**Investigation of candidate genes reveals significant statistical epistasis between DISC1 and TPH2 in Bulgarian affective disorder patients**

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**ABSTRACT**

The aim of the present study was to search for joint influence of variants in affective disorder (AD) candidate genes by investigating statistical epistasis. Overall 24 single nucleotide polymorphisms (SNPs) in 9 AD candidate genes were analysed in 304 AD cases (270 bipolar disorder (BD) type I; 29 BD type II; 5 schizoaffective disorder bipolar type, 110 major depressive disorder) and 205 healthy prescreened controls. The results demonstrated statistical epistasis between variants in DISC1, TPH2, CRH, CLOCK, BDNF, ANK3 and SLC6A4. Multiple interactions involving TPH2, both protective and increasing the AD risk, were detected. Protective epistasis surviving Bonferroni correction was observed between DISC1 and TPH2, justifying further analysis, given their role in neurogenesis and synaptic plasticity and serotonin biosynthesis.

**Introduction**

Affective disorders (AD) arise from complex interactions of genetic, environmental and developmental factors and epistasis between them has been described in bipolar disorder (BD) [1]. Epistasis between dopamine and serotonin systems genes has been reported in different psychopathologic conditions [2–4]. Despite the extensive investigations of neuroplasticity candidate-genes such as DISC1 (Disrupted in schizophrenia 1) and BDNF (Brain-derived neurotrophic factor), not many have considered epistasis. Meanwhile, genome-wide association studies (GWAS) meta-analysis has identified the strongest association with BD for variants in CACNA1C (Calcium channel, voltage-dependent 1C subunit) and ANK3 (Ankyrin-3), participating in channels clustering and in membrane structural maintenance [5]. Two other studies have drawn the attention to the interaction between membrane channels genes and circadian rhythm pathways [1,6]. The aim of this study was to investigate the interaction between different polymorphisms in candidate genes and to test hypotheses based on neurotransmission, neuroplasticity changes and inefficient communication between neurons in AD.

**Subjects and methods**

The cohort consisted of 304 AD cases (270 BD type I; 29 BD type II; 5 schizoaffective disorder bipolar type (SAD), 110 major depressive disorder (MDD)) and 205 healthy controls matched by gender, ethnicity and age. The AD cases were assessed with SCAN [7] and DIP [8]. All cases met the DSM-IV criteria [9] and all participants provided written informed consent. The study was approved by the Ethics Committee at the Medical University of Sofia.

Genomic DNA was extracted from venous blood (Chemagen, PerkinElmer, Waltham, MA, U.S.A.). Genotyping of 24 single nucleotide polymorphisms (SNPs) in nine candidate genes (Disrupted in schizophrenia 1 (DISC1), Circadian Locomotor Output Cycles Kaput (CLOCK), Corticotropin releasing hormone (CRH), Ankyrin 3 (ANK3), Brain derived neurotrophic factor (BDNF), Dopamine receptor D2 (DRD2), Calcium voltage-gated channel subunit alpha1 C (CACNA1C), Tryptophan hydroxylase 2 (TPH2) and Solute carrier family 6 member 4 (SLC6A4)) was performed with the TaqMan™ method (Applied Biosystems), with a call rate for 384 plates over 95%.

The investigated variants were: DISC1 – rs3738401 (Arg264Gln), rs6675281 (Leu607Phe), rs821577, rs821616...
(Ser704Cys), rs980989; CLOCK – rs3805154; CRH – rs12721510; ANK3 – rs9804190, rs10994336; BDNF – rs6265 (Val66Met), rs16917237, rs12273363; DRD2 – rs6277 (957C/T), rs12800853, rs7350522, rs6589377; CACNA1C – rs1006737; TPH2 – rs4570625 (703G/T), rs11178998 (A90G), rs1386483, rs4290270 (A57T), rs1872824; SLC6A4 – rs12150214 and HTTPPR.

