	0.84 (0.54–1.30)
rs2860183 (=*SNP81*)	4,857	A/G (−)	0.96	0.57	39.4 (A)	37.1 (A)	0.43	1.11 (0.86–1.42)
rs2115386	7,190	A/G (−)	0.24	0.97	48.5 (A)	48.0 (G)	0.25	1.15 (0.91–1.46)
rs4499341	4,425	A/G (−)	0.62	1.00	38.8 (G)	36.1 (G)	0.35	0.89 (0.70–1.14)
rs3745545	10,851	A/G (−)	0.99	0.75	14.9 (G)	14.1 (G)	0.72	0.94 (0.67–1.32)
rs4804404	6,541	A/C (+)	0.08	0.19	14.3 (C)	15.2 (C)	0.66	0.93 (0.66–1.30)
rs7508679	4,450	A/G (−)	0.90	0.68	43.2 (A)	38.9 (A)	0.15	0.84 (0.66–1.07)
rs890860	5,333	A/G (−)	0.25	0.09	22.1 (A)	22.7 (A)	0.81	1.04 (0.78–1.38)
rs3852876	11,390	A/G (+)	0.63	0.69	30.5 (G)	30.9 (G)	0.90	1.02 (0.78–1.32)
rs10404318	8,072	A/G (−)	0.95	0.98	0.4 (G)	0.2 (G)	0.57	0.51 (0.05–5.60)
rs4247374	5,129	A/G (−)	0.15	0.32	14.8 (A)	16.9 (A)	0.35	1.17 (0.84–1.62)
rs4804195	2,188	C/G (−)	0.62	0.96	38.8 (G)	38.7 (G)	0.97	0.99 (0.78–1.27)
rs919275	6,497	A/G (−)	**0.02**	0.78	37.7 (G)	37.7 (G)	1.00	1.00 (0.78–1.28)
rs6510975	5,437	A/G (−)	0.55	0.39	49.1 (A)	47.0 (A)	0.50	1.09 (0.86–1.38)
rs7248939	1,560	A/G (+)	0.35	0.19	39.9 (A)	35.5 (A)	0.14	1.21 (0.94–1.54)
rs7254060	14,093	A/G (+)	0.64	0.65	7.5 (A)	7.4 (A)	0.95	1.01 (0.65–1.60)
rs8111710	9,169	A/C (−)	0.43	0.72	22.9 (A)	22.0 (A)	0.73	0.95 (0.71–1.27)
rs7507911	5,512	A/G (−)	0.29	0.10	17.7 (A)	13.9 (A)	0.10	1.32 (0.95–1.84)

Genotyping results and statistics for 35 SNPs at the *INSR* locus analyzed in subsample 1. p values ≤0.05 are in bold. HWE, Hardy–Weinberg equilibrium. OR, odds ratio. CI, confidence interval. SNPs that were reported to be associated with migraine [4] are given in italic, with the original designation written in parentheses after the rs ID.

