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Migraine polygenic risk score associates with efficacy of migraine-specific drugs

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Abstract

Objective

To assess whether the polygenic risk score (PRS) for migraine is associated with acute and/or prophylactic migraine treatment response.

Methods

We interviewed 2,219 unrelated patients at the Danish Headache Center using a semistructured interview to diagnose migraine and assess acute and prophylactic drug response. All patients were genotyped. A PRS was calculated with the linkage disequilibrium pred algorithm using summary statistics from the most recent migraine genome-wide association study comprising ~375,000 cases and controls. The PRS was scaled to a unit corresponding to a twofold increase in migraine risk, using 929 unrelated Danish controls as reference. The association of the PRS with treatment response was assessed by logistic regression, and the predictive power of the model by area under the curve using a case-control design with treatment response as outcome.

Results

A twofold increase in migraine risk associates with positive response to migraine-specific acute treatment (odds ratio [OR] = 1.25 [95% confidence interval (CI) = 1.05–1.49]). The association between migraine risk and migraine-specific acute treatment was replicated in an independent cohort consisting of 5,616 triptan users with prescription history (OR = 3.20 [95% CI = 1.26–8.14]). No association was found for acute treatment with non–migraine-specific weak analgesics and prophylactic treatment response.

Conclusions

The migraine PRS can significantly identify subgroups of patients with a higher-than-average likelihood of a positive response to triptans, which provides a first step toward genetics-based precision medicine in migraine.

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Glossary

ACE = angiotensin-converting enzyme; **AUC** = area under the curve; **CI** = confidence interval; **DBDS** = Danish Blood Donor Study; **GWAS** = genome-wide association study; **HET** = heterozygosity; **IHGC** = International Headache Genetics Consortium; **LD** = linkage disequilibrium; **MA** = migraine with aura; **MO** = migraine without aura; **OR** = odds ratio; **PC** = principal component; **PRS** = polygenic risk score; **SNP** = single nucleotide polymorphism.

For complex diseases, there is an expected interindividual variation in the response to pharmacologic treatment. The current trend in medical science focuses on precision medicine, tailoring treatments to subsets of patients. Treatment can be improved by considering individual genomic prediction relating to drug metabolism.[1,2] Genome-wide association studies (GWASs) have been used in many complex diseases to detect genetic variants associated with diseases, and subsequently to generate polygenic risk scores (PRSs), which includes the additive effect of all variants of the disease. To date, PRS analysis is gaining ground in disease risk prediction,[3] identifying and quantifying comorbidities and endophenotypes,[4] and drug responses.[5,6]

Migraine is a polygenic disorder with an estimated heritability of 40%–60%[7–9] and a worldwide prevalence of 18%.[10] The acute treatment of migraine is dominated by the highly receptor-specific triptans. Approximately 25% of patients with migraine do not respond to triptans. In case of a high frequency of migraine attacks, many different nonspecific prophylactic drugs may be prescribed. It is unknown to what degree this variation in treatment response is related to genetic variants.[11]

We aim to test whether the genetic burden of migraine risk variants, defined by a PRS derived from the recent meta-analysis on migraine,[12] is associated with acute and prophylactic migraine treatment.

Methods

Study population—the target sample

The study population consisted of 2,591 patients with migraine who were recruited at the Danish Headache Center in 1999–2002, 2005–2006, and 2010–2011.[13,14] All patients with migraine were interviewed face to face or by telephone by a trained physician or trained senior medical student using a semistructured interview. The interview was designed by head of classification committee Prof. Jes Olesen to phenotype and classify migraine diagnosis according to the International Classification of Headache Disorders, second edition.[15]

Migraine drug response

The semistructured interview included questions covering the necessary clinical data for migraine diagnoses and information on the effect of migraine treatment. Acute treatment effect was considered to be positive in cases where the patient reported at least 50% pain reduction within 2 hours after taking medication. Prophylactic treatment effect was considered to be positive in cases where the patient reported a reduction of over 50% in migraine attacks. For acute treatment, the patient was asked about efficiency of (1) triptans and (2) ergotamine, which are both migraine-specific drugs, and (3) weak analgesics, which is nonspecific for migraine treatment. For prophylactic treatment, the patient was asked about the efficiency of (1) β-blockers, (2) Ca^{2+} antagonists, (3) angiotensin II receptor blockers, (4) angiotensin-converting enzyme (ACE) inhibitors, (5) anticonvulsants, (6) antidepressants, and (7) hormone treatment. Both generic and commercial names were mentioned, where the interviewer used pro.medicin.dk as reference. The questioned drug needed to be taken specifically for treatment of migraine. For all questions, the answer "Do not know" was considered as missing data.

Genotyping

All patients with migraine were genotyped on the Illumina HumanOmniExpress 12v1 (n = 2,152) or Illumina HumanOmniExpress 24v1 (n = 439) chip. For each data set, the quality control of genotypes was performed using PLINK 1.9.[16] We used genotypes for 2,766 ethnicity-sensitive single nucleotide polymorphisms (SNPs) common to all Illumina SNP arrays to estimate European, Asian, and African ancestry probabilities with STRUCTURE[17] and excluded individuals with <90% European ancestry. SNPs with <0.95 genotyping rate, <0.01 minor allele frequency, or $p < 1 \times 10^{-6}$ for Hardy-Weinberg Equilibrium were excluded, and individuals with <0.98 genotype rate were removed. Next, we created a subset of markers independent of each other with respect to linkage disequilibrium (LD) using a window size of 100 markers shifting by 25 markers at a time and removed 1 half of every SNP pair with genotypic $r^2 > 0.1$. This was performed to avoid overestimating the effect by including mutually dependent SNPs, i.e., SNPs in LD. Using this subset of markers, we calculated heterozygosity (HET) and sex and removed (1) all individuals with outlying HET values (>5 SD from the median of the whole sample) and (2) all individuals where sex determined from genotype did not match reported sex. We then removed all A/T and C/G markers to avoid strand issues. Related individuals were detected based on their genotype data, and 1 random individual per related couple (Pihat > 0.10) was removed. After filtering and quality control, 542,168 SNPs and 2,219 individuals were retained for analyses. The total data set of 2,219 patients with migraine consisted of 1,201 patients who had migraine without aura (MO) and 1,018 patients who had migraine with aura (MA). Cases with probable migraine (with or without aura) were included in the analysis, and in case the individual had both MA and MO, they were assigned to the MA subgroup.

PRS calculation

The PRS was calculated using LDpred, which adjusts for LD between markers and further rescales allelic effects based on the likelihood of each marker belonging to the fraction of markers assumed to be causal.[18] We calculated PRSs using the default models for causal variant fraction in LDpred (i.e., 1, 0.3, 0.1, 0.03, 0.01, 0.003, and 0.001). The LD information was retrieved from the subjects with migraine and 929 unrelated Danish controls, who were genotyped on the same genotype chip (Illumina HumanOmniExpress 12v1). To calculate PRSs for migraine, we used p values and $\log_{10}$ odds ratios (ORs) from a subset of the International Headache Genetics Consortium (IHGC) migraine GWAS meta-analysis (n_{case} = 59,674; $n_{control}$ = 316,078)[12] from which all individuals of Danish origin (1,771 cases and 1,000 controls) had been removed to avoid overlap between the discovery and target sample and a resulting overestimation of allelic effects.

To investigate which fraction of causal variants gives the best prediction of migraine, we compared the PRSs of our migraine sample (n = 2,219) with the 929 Danish controls. Migraine was most significantly predicted with a model assuming the fraction of causal variants to be 0.03 ($p = 6.91 \times 10^{-27}$). The PRS generated under this model predicted both MO and MA significantly ($p = 3.69 \times 10^{-26}$ and 4.98×10^{-17}). Next, we investigated whether the PRSs of the migraine subtypes could predict the respective subtype better than the PRS of migraine, using the GWAS on the clinical subset (5,557 MA and 7,352 MO) of the IHGC meta-analysis.[13] This was not the case, likely because of the limited sample size of the discovery cohort; the PRS of MO was predicted with a p value of 2.70×10^{-12} and the PRS of MA predicted MA with a p value of 1.61×10^{-3}. Therefore, all analyses were conducted using the PRS of migraine. We then rescaled the migraine PRS to a mean of zero and a unit corresponding to a twofold genetic increased risk for migraine in the target population; this was done by first subtracting the mean PRS from each subject's PRS and then multiplying it by log(OR)/log(2), where the OR was extracted from the model predicting migraine using the 2,219 cases and 929 controls.

Statistical analysis

The rescaled PRS for migraine was tested for its association with drug response using a logistic regression model including age, sex, genotype chip, and the first 10 principal components (PCs) of the genotypes as covariates. The PCs were calculated in PLINK[16] and included in the model to correct for population stratification. As triptan and ergotamine are both migraine-specific drugs used for acute treatment and act through the same serotonin receptors (5-HT_{1B} and 5-HT_{1D}), they were analyzed together to increase the statistical power. The mode of action of prophylactic treatments is unknown; therefore, they were analyzed together. The association of migraine-specific acute, migraine nonspecific acute, and prophylactic treatment with the PRS was corrected for multiple testing (n = 3) using Bonferroni correction resulting in adjusted p values (p_{adj}). As prophylactic treatment is potentially confounded by comorbid hypertension or epilepsy, we tested whether these comorbidities had a significant effect on treatment response. In case they were statistically significantly associated with treatment response, they were included as covariates.