All statistical analyses were conducted with PLINK [10] and SPSS [11] under narrow affection status definition (A1) including subjects with BD I, BD II and SAD and under broad definition (A2) where MDD patients were also included. Hardy–Weinberg equilibrium test, two-tailed Pearson and Fisher exact tests, as well as screening test for strong linkage disequilibrium (LD), integrated in PLINK were applied. The case–control epistasis function of PLINK was used as a screening method for evaluation of the statistical interaction between SNP pairs. Multinomial logistic regression was applied for more detailed examination of the gene–gene interactions. In certain cases, when dividing the sample into nine subpopulations in order to determine the interaction between possible genotype combinations, no estimation could be performed because some groups did not include a sufficient number of cases and singularities in Hessian matrix were displayed by the SPSS program. In these cases, the categories were merged and allele interaction was examined instead of genotype.

Results and discussion

No deviation from the Hardy–Weinberg equilibrium was detected and strong linkage disequilibrium was excluded. Significant association was detected under narrow phenotype definition (A1) for allele G of rs16917237 in BDNF with higher frequency among patients (78.4%) compared to controls (70.9%); $p = 0.015$ and allele C of rs12150214 in SLC6A4, with higher frequencies, respectively, in patients (22.4%) compared to controls (14.8%); $p = 0.01$.

Statistical epistasis with protective effect between variants in DISC1, BDNF, CLOCK, TPH2, SLC6A4, CRH and ANK3 were detected and, furthermore, one of the interactions between DISC1 and TPH2 survived the conservative Bonferroni correction. Epistasis with increasing the AD risk effect was observed between DISC1 and CRH as well as DISC1 and TPH2. The results are summarized in Tables 1 and 2.

**DISC1–TPH2**

The genetic variant rs6675281 (DISC1) was found to interact with three consequently situated SNPs in the TPH2 gene. Both protective interactions and interactions contributing to increased AD risk were detected. The obtained results were suggestive of protective epistasis between allele C of rs6675281 (DISC1) and rs4290270 and rs1872824 (TPH2) as well as between allele A of rs821616 (DISC1) and allele G of rs1386483 (TPH2). Interaction contributing to increased AD risk was observed between allele C of rs6675281 (DISC1) and allele G of rs1386483 (TPH2).

The interaction surviving Bonferroni correction was shown to be protective. It is between allele A (Ser) of rs821616 (DISC1), which is associated with grey matter volume alterations [12] and increased functional but decreased anatomical connectivity in healthy individuals [13], and allele G of rs1386483 (TPH2). The literature review showed epistasis of the non-synonymous DISC1 polymorphism rs821616 (Ser704Cys) with COMT and NDP1 variants influencing schizophrenia [14] and having impact on DISC1 binding capacity with the neurodevelopment proteins NDE1 and NDEL1 [15]. Apart from the protective interaction involving rs821616 in DISC1, epistasis of allele G of rs1386483 (TPH2) with rs6675281 (DISC1) was observed to be associated with elevated AD risk. Similar context-dependent influence for the TPH2 variant has been described to have impact on impulsivity [16], a common trait in AD psychopathology.

Although there are multiple cases of evidence of association with psychiatric disorder traits for allele C of rs6675281 [12,17], to the best of our knowledge, no data of interaction had been previously reported. Interestingly, rs821616 and rs6675281 jointly have been also reported to influence cortical thinning [18].

Our findings indicated rs6675281 influence only through interaction and demonstrated DISC1 and TPH2 epistasis with greater significance in the more heterogeneous group when BD and MDD patients were investigated together. This can reflect relatedness to a common endophenotype for both affective disorders. Another plausible explanation could be that a higher statistical power of the combined sample is achieved, allowing us to detect such influences. These results justify the need of further analysis, given the crucial role of DISC1 in neurogenesis and synaptic plasticity, the functional effect of some of the polymorphisms in the epistasis and the TPH2 role in the serotonin biosynthesis as a rate-limiting enzyme.

**DISC1 rs980989–BDNF rs16917237/CLOCK rs3805154**

Protective epistasis of allele G of rs980989 in DISC1, which has been reported to influence cognitive traits and psychomotor processing speed [19], with allele G of rs16917237 in BDNF, as well as with allele C of rs3805154...
Table 1. Significant statistical epistasis with protective effect ($p < 0.05$).