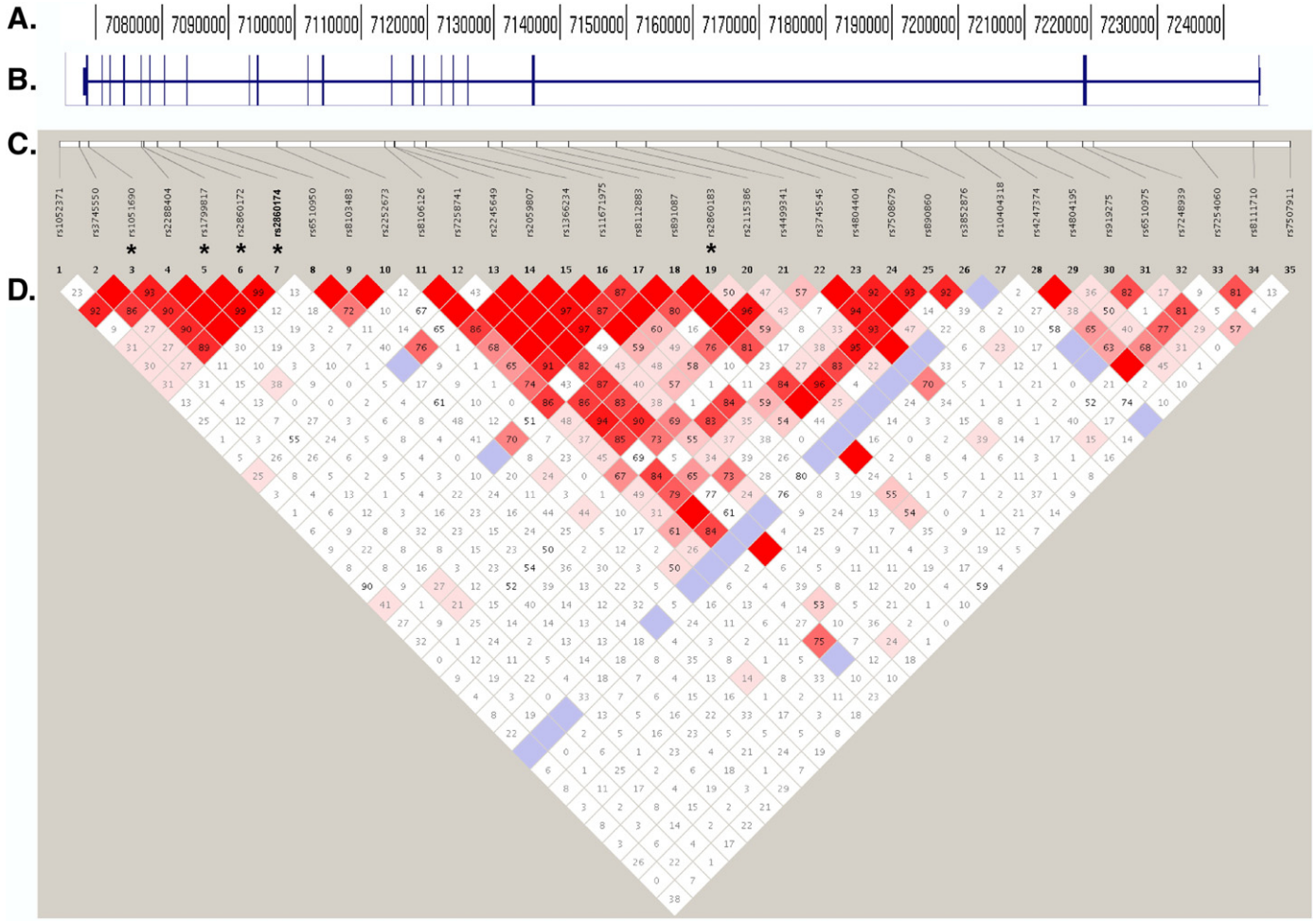

Fig. 1. Schematic representation of the *INSR* gene. (A) Chromosome 19 position in bases, based upon NCBI build 35 of the human genome. (B) Genomic structure of the *INSR* gene. Small vertical bars represent 5′ untranslated regions, large vertical bars coding exons. (C) Relative positions and rs IDs of the 35 SNPs genotyped in this study. SNPs previously reported to be associated with migraine [4] are marked by an asterisk. (D) LD plot with HaploView 3.11. Solid red squares indicate complete LD between SNPs. *D′* values <1 are given within each square.

patients and 4.8% in controls, whereas the G-A haplotype was more common among controls (76.2% versus 70.9%). Because 4 of the 5 previously reported associated SNPs fall within the 23-kb interval between these two SNPs, a potential susceptibility variant would most likely reside in this region. We finally evaluated all possible two-marker combinations over all 35 genotyped SNPs, but did not find any more pronounced differences that could withstand correction for multiple testing.

Table 2
Single marker association results of rs2860174 in the various MA samples of our study and the initial report [4]

Sample	Controls (*n*)	MA patients (*n*)	Allele frequency				Genotype frequency						Allele A versus T	
			Controls (*n*)		MA patients (*n*)		Controls (*n*)			MA patients (*n*)				
			A	T	A	T	AA	AT	TT	AA	AT	TT	*p* value	OR (95% CI)
Subsample 1 (this study)	263	270	0.842 (443)	0.158 (83)	0.796 (430)	0.204 (110)	0.703 (185)	0.278 (73)	0.019 (5)	0.633 (171)	0.326 (88)	0.041 (11)	0.0516	1.37 (1.00–1.87)
Subsample 2 (this study)	368	679	0.837 (616)	0.163 (120)	0.825 (1120)	0.175 (238)	0.696 (256)	0.283 (104)	0.022 (8)	0.672 (456)	0.306 (208)	0.022 (15)	0.4784	1.09 (0.86–1.39)
Subsamples 1+2 (this study)	631	949	0.839 (1059)	0.161 (203)	0.817 (1550)	0.183 (348)	0.699 (441)	0.281 (177)	0.021 (13)	0.661 (627)	0.312 (296)	0.027 (26)	0.1026	1.17 (0.97–1.42)
Sample S1 (initial study)	279	175	0.849 (474)	0.151 (84)	0.837 (293)	0.163 (57)	0.720 (201)	0.258 (72)	0.022 (6)	0.703 (123)	0.269 (47)	0.029 (5)	0.6179	1.10 (0.76–1.58)
Sample S2 (initial study)	427	154	0.847 (723)	0.153 (131)	0.776 (239)	0.224 (69)	0.717 (306)	0.260 (111)	0.023 (10)	0.604 (93)	0.344 (53)	0.052 (8)	0.0049	1.59 (1.15–2.21)
Samples S1+S2 (initial study)	706	329	0.848 (1197)	0.152 (215)	0.809 (532)	0.191 (126)	0.718 (507)	0.259 (183)	0.023 (16)	0.657 (216)	0.304 (100)	0.040 (13)	0.0251	1.32 (1.04–1.68)
All samples	1337	1278	0.844 (2256)	0.156 (418)	0.815 (2082)	0.185 (474)	0.709 (948)	0.269 (360)	0.022 (29)	0.660 (843)	0.310 (396)	0.031 (39)	0.0051	1.23 (1.06–1.42)

MA, migraine with aura; CI, confidence interval.

Joint analysis

As both in our study and in the initial study [4] the T allele of rs2860174 displayed a moderately increased frequency in MA patients, we performed a combined analysis of both studies including the original, unpublished genotype frequency data for the patients of Caucasian descent in the S1 and S2 populations from Northern America. This combined analysis comprises 1278 patients with MA and 1337 control individuals from three different sampling units. The three sampling units were homogeneous with respect to ethnicity (=Caucasian) and clinical diagnosis (=migraine with aura according to the International Headache Society criteria). The genotype frequencies of any of the single samples as well as of the combined sample did not deviate from the Hardy–Weinberg equilibrium as tested by the exact test (e.g., for the combined analysis of all samples, $p=0.53$ and $p=0.40$, for the control and patient sample, respectively). Moreover, the allele frequencies of the three different control samples did not differ from one another by more than 1.2%, which proves the good comparability and homogeneity of cohorts. The combined statistical analysis showed a p value of 0.0051 (Table 2) compatible with a small but causative involvement of the *INSR* gene in MA pathogenesis.

Discussion

As a follow-up of the association study published by McCarthy et al. [4] we performed a comprehensive replication study of the *INSR* gene in a large MA case–control sample. Indeed, 2 of 35 genotyped SNPs (rs1052371 and rs2860174) showed borderline-significant allelic association with MA ($p=0.05$) in our single-marker analysis, a finding that, however, does not withstand a correction for multiple testing. Among the *INSR* SNPs previously reported to be associated with migraine, MA, or MO, only rs2860174 could nominally be replicated (with $p=0.05$) in our stage 1 sample, but not in our larger stage 2 sample, in which we subsequently genotyped this SNP. Furthermore, a haplotype-based analysis capturing the common haplotype variation at the *INSR* locus in the European population could also not detect convincing evidence for association.

However, in the combined analysis of our two samples, rs2860174 still showed a nonsignificant trend (allelic p value=0.1), with the same allele as the putative risk-conferring variant as reported by McCarthy et al. We therefore contacted the investigators of the initial study and performed a joint analysis of both studies for rs2860174. This joint analysis, including the formerly unpublished genotype frequencies of the initial study for patients with migraine with aura and for controls of Caucasian descent, revealed a p value of 0.005. The analysis included 1278 patients with MA, uniformly diagnosed according to the International Headache Society criteria, and 1337 control individuals. It was ethnically homogeneous (of Caucasian descent) and displayed almost identical allele frequencies in the control samples, so that population stratification (as a frequent cause of false-positive results) is a rather unlikely explanation for the observed differences. A possible explanation for these allele frequency differences in the joint analysis may be random effects on allele distribution, attributable to the fact that both studies (this study and the study by McCarthy et al.) included multiple SNPs. However, as this observation is based on one of the largest MA samples analyzed in migraine research so far, further association studies for rs2860174 with even larger numbers of migraine patients and control individuals are required to exclude or confirm definitely a small effect of this SNP on migraine susceptibility.

Materials and methods

Patients

In total 949 German patients with MA, recruited at a single clinical center, were included in the study and randomly assigned to sample 1 or 2 to enable a two-stage study design. All patients gave their written informed consent and were diagnosed according to the revised criteria of the International Headache Society [2] by experienced physicians as described previously[17–19]. The composition of our two patient subsamples used in different parts of this study and a detailed description of clinical features of the participants is given in Table 3. The study was approved by the local university ethics committees. The population-based control sample consisted of 641 gender- and ethnically matched German individuals.