All analyses were performed for the complete set of patients with migraine. Subsequently, it was tested whether there was a statistically significant difference between the migraine subtypes by including an interaction term between the PRS and migraine subtype. We presented the area under the curve (AUC), representing the prediction accuracy and ORs, using the partial Receiver Operating Caracteristic R-package.[19] The AUC was calculated for both the model including only the covariates and the full model including the PRS and the covariates. The difference between the 2 AUCs was tested using the DeLong test in the partial Receiver Operating Caracteristic R-package. ORs were presented with 95% confidence intervals (CIs). All analyses were performed in R (version 3.4.3.).[20]

Replication cohort

The Danish Blood Donor Study (DBDS) genomic cohort (n = 79,595) was used as the replication cohort (see detailed description elsewhere).[21] The PRS for migraine was calculated as done for the clinical cohort. Using a subpopulation of the DBDS genomic cohort (n = 17,222) with information on self-reported migraine ($n_{migraine}$ = 3,906), we estimated the OR for migraine within the DBDS genomic cohort (OR = 3.98, 95% CI = 3.18–4.98). The OR for migraine was used for subsequent normalization of the PRS as done for the clinical cohort. Using the prescription register of the 79,595 participants, we identified 5,616 users of migraine-specific treatment (1,372 males and 4,244 females). Positive triptan responders were defined as having 10 or more purchases of triptans, as previously suggested to be a reliable indicator of positive treatment response.[22] This resulted in 1,246 triptan responders (213 males and 1,033 females). In the regression model, age, sex, and the 10 first PCs were included as covariates.

Standard protocol approval, registrations, and patient consents

Written informed consent was obtained from all participants. The study was approved by the Danish Ethical Standards Committee (H-2-2010-122) and the Danish Data Protection Agency (01080/GLO-2010-10).

Data availability

Summary statistics of the GWAS are available upon agreement with the IHGC due to embargo with 23andMe. Genotype data of our clinical cohort are available upon agreement with the senior author and upon material transfer agreement.

Results

Sample characteristics

Our data set consists of 2,219 patients with migraine including 1,201 MO and 1,018 MA patients. The male:female ratio in patients with migraine was 1:4.7; this was slightly lower in

MO (1:5.8) than in MA (1:3.8) ($p = 2.7 \times 10^{-4}$). The patients with migraine were on average 44.2 years old with an SD of 12.8. There was no significant difference in age (SD) between MO and MA (44.0 [12.1] years and 44.4 [13.6] years, respectively). A higher response rate was found for MO than MA in acute and prophylactic treatment response (table 1). The difference in response rates implies a potential difference in association with the PRS across migraine subtypes, and therefore, we tested whether such difference was evident. There was a significantly higher response rate for female patients with migraine than male patients with migraine for acute treatment ($p = 0.03$). Furthermore, among the responders to prophylactic treatment, there were a higher number of patients with migraine with hypertension (table 2).

Association with acute treatment response

Acute treatment response was assessed by 2 different classes of drugs: migraine-specific and nonspecific drugs (figure 1). The PRS was statistically significantly associated with positive migraine-specific acute treatment response: a unit increase in the PRS (corresponding to a twofold increased migraine risk) was associated with an OR of 1.25 (95% CI = 1.05–1.49, $p_{adj} = 1.25 \times 10^{-2}$). Although the PRS was statistically significantly associated with acute treatment response, there was no statistically significant improvement of the accuracy when added to a model that included treatment covariates ($p = 0.50$): the AUC for the full model was 0.603 (95% CI = 0.569–0.637), and the model including all covariates except the PRS was 0.598 (95% CI = 0.563–0.633). No statistically significant interaction was present between the PRS and migraine subtypes, age, or sex. However, testing the association of acute treatment response with genetic load for each sex separately showed a strong signal for males (OR = 2.17 [1.36–3.57], $p = 1.55 \times 10^{-3}$) but not for females (OR = 1.15 [0.95–1.39], $p = 0.16$).

To ensure that the signal we are detecting is between migraine-specific drugs and the genetic load of migraine, we used migraine nonspecific drugs (weak analgesics) as negative control and saw no significant association. As a secondary analysis, we split the migraine-specific drugs into triptans and ergotamine; we saw only a statistically significant association for triptans (OR = 1.27 [1.07–1.51], $p = 7.60 \times 10^{-3}$). The stronger signal between the PRS and treatment response among males was still present among triptan response (OR = 2.08 [1.31–3.39], $p = 2.43 \times 10^{-3}$) and not for females (OR = 1.17 [0.97–1.42], $p = 0.10$).

Association with prophylactic treatment response

Migraine can be preventively treated with β-blockers, calcium antagonists, angiotensin II receptor antagonists, ACE inhibitors, antiepileptics, antidepressants, and by hormone treatment. Because their mode of action on migraine is unknown, we analyzed all prophylactic treatments together (figure 2). We did not find a statistically significant association between the migraine PRS and a positive prophylactic treatment response: a unit increase in the PRS (corresponding to a twofold increased migraine risk) resulted in an OR of 1.07 (95% CI = 0.90–1.27).