| Locus 1 | Locus 2 | Case-control test | Regression analysis | Pseudo $R^2$ |
|---------|---------|-------------------|--------------------|-------------|
| Gene    | SNP     | Chr   | Gene    | SNP     | Chr   | $P$ | AS | $B$ | OR | $p$ | AS | $R^2$ |
| DISC1   | rs6675281 | 1     | TPH2    | rs4290270 | 12    | 0.04 | A2 | -2.64 | 0.07 | 0.02 | A2 | 0.04 |
| DISC1   | rs6675281 | 1     | TPH2    | rs4290270 | 12    | 0.04 | A1 | -2.56 | 0.08 | 0.03 | A1 | 0.05 |
|          |         |       |         | rs1872824 | 12    | 0.005 | A2 | -1.43 | 0.24 | 0.005* | A1 | 0.04 |
| DISC1   | rs6675281 | 1     | TPH2    | rs4290270 | 12    | 0.005 | A2 | -2.61 | 0.07 | 0.02 | A2 | 0.05 |
| DISC1   | rs6675281 | 1     | TPH2    | rs4290270 | 12    | 0.005 | A2 | -1.43 | 0.24 | 0.004* | A2 | 0.03 |
| DISC1   | rs980989  | 1     | CLOCK   | rs3805154 | 4     | 0.03 | A2 | -1.61 | 0.20 | 0.008* | A2 | 0.02 |
| DISC1   | rs980989  | 1     | CLOCK   | rs3805154 | 4     | 0.03 | A2 | -1.03 | 0.36 | 0.02 | A2 | 0.03 |
| CLOK    | rs3805154 | 1     | BDNF    | rs16917237 | 11    | 0.02 | A2 | -0.82 | 0.44 | 0.03 | A2 | 0.02 |
| CLOK    | rs3805154 | 1     | BDNF    | rs16917237 | 11    | 0.04 | A1 | -1.03 | 0.36 | 0.03 | A1 | 0.03 |
| CRH     | rs12721510 | 8     | ANK3    | rs9804190 | 10    | 0.03 | A1 | -0.92 | 0.40 | 0.04 | A2 | 0.02 |
| CRH     | rs12721510 | 8     | ANK3    | rs9804190 | 10    | 0.04 | A2 | -1.55 | 0.21 | 0.02 | A1 | 0.02 |
| SLC6A4  | 5-HTTLPR | 17    | TPH2    | rs1386483 | 12    | NS | A1 | -1.45 | 0.23 | 0.02 | A2 | 0.02 |
| SLC6A4  | 5-HTTLPR | 17    | TPH2    | rs1386483 | 12    | 0.04 | A2 | -3.14 | 0.04 | 0.01 | A1 | 0.04 |
|         |         |       |         | rs1386483 | 12    | 0.04 | A2 | -2.89 | 0.06 | 0.02 | A1 | 0.04 |
| AS, affection status; Chr, chromosome; $R^2$, maximum pseudo $R^2$. * Statistical significance surviving Bonferroni correction.
in **CLOCK** were identified under the A2 definition. The regression analysis replicated the previously reported tendency for the two to participate in the interaction alleles of rs980989 and rs16917237 in Bulgarian AD patients [20,21]. Since **DISC1** and **BDNF** are both involved in neuronal development, migration and synapse formation, the identified epistasis may reflect true biological interaction and participation in common networks influencing AD aetiology. This hypothesis received further support by two studies of animal models where investigation of Disc1-knockout mice revealed **DISC1**-mediated regulation of synaptic plasticity across specific trimeric complex [22] and the analysis of mice lacking one of these complex components described dendritic localization impairment and BDNF-induced synthesis of one of the complex components [23]. The identified epistasis of **DISC1** with **CLOCK**, which encodes a transcription factor participating in circadian rhythms and sleep control, further supports the possible influence of **DISC1** on circadian rhythms as suggested in a study reporting association of a particular **DISC1** expression profile with altered sleep in *Drosophila* [24].

**CLOCK rs3805154–BDNF rs16917237**

The **CLOCK** variant (rs3805154, allele C) participates in another protective interaction with allele G of rs16917237 of **BDNF** for which no data of epistasis is available. However, there are some reports on interactions with the functional rs6265 in the same gene instead [2,3,23,25,26]. Although rs6265 was investigated in our study, no interaction was identified in our cohort.