Genetic analysis

SNP genotyping on genomic DNA of subsample 1 (=stage 1 of the study) was performed on an Illumina platform according to the manufacturer's protocol. For genotyping of SNP rs2860174 in our subsample 2 (=stage 2 of the study), a 587-bp genomic fragment was amplified by a standard PCR with a touchdown protocol (annealing temperature decreased from 63 to 55 °C within 9 PCR cycles, followed by 28 cycles with 55 °C annealing temperature) with the primer pair 5′-GAAGTGAACAGTA-GACACCG-3′ and 5′-GGTTGCAGTGAGCCGACATC-3′. The PCR products were digested with the restriction enzyme *Bgl*II, as the minor allele of rs2860174 introduces a *Bgl*II restriction site into this fragment. Digested PCR products were analyzed on a 2% agarose gel after electrophoresis. Genotyping of individuals was independently performed by two investigators.

SNP assortment

The SNPs rs1051690, rs1799817, rs2860172, rs2860174, and rs2860183 were included because they were reported to be associated with migraine (MA and/or MO) in at least one of the three case–control samples analyzed previously [4]. Because in the initial study the rs nomenclature was not used, we assigned the rs IDs to all SNPs by using the sequence information given in the initial publication. For those SNPs genotyped in both studies, we included the initial designation in Table 1 (e.g., rs2860174 corresponds to SNP90 in the former study). The haplotype-tagging (ht-) SNPs were chosen based on the HapMap database (http://www.hapmap.org; version September 2004) to discriminate between all common haplotypes (with an estimated frequency >5%) within haplotype blocks in the Central European sample. Haplotype blocks were defined as regions in which >85% of total haplotype diversity is covered by common haplotypes, using the program Hapblock [20].

Statistics

Allele and genotype distributions were compared between cases and controls by a χ^2 test with the appropriate degrees of freedom. Tests of Hardy–Weinberg equilibrium were performed using a χ^2 goodness-of-fit test. For the comparison of haplotype frequencies between cases and controls we used the program Cocaphase, which is contained in the Unphased package [21]. This program estimates maximum-likelihood haplotype frequencies using an expectation-maximization algorithm and compares haplotype frequencies using a likelihood ratio test.

Power calculation

A power analysis was performed with the Genetic Power Calculator [22]. We estimate that, under the assumption of complete LD between the marker tested and the disease-causing variant, we had 78% power to detect a true difference in allele frequency between the 270 patients with MA and 273 controls (i.e., in the first stage of

Table 3
Clinical characteristics of patients with migraine with aura

Characteristic	Stage 1 sample (=subsample 1)	Stage 2 sample (=subsample 2)	Full sample (=subsample 1+2)
Subjects (n)	270	679	949
Men/women (n)	77/193	128/551	205/744
Age (years)	48±13.5	42.9±12.9	44.4±13.2
Mean age at onset (years)	19.5±11.1	17.7±9.6	18.2±10.1
Mean duration of one attack (h)	44.9±23.7	50.5±22.5	48.9±23.0
Mean number of attacks/month	2.6±1.4	2.7±1.3	2.6±1.3
Visual aura symptoms (%)	96.6	93.5	94.4
Sensory aura symptoms (%)	40.4	36.8	37.8
Dysarthria/aphasia (%)	32.8	28.8	29.9
Nausea (%)	87.4	90.1	89.4
Vomiting (%)	66.0	64.3	64.8
Photophobia (%)	91.6	88.3	89.2
Phonophobia (%)	88.9	87.6	88.0
Unilateral location (%)	84.6	82.7	83.2
Pulsating pain (%)	80.8	84.6	83.5

our study) with a single-marker association analysis ($\alpha = 0.05$), further assuming a frequency of the disease-associated allele A of 0.18, a relative risk of 1.5 for genotype Aa and of 2.25 for genotype AA, and a prevalence of MA in the general population of 8%. Using the same parameters, the estimated power increases to >98% in a sample of 949 patients and 641 controls (i.e., in our complete sample).

Acknowledgments

We thank Katrin Friedrich for technical assistance, Doris Wegner for support in database maintenance, and all the participating individuals for their cooperation. This study was supported by grants from the Deutsche Forschungsgemeinschaft to C.K. and H.G. (FOR 423, TPA2), the National Genome Network of the Bundesministerium für Bildung und Forschung to C.K., and the Center for Molecular Medicine Cologne to C.K. Linda C. McCarthy and Allen D. Roses are full-time employees of GlaxoSmithKline.

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