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

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Abstract

Introduction: Migraine is a prevalent and disabling disease with an incompletely understood etiopathology. **Aims and objectives:** The basic aim of the study is to analyse the migraine polygenic risk score associates with efficacy of migraine-specific drugs. **Material and methods:** This descriptive study was conducted in Baqai MedicalUniversity, Karachi during August 2019 till December 2019. The data was collected with the permission of ethical committee of hospital. The data was collected through a qualitative method. All patients with migraine were interviewed face to face or by telephone by a trained physician or trained senior medical student using a semi-structured interview. The semistructured interview included questions covering the necessary clinical data for migraine diagnoses and information on the effect of migraine treatment. **Results:** The data consisting of 200 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. **Conclusion:** It is concluded that PRS may be useful in the investigation of shared genetic risk with comorbidities, in studying the relation between primary headache disorders and their sub-forms, and to personalize migraine treatment.

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Introduction

Migraine is a prevalent and disabling disease with an incompletely understood etiopathology. The hereditary component of migraine, i.e. the proportion of individual differences explained by genetic variation in migraine, is estimated to be between 38 and 53% and is likely to arise from the combined effect of many common risk variants each with small effect sizes, thus characterizing migraine as a common complex, polygenic disease [1].

There is a wide range of allelic variation in human disease genes, and one common form of variation is the Single Nucleotide Polymorphism (SNP). SNPs have been valuable as genomic “markers” in the search for causal variants that influence susceptibility to common diseases, or as causal variants with marginal effect [2]. The most common way to discover common variants is through Genome-Wide Association Studies (GWAS). A GWAS is based on the common-disease common-variant (CDCV) hypothesis and seeks to explore many SNPs randomly distributed across the human genome [3]. A GWAS is a relatively simple way to test multiple SNPs and their contribution to disease susceptibility by comparing risk allele frequencies in cases against healthy controls [4].

To date, 38 genetic loci with common SNPs associated with migraine have been discovered [5], where the individual SNP only explains a marginal proportion of the genetic variance. Calculating the Polygenic Risk Score (PRS) is one way to assess the additive effect of several (associated) SNPs [6]. Using a PRS calculated from sufficiently powered studies is a better way to estimate the genetic variance of the disease assessed than the individual genome-wide significant SNPs [7]. Further, some PRS methods allow researchers to assess genetic overlaps between comorbid diseases, i.e. genetic correlations, which have previously only been identified by epidemiological or clinical studies [8].

Migraine is a polygenic disorder with an estimated heritability of 40%–60% and a worldwide prevalence of 18%. 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 [10].

Aims and objectives

The basic aim of the study is to analyse the migraine polygenic risk score associates with efficacy of migraine-specific drugs.

Material and methods

This descriptive study was conducted in Baqai MedicalUniversity, Karachi during August 2019 till December 2019. The data was collected with the permission of ethical committee of hospital. The data was collected through a qualitative method. All patients with migraine were interviewed face to face or by telephone by a trained physician or trained senior medical student using a semi-structured interview. 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.

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 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.

Results

The data consisting of 200 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. 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 ($p = 0.03$).

Table 01: Analysis of response rate of acute and prophylactic drugs in patients with MO and MA

	% (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

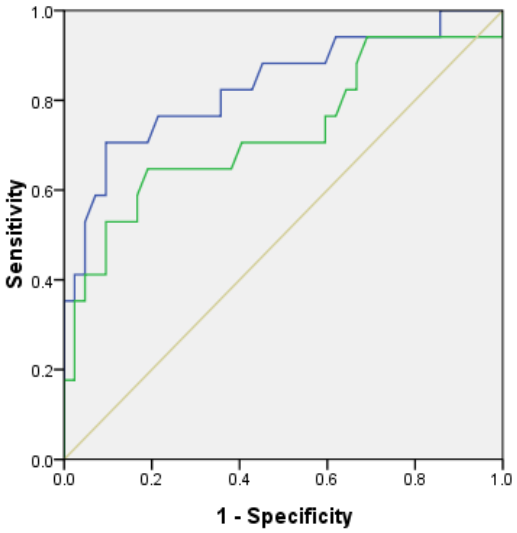

Figure 01: ROC curve of specificity and sensitivity of drugs

Discussion

It should be noted that the performance of the PRS is influenced by several parameters such as the underlying genetic architecture of the disease in terms of the number of causal variants and whether these have an additive effect, the effect sizes of individual causal variants, and allele frequency at the causal variants [11]. As an example, a larger discovery sample is necessary if the genetic architecture consists of many low frequent variants with small effect sizes, as opposed to a genetic architecture that has fewer frequent variants with relatively high effect sizes.

Thus, the PRS performance relies on the sample size; by increasing the discovery sample, the variance explained increases, which further increases the accuracy of the PRS for each individual [12]. Furthermore, it has been estimated that when a target sample reaches ~ 2000 cases there should be sufficient power to detect a variance that is different from zero. Other factors that may influence PRS performance may be the heterogeneity of the phenotype,

which paradoxically is often compromised in GWAS studies in the need for large sample sizes and better prediction power [13].

Most studies of shared genetics have been investigated in bi- and multivariate twin model studies. These studies were hampered by the need for large twin cohorts with two or more traits of interest. A great opportunity is therefore offered by PRS analysis which may confirm these findings, and enable further investigation at a genotype level [14]. Two migraine studies using a PRS based on small migraine GWAS datasets have already been performed. These studies compared the PRS in migraine and two important migraine co-morbidities; depression and stroke [15].

Ligthart et al. found genetic components shared between migraine and major depressive disorder (MDD). The PRS derived from GWAS on MDD could significantly predict the comorbid MDD and migraine phenotype ($P = 0.0015$), but the MDD PRS could not predict migraine without comorbid MDD ($P = 0.058$). It is important that the discovery and target sample are independent. Thus, patients of the same ethnicity as the target sample are often excluded from the discovery sample to avoid an overestimation of the effects of the PRS [16].

Conclusion

It is concluded that PRS may be useful in the investigation of shared genetic risk with comorbidities, in studying the relation between primary headache disorders and their sub-forms, and to personalize migraine treatment. 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.

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