Table 1 Response rates of the investigated acute and prophylactic drugs in all patients with migraine, patients with migraine without aura, and patients with migraine with aura

	% (Total number of patients)			Migraine without vs with aura		
	Migraine	MO	MA	OR	95% CI	*p* Value
Acute treatment response[a]	81.5 (1,840)	87.0 (1,116)	73.1 (724)	0.41	0.32–0.51	5.29×10^{-14}
Triptan	80.9 (1,828)	86.6 (1,113)	72.0 (715)	0.40	0.31–0.50	9.99×10^{-15}
Ergotamine	40.0 (255)	43.1 (102)	37.9 (153)	0.80	0.48–1.34	0.40
Weak analgesics	27.6 (1,626)	21.2 (848)	34.5 (778)	1.92	1.56–2.43	2.54×10^{-9}
Prophylactic treatment response[b]	54.2 (1,106)	53.8 (651)	55.0 (455)	1.05	0.82–1.33	0.70
β-blocker	29.9 (782)	30.0 (460)	29.8 (322)	0.99	0.73–1.35	0.96
Ca2+ antagonist	15.9 (201)	15.4 (117)	16.7 (84)	1.10	0.51–2.36	0.81
Ang. II receptor antagonist	41.2 (580)	42.2 (358)	39.6 (222)	0.90	0.64–1.27	0.55
ACE inhibitors	25.5 (102)	26.8 (56)	23.9 (46)	0.86	0.35–2.11	0.74
Anticonvulsants	27.9 (495)	25.9 (293)	30.7 (202)	1.26	0.85–1.88	0.25
Antidepressants	24.3 (136)	18.1 (83)	34.0 (53)	2.33	1.05–5.17	0.04
Hormone treatment	37.0 (81)	37.8 (45)	36.1 (36)	0.93	0.38–2.31	0.88

Abbreviations: ACE = angiotensin-converting enzyme; Ang. II receptor antagonist = angiotensin II receptor antagonist; CI = confidence interval; MA = migraine with aura; MO = migraine without aura; OR = odds ratio.
Presented ORs and *p* values are for MO vs MA, with MO as the reference level for presented ORs.
[a] Acute treatment response only includes triptans and ergotamine (both 5-$HT_{1B/D}$ receptor antagonists).
[b] Prophylactic treatment response includes all medications questioned.

Table 2 Descriptive statistics of potential confounding factors

	Nonresponders	Responders	OR	95% CI	*p* Value
Acute treatment					
Age (mean [SD])	41.71 (13.09)	44.87 (12.05)	−3.16[a]	−3.53 to −2.79	5.28×10^{-5}
Sex (M: F ratio)	1:4.31	1:6.11	1.42	1.04 to 1.93	0.03
Migraine subtype (% MO)	42.65	64.73	2.47	1.94 to 3.14	5.3×10^{-14}
Epilepsy (%)	3.62	2.74	0.75	0.38 to 1.50	0.42
Hypertension (%)	15.00	17.69	1.22	0.88 to 1.69	0.24
Prophylactic treatment					
Age (mean [SD])	43.49 (13.27)	45.17 (12.15)	−1.68[a]	−2.03 to −1.33	0.03
Sex (M: F ratio)	1:4.82	1:5.82	1.21	0.87 to 1.67	0.25
Migraine subtype (% MO)	59.49	58.33	0.95	0.75 to 1.21	0.70
Epilepsy (%)	2.96	3.17	1.07	0.54 to 2.13	0.85
Hypertension (%)	15.61	23.04	1.60	1.19 to 2.20	1.97×10^{-3}

Abbreviations: CI = confidence interval; MO = migraine without aura; OR = odds ratio.
[a] As this is a continuous variable, we showed the difference in age between nonresponders and responders, instead of an OR.
For all ORs the nonresponders are used as reference.

Again, we did not see any statistically significant interaction between the PRS and migraine subtypes.

To test whether treatment of comorbidities was masking the association between the PRS and treatment response, we tested each drug separately. Comorbid hypertension was statistically significantly associated with angiotensin II receptor blockers and ACE inhibitors ($p = 2.85 \times 10^{-4}$ and 4.51×10^{-2}, respectively), and epilepsy was statistically significantly associated with anticonvulsants ($p = 8.88 \times 10^{-3}$). We found no statistically significant associations between any prophylactic treatment response and the PRS, although it should be noted that prophylactic treatments were used only by a relatively small proportion of the patients.

