Biotechnology & Biotechnological Equipment

ISSN: 1310-2818 (Print) 1314-3530 (Online) Journal homepage: https://www.tandfonline.com/loi/tbeq20

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To cite this article: Mina Ivanova-Stoevska, Mladen Penchev, Vessela Stoyanova, Rossitza Vladimirova, Vihra Milanova, Ivo Kