gene, a significantly lower proportion of subjects suffering from schizophrenia carried the rs2717 A/G genotype when compared with healthy control subjects ($p = 0.01$); with respect to rs6926279, a significant lower proportion of subjects suffering from schizophrenia carried the C/T genotype when compared with healthy control subjects ($p = 0.02$). About the EPM2A gene, we found a lower proportion of subjects suffering from schizophrenia carried the rs702304 G/A genotype compared to the healthy subjects ($p = 0.02$). Finally, the G/G genotype and the G allele of rs2235481 were found in a greater proportion of schizophrenia patients compared to the healthy controls ($p < 0.001$ and $p = 0.002$, respectively). No further significant difference was observed between the two groups concerning the remaining genotype and allelic frequencies. With regard to the influence of the investigated polymorphisms on clinical improvement, repeated-measure ANOVA showed a significant effect of rs1415744 within the EPM2A gene and clinical improvement in the PANSS negative subscale ($p = 0.02$). The results remained the same after inclusion of the covariates and were partially confirmed in the allelic and haplotype analyses.

Conclusion: Our preliminary findings suggest that rs2717 and rs6926279 within the NMBR gene and rs702304 and rs2235481 within the EPM2A gene could be associated with schizophrenia susceptibility. Further, the investigated EPM2A gene variants could be associated with the antipsychotic response of negative symptomatology. Nonetheless, further research is needed to confirm our findings.

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P.1.a.004 Financial hardship may trigger migraine through circadian dysregulation – a possible role for the CLOCK gene

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Objectives: Patients with mood disorder often show biological rhythm-related symptoms, and evidence suggest connection between mood disorders and different circadian genes [1]. There is a well-known comorbidity between migraine and mood disorders, with an overlap in their genetic factors [2], and migraine attacks are frequently triggered by different external and internal changes in rhythmicity – such as stress, hormonal fluctuations, weather changes, sleep deprivation and other alterations of daily routine [3]. Therefore, circadian genes could also play a role in migraine. The CLOCK gene is a central component of the circadian clock, a transcriptional activator effecting the transcription of downstream circadian genes; and it has been associated with mood disorders [1], thus it's a good canditate gene for migraine, too. Our goal was to test two functional SNPs of the circadian CLOCK gene (rs10462028 and rs3749474) to identify their possible influence on migraine.

Methods: 2349 subjects (720 males and 1629 females) were recruited through general practices and advertisements from Manchester ($n = 1350$) and Budapest ($n = 999$) (aged between 18 and 60). The probability of migraine status was measured by the ID-Migraine Questionnaire. Chronic stress was defined by financial status derived from the background questionnaire of the study. Genomic DNA was extracted from buccal mucosa cells. The main effect of the CLOCK gene SNPs and the SNPs x chronic stress interaction effects were tested on migraine using logistic regression models with additive, dominant and recessive models in the total population and in both subpopulations. All statistical models were adjusted for population, gender and age. Statistical analyses were made using PLINK 1.9 and IBM SPSS Statistics 23.

Results: None of the SNPs showed main genetic effects on possible migraine, but both of them showed significant interaction with financial status on possible migraine (for rs10462028: $OR = 0.79$, $p < 0.001$; for rs3749474: $OR = 1.22$, $p < 0.05$). The significant effects of the SNPs (except one) were replicated in the subpopulations (in Manchester: for rs10462028: $OR = 0.52$, $p < 0.05$; for rs3749474: not significant; and in Budapest: for rs10462028: $OR = 0.6$, $p < 0.001$; for rs3749474: $OR = 1.6$, $p < 0.05$).

Conclusions: Our results suggest that the CLOCK gene might have a role in migraine in the presence of chronic stress represented by financial hardship. Thus, financial difficulties may trigger migraine by influencing circadian rhythmicity. Dysregulation of the circadian clock has also been implicated in the pathogenesis of various diseases (such as seasonal affective disorder, hypertension, asthma and cancer) [4], therefore a stress-elicited circadian dysregulation in migraineurs could be a factor in the onset of other illnesses, too. The investigated SNPs in the CLOCK gene affect miRNA binding, and evidence suggest that miRNAs have a distinct role in clock physiology, therefore they present novel therapeutic targets for diseases related to the circadian rhythm [4]. Further investigation of the potential functions of circadian genes in the pathophysiology of migraine, especially in patients with serious life stressors, may provide new treatment strategies.

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P.1.a.005 Genome-wide gene-based tests replicate the association of the SORCS3 gene with neuroticism

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Introduction: Among the Big Five personality dimensions, neuroticism has the strongest phenotypic as well as genotypic correlations with lifetime major depression [1]. Previous genome-wide association studies (GWAS) have applied SNP (single nucleotide polymorphism)-based and gene-based tests to find SNPs and genes in the background of neuroticism. However, in those GWAS implementing gene-based tests, only one method was used.

Aim: In the present study, we conducted a GWAS on neuroticism, both with SNP-based and with five distinct gene-based tests.

Methods: Among a European white sample (N = 1770) recruited in Budapest and Manchester, linear regression models were run with each of the genome-wide genotyped 86,232 SNPs, gender, age and the top ten principal components of the genome as predictor variables, and neuroticism as the outcome. The yielded SNP-based results then served as the input of the gene-based GATES test. False discovery rate (FDR) method was used to correct for multiple testing both at the SNP- and the gene-level, with an error rate of 0.05. As post hoc tests without correction, four additional gene-based tests were implemented according to FORGE and SETSCREEN methods.

Results: 63,326 SNPs (64.46% of all) reside within genes, and 18,264 genes were identified. None of the SNPs or genes survives the FDR correction. However, among the more than fifty genes identified as candidates in previous neuroticism GWAS studies either by a gene-based test or by locating any significant SNP into a gene, we found that TACC2 (transforming acidic coiled-coil containing protein 2) and SORCS3 (sortilin related VPS10 domain containing receptor 3) genes are nominally significant ($p \leq 0.05$) to neuroticism in our study (Table 1). Nonetheless, TACC2 does not show any significant ($p \leq 0.05$) association with neuroticism according to our post hoc gene-based tests, but the effect of SORCS3 is significant in all of the four tests (Table 1).

Conclusion: Our GWAS study is the first one to report the gene-level association of the SORCS3 gene with neuroticism, since the original GWAS from which we chose this gene for replication did not use a gene-based, but only a SNP-based approach [2]. Moreover, we further underpinned this gene-personality association with four additional methods. SORCS3 SNPs have been reported to be associated with Alzheimer's disease, and the expression level of this gene was lower in Alzheimer's patients' than in controls' amygdala, but there was no such between-group difference in occipital lobe or cerebellum [3]. Given the well-grounded importance of the amygdala in depression risk and neuroticism, further studies are needed to elucidate the precise role of the SORCS3 gene and SORCS3 protein in neuroticism and depression, and to reveal whether or not their association with Alzheimer's disease is mediated by this personality trait.

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Table 1. (Abstract P.1.a.005) Gene-based methods to assess the association of neuroticism with two genes reported in previous GWAS.

	GATES method	Post hoc tests				
Gene	Nominal P value	FDR-corrected P value	FORGE PSidak	FORGE Zfix	SETSCREEN P1	SETSCREEN P2
TACC2	0.0449	0.9696	0.9089	0.9857	0.9599	0.9698
SORCS3	0.0130	0.9296	0.0201	0.0106	0.0177	0.0437