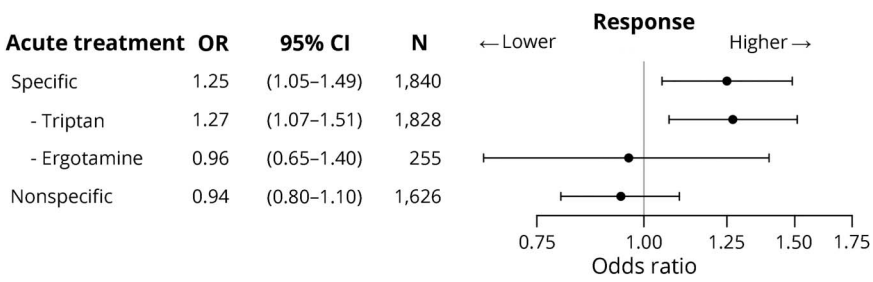
Replication of the association with triptan response

As it has been shown that pharmacy databases are a valuable source to identify treatment responders, we used the DBDS Genomic Cohort to replicate the association between genetic load of migraine and triptan response. We found a statistically significant association between the PRS of migraine and triptan response with an OR of 1.78 (95% CI = 1.20–2.64, $p = 3.36 \times 10^{-2}$). We found an association for both males and females (OR = 3.20 [1.26–8.14] and 1.63 [1.05–2.53], respectively). Although the OR was higher for males, the difference was not statistically significant. The prediction showed an increased rate of triptan response among the individuals with higher genetic load for migraine (figure 3).

Discussion

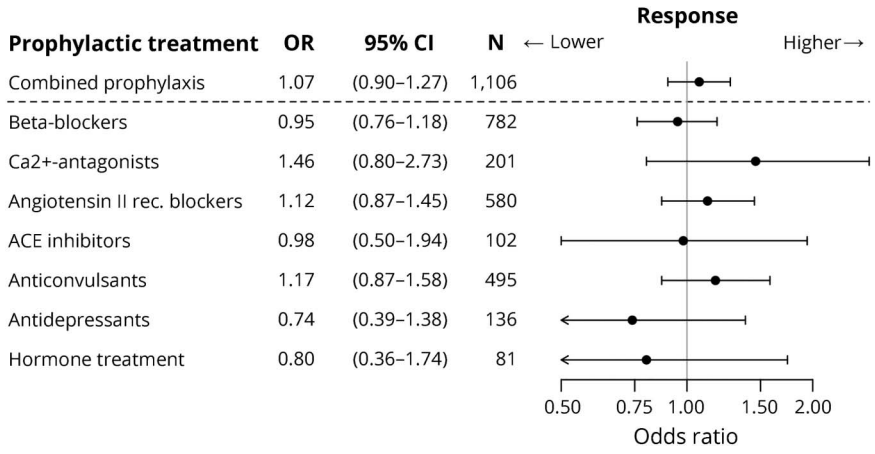
We show that the genetic burden of migraine is associated with the response to pharmacologic treatment. The PRS for migraine was statistically significantly associated with response to migraine-specific treatment: triptans and/or ergotamine. Neither the response to weak analgesics nor the response to prophylactic treatment, which are not migraine specific, was associated with the PRS.

Figure 1 Association of the polygenic risk score with acute treatment response



ORs and the 95% CI are shown on the left-hand side, and the corresponding forest plot is shown on the right-hand side. An OR below 1 represents a lower response rate to the drug. An OR above 1 represents a higher response rate to the drug. Migraine-specific acute treatment includes both triptan and ergotamine, as both are acting on the same 5-$HT_{1B/D}$ receptors. Migraine nonspecific treatment is represented by the weak analgesics. CI = confidence interval; OR = odds ratio.

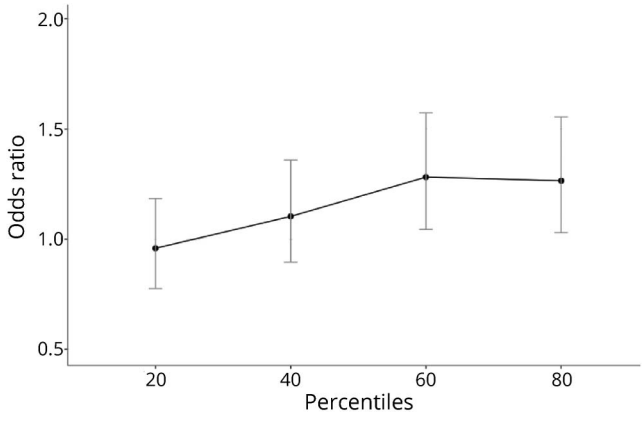
Figure 2 Associations of the polygenic risk score with prophylactic treatment response



ORs and the 95% CI are shown on the left-hand side, and the corresponding forest plot is shown on the right-hand side. An OR below 1 represents a lower response rate to the drug. An OR above 1 represents a higher response rate to the drug. Acute treatment includes both triptan and ergotamine, as both are acting on the same 5-$HT_{1B/D}$ receptors. Prophylactic treatment response includes all questioned treatments summed up (positive response to any prophylactic drug vs response to none). ACE = angiotensin-converting enzyme; CI = confidence interval; OR = odds ratio.