Interactions with the participation of **CLOCK** variants were reported to influence sleep disturbances, often observed in AD patients [27]. Simultaneously, physiological data have demonstrated that BDNF can potentiate glutamate-induced phase shifts of the circadian rhythm [28] and that oscillation in BDNF expression is related to circadian variations in normal individuals [29]. A systematic analysis of the functional gene networks involved in chronic stress-related lifestyle diseases pointed out **CLOCK** and **BDNF** as genes having crucial role on depression [30], confirming the potential relationship between them.

**CRH rs12721510–DISC1 rs821577/ANK3 rs9804190**

Participation of rs12721510 (**CRH**) in both protective and increasing AD risk epistasis was observed. The interaction between genotype C/C of rs12721510 (**CRH**) and rs821577 (**DISC1**, genotype G/G), which is associated with BD and high social anhedonia [31], increases the AD risk. This is in line with the reported participation of rs821577 in the interplay increasing or decreasing the BD risk [31].

The protective interaction between the C allele of the **CRH** variant and allele C of rs9804190 in **ANK3** supports **ANK3** engagement in epistasis influencing BD as outlined before [1,6]. The **ANK3** variant has also been associated with BD [32], posttraumatic stress disorder [33], lower mRNA expression [34] and working memory circuit [35].

**Table 2. Significant statistical epistasis increasing the AD risk (p < 0.05).**

| Locus 1 | Locus 2 | Plink | Regression analysis | Pseudo R² |
|---------|---------|-------|---------------------|-----------|
| Gene    | SNP     | Chr   | Gene    | SNP     | Chr   | Case-control test | Regression analysis | P | AS | B | OR | p | AS | R² |
| **DISC1** | rs6675281 | 1   | **TPH2** | rs1386483 | 12 | 0.02 | A2 | 1.71 | 5.54 | 0.02 | A2 | 0.02 |
| **DISC1** | rs821577 | 1   | **CRH** | rs12721510 | 8 | 0.03 | A1 | 2.63 | 13.91 | 0.04 | A1 | 0.02 |
| **DISC1** | rs821577 | 1   | **CRH** | rs12721510 | 8 | 0.03 | A2 | 2.64 | 14.0 | 0.04 | A2 | 0.02 |

**Note:** The *p*-values presented are unadjusted for the multiple testing.

**TPH2 rs1386483 – SLC6A4 5-HTTLPR**

Another protective epistasis was detected between genotypes GG and GA of rs1386483 in **TPH2** and genotype LL of 5-HTTLPR in SLC6A4, whose product is targeted by antidepressants. This finding corresponds to the described epistasis between the same genes predicting novelty seeking in women with bulimia nervosa [36].

**SLC6A4** variants participate in interactions having impact on stress resilience [37] and MDD risk [38], while in the present cohort, the detected influence was both on MDD and BD risk. A few studies have described epistasis between **SLC6A4** and **BDNF** having influence on different psychiatric conditions [4], although no interaction could be detected in the present cohort. A recent study described a novel interaction between **TPH2** and **BDNF** polymorphisms related to behavioural inhibition of negative emotions in healthy adults [39].
Limitations and future perspectives

Overall, the interpretation of the results obtained in this study should be considered in the light of some limitations of the study. The logistic regression demonstrated maximum pseudo $R^2$ of 0.05, indicating that a relatively small fraction of the AD susceptibility variance could be attributed to the interaction between the investigated polymorphisms.

The statistical epistasis gives an opportunity for revealing the influence of genetic variants on certain phenotypes in the context of epistasis. However, the presence of statistical epistasis does not necessarily correspond to participation in joint biological mechanisms and may occur by chance. The cohort size in the present study was not sufficient to detect epistasis between genotypes, as there were not enough available observations for all of them. Notwithstanding the exploratory character of the obtained results, they could be helpful for prioritization in future studies, possibly with larger cohorts and more rigorous phenotype definition.

Conclusions

In this study, multiple statistical interactions – both protective and increasing the AD risks – between variants in DISC1, TPH2, CRH, CLOCK, BDNF, ANK3 and SLC6A4 genes were identified. Epistasis with protective effect was detected between variants in DISC1, BDNF and CLOCK as well as between TPH2–SLC6A4 and CRH–ANK3, whereas an effect increasing the AD risk was observed for the interaction between CRH and DISC1. The identified protective epistasis between variants in DISC1 and TPH2 survived Bonferroni correction. The obtained results lay the ground for further studies.

Disclosure statement

No conflicts of interest have been reported by the authors.

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