Genomics play an important role in the variability of drug response, which is best understood in relation to pharmacokinetics.[23,24] Recently, PRS studies have predicted drug response in psychiatric diseases. A PRS of major depressive disorder explained 1.2% of the antidepressant response.[25] In schizophrenia, no statistically significant association was found between the response to clozapine and PRS of schizophrenia, although not significant.[26] The PRS could not predict treatment-resistant schizophrenia,[6] but a lower PRS for schizophrenia was associated with a positive response to lithium in bipolar affective disorder.[5] A better understanding of the genetic contribution in migraine drug response could pave the road to personalized treatment of migraine or deepen our understanding of the underlying pathophysiology. Recently, a PRS of migraine has been associated with migraine (OR = 1.76), migraine subtypes (OR MO = 1.57; OR MA = 1.85), and severity of migraine (OR = 1.29).[27] Although information about migraine treatment response was not available in their cohort, they report a higher PRS among individuals who had self-reported use of triptans (OR = 1.12).

Figure 3 Replication of the association of the polygenic risk score (PRS) with acute treatment response



Odds ratio by PRS within each 20 percentiles for n = 5,616 triptan users in the Danish Blood Donor Study replication cohort.

Previously, the association between the cumulative genetic risk score, based on the count of number of risk alleles of 12 migraine-associated SNPs, and migraine drug response was investigated.[14] The OR was 1.09 (95% CI = 1.03–1.15) for acute treatment response, but no significant correlation of the cumulative genetic risk score with prophylactic treatment was found. In the current study, we found higher estimates than previously for acute treatment response. This may be a consequence of increased sample size in the discovery sample resulting in improved accuracy of the effect size of the genetic variants. Furthermore, the cumulative genetic risk score previously used is not comparable with this study, as we used a weighted risk score and included all genotyped SNPs.

Treatment response shows, for migraine as well as other conditions, a large inter-individual variation and, therefore, a precise measurement of positive treatment response is not easily defined. Many factors may affect treatment response, e.g., polypharmacy, comorbidity, and body mass index. To obtain enough power, we have analyzed the different drugs collectively, which may not be optimal, as a patient may not have tried all drugs questioned and, therefore, may be incorrectly defined as a nonresponder. Furthermore, although we used a semistructured interview, recall bias and negativity bias are inherent limitations. Our PRS is based on the effect sizes of common SNPs that explain an estimated 14.63% of the overall of the migraine phenotype.[12] Patients with migraine with a low PRS might nevertheless have a high genetic burden if they carry rare genetic variants with relatively high effect estimates. On the other hand, a high genetic burden of migraine may be associated with specific symptoms of migraine or, for example, severity of migraine. Patients in this study were recruited from the Danish Headache Center, which is a tertiary referral center. Patients therefore have

a relatively severe migraine. In other diseases, genes in the monoamine oxidase (MAO) A and cytochrome P450 superfamily are associated with drug response,[2,28] showing the genetic contribution of drug metabolic pathways. There is no evidence that those genes are interacting with migraine-associated genes, and therefore, those are not represented by the PRS. Future and larger studies may focus on other models, such as Bayesian methods extensively used in plant and animal breeding, and/or they may include epistatic interaction effects that potentially have a higher predictive power to predict the genetic risk score of patients with migraine.

While currently the effect size is too small to be clinically important, the study provides an important proof of concept. Furthermore, we were able to replicate the association in an independent cohort of Danish blood donors, although the response phenotype is affected by noise (sensitivity of 82% and a specificity of 66%). We expect that we will see increased predictive power with an increased sample size in the migraine GWAS and/or a future GWAS focusing on migraine treatment response. Thus, future studies might enable us to define more homogeneous groups of patients benefitting from specific treatments using genetic data. With the arrival of new migraine treatments, such as the novel but expensive calcitonin gene-related peptide antibodies, a genetic classifier to identify patients who are likely to benefit from the treatment could have great clinical impact.

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Disclosure

Disclosures available: Neurology.org/NG.

Publication history

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Appendix 1 Authors

Name	Location	Role	Contribution
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Thomas Folkmann Hansen, PhD	Rigshospitalet Glostrup, Denmark	Author	Conception and design of the study; acquisition and analysis of data; and drafting a significant portion of the manuscript or figures

Appendix 2 Members of the DBDS Genomic Consortium (DBDS-GC)

Name	Location	Role	Contribution
Daniel Gudbjartsson	deCODE Genetics, Reykjavik, Iceland	Member of the DBDS-GC	Acquisition of data
Omar Gastafsson	deCODE Genetics, Reykjavik, Iceland	Member of the DBDS-GC	Acquisition of data

Continued

Appendix 2 *(continued)*

Name	Location	Role	Contribution
Kari Stefansson	deCODE Genetics, Reykjavik, Iceland	Member of the DBDS-GC	Acquisition of data
Hreinn Stefansson	deCODE Genetics, Reykjavik, Iceland	Member of the DBDS-GC	Acquisition of data
Unnur Þorsteinsdóttir	deCODE Genetics, Reykjavik, Iceland	Member of the DBDS-GC	Acquisition of data
Steffen Andersen	Department of Finance, Copenhagen Business School, Denmark	Member of the DBDS-GC	Acquisition of data
Karina Banasik	Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark	Member of the DBDS-GC	Acquisition of data
Søren Brunak	Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark	Member of the DBDS-GC	Acquisition of data
Alfonso Buil	Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Copenhagen University Hospital, Roskilde, Denmark	Member of the DBDS-GC	Acquisition of data
Kristoffer Burgdorf	Department of Clinical Immunology, the Blood Bank, Rigshospitalet, Copenhagen University Hospital, Denmark	Member of the DBDS-GC	Acquisition of data
Christian Erikstrup	Department of Clinical Immunology, Aarhus University Hospital, Denmark	Member of the DBDS-GC	Acquisition of data
Thomas Folkmann Hansen	Danish Headache Center, Department of Neurology Rigshospitalet, Glostrup & Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Copenhagen University Hospital, Roskilde, Denmark	Member of the DBDS-GC	Acquisition of data
Henrik Hjalgrim	Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark	Member of the DBDS-GC	Acquisition of data
Jemec Gregor	Department of Clinical Medicine, Sealand University Hospital, Roskilde, Denmark	Member of the DBDS-GC	Acquisition of data
Poul Jennum	Department of Clinical Neurophysiology at University of Copenhagen, Denmark	Member of the DBDS-GC	Acquisition of data
Kasper Rene Nielsen	Department of Clinical Immunology, Aalborg University Hospital, Denmark	Member of the DBDS-GC	Acquisition of data
Mette Nyegaard	Department of Biomedicine, Aarhus University, Denmark	Member of the DBDS-GC	Acquisition of data
Helene Mariana Paarup	Department of Clinical Immunology, Odense University Hospital, Denmark	Member of the DBDS-GC	Acquisition of data
Ole Birger Pedersen	Department of Clinical Immunology, Naestved Hospital	Member of the DBDS-GC	Acquisition of data
Erik Sørensen	Department of Clinical Immunology, the Blood Bank, Rigshospitalet, Copenhagen University Hospital, Denmark	Member of the DBDS-GC	Acquisition of data
Henrik Ullum	Department of Clinical Immunology, the Blood Bank, Rigshospitalet, Copenhagen University Hospital, Denmark	Member of the DBDS-GC	Acquisition of data
Thomas Werge	Institute of Biological Psychiatry, Mental Health Centre Sct. Hans, Copenhagen University Hospital, Roskilde, Denmark & Department of Clinical Medicine, University of Copenhagen, Denmark	Member of the DBDS-GC	Acquisition of data

Appendix 3 Members of the International Headache Genetics Consortium (IHGC)

Name	Location	Role	Contribution
Verneri Anttila	Broad Institute of MIT and Harvard, Cambridge	Member of the IHGC	Acquisition of data
Ville Artto	Department of Neurology, Helsinki University Central Hospital, Finland	Member of the IHGC	Acquisition of data
Andrea Carmine Belin	Karolinska Institute, Stockholm, Sweden	Member of the IHGC	Acquisition of data
Irene de Boer	Leiden University Medical Centre, The Netherlands	Member of the IHGC	Acquisition of data

Appendix 3 *(continued)*

Name	Location	Role	Contribution
Dorret I. Boomsma	VU University, Amsterdam, The Netherlands	Member of the IHGC	Acquisition of data
Sigrid Børte	Oslo University Hospital and University of Oslo, Norway	Member of the IHGC	Acquisition of data
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Lynn Cherkas	Department of Twin Research and Genetic Epidemiology, King's College London, UK	Member of the IHGC	Acquisition of data
Anne Francke Christensen	Danish Headache Center, Department of Neurology, Rigshospitalet, Glostrup Hospital, University of Copenhagen, Denmark	Member of the IHGC	Acquisition of data
Bru Cormand	University of Barcelona, Spain	Member of the IHGC	Acquisition of data
Ester Cuenca-Leon	Broad Institute of MIT and Harvard, Cambridge	Member of the IHGC	Acquisition of data
George Davey-Smith	Medical Research Council (MRC) Integrative Epidemiology Unit, University of Bristol, UK	Member of the IHGC	Acquisition of data
Martin Dichgans	Institute for Stroke and Dementia Research, Munich, Germany	Member of the IHGC	Acquisition of data
Cornelia van Duijn	Erasmus University Medical Centre, Rotterdam, The Netherlands	Member of the IHGC	Acquisition of data
Tonu Esko	Estonian Genome Center, University of Tartu, Estonia	Member of the IHGC	Acquisition of data
Ann-Louise Esserlind	Danish Headache Center, Department of Neurology, Rigshospitalet, Glostrup Hospital, University of Copenhagen, Denmark	Member of the IHGC	Acquisition of data
Michel Ferrari	Leiden University Medical Centre, The Netherlands	Member of the IHGC	Acquisition of data
Rune R. Frants	Leiden University Medical Centre, The Netherlands	Member of the IHGC	Acquisition of data
Tobias Freilinger	University of Tuebingen, Germany	Member of the IHGC	Acquisition of data
Nick Furlotte	23andMe Inc., Mountain View	Member of the IHGC	Acquisition of data
Padhraig Gormley	Broad Institute of MIT and Harvard, Cambridge	Member of the IHGC	Acquisition of data

Appendix 3 *(continued)*

Name	Location	Role	Contribution
Lyn Griffiths	Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia	Member of the IHGC	Acquisition of data
Eija Hamalainen	Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Finland	Member of the IHGC	Acquisition of data
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Risto Kajanne	Institute for Molecular Medicine Finland (FIMM), University of Helsinki	Member of the IHGC	Acquisition of data
Mikko Kallela	Department of Neurology, Helsinki University Central Hospital, Finland	Member of the IHGC	Acquisition of data
Jaakko Kaprio	Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Finland	Member of the IHGC	Acquisition of data
Mari Kaunisto	Folkhälsan Institute of Genetics, Helsinki, Finland	Member of the IHGC	Acquisition of data
Lisette J.A. Kogelman	Danish Headache Center, Department of Neurology, Rigshospitalet, Glostrup Hospital, University of Copenhagen, Denmark	Member of the IHGC	Acquisition of data
Christian Kubisch	University Medical Center Hamburg-Eppendorf, Germany	Member of the IHGC	Acquisition of data
Mitja Kurki	Broad Institute of MIT and Harvard, Cambridge	Member of the IHGC	Acquisition of data
Tobias Kurth	Harvard Medical School, Boston	Member of the IHGC	Acquisition of data
Lenore Launer	National Institute on Aging, Bethesda	Member of the IHGC	Acquisition of data
Terho Lehtimaki	School of Medicine, Unviersity of 3 Tampere, Finland	Member of the IHGC	Acquisition of data

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Appendix 3 *(continued)*

Name	Location	Role	Contribution
Davor Lessel	University Medical Center Hamburg-Eppendorf, Germany	Member of the IHGC	Acquisition of data
Lannie Ligthart	VU University, Amsterdam, The Netherlands	Member of the IHGC	Acquisition of data
Nadia Litterman	23andMe Inc., Mountain View	Member of the IHGC	Acquisition of data
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Alfons Macaya	Vall d'Hebron Research Institute, Barcelona, Spain	Member of the IHGC	Acquisition of data
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Massimo Mangino	Department of Twin Research and Genetic Epidemiology, King's College London, UK	Member of the IHGC	Acquisition of data
George McMahon	Medical Research Council (MRC) Integrative Epidemiology Unit, University of Bristol, UK	Member of the IHGC	Acquisition of data
Bertram Muller-Myhsok	Max Planck Institute of Psychiatry, Munich, Germany	Member of the IHGC	Acquisition of data
Benjamin M. Neale	Broad Institute of MIT and Harvard, Cambridge	Member of the IHGC	Acquisition of data
Carrie Northover	23andMe Inc., Mountain View	Member of the IHGC	Acquisition of data
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Jes Olesen	Danish Headache Center, Department of Neurology, Rigshospitalet, Glostrup Hospital, University of Copenhagen, Denmark	Member of the IHGC	Acquisition of data
Aarno Palotie	Broad Institute of MIT and Harvard, Cambridge	Member of the IHGC	Acquisition of data
Priit Palta	Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Finland	Member of the IHGC	Acquisition of data
Linda Pedersen	Oslo University Hospital and University of Oslo, Norway	Member of the IHGC	Acquisition of data
Nancy Pedersen	Karolinska Institutet, Stockholm, Sweden	Member of the IHGC	Acquisition of data
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Markus Schürks	Harvard Medical School, Boston	Member of the IHGC	Acquisition of data
Celia Sintas	University of Barcelona, Spain	Member of the IHGC	Acquisition of data
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Hreinn Stefansson	deCODE Genetics Inc., Reykjavik, Iceland	Member of the IHGC	Acquisition of data
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Bendik S. Winsvold	Oslo University Hospital and University of Oslo, Norway	Member of the IHGC	Acquisition of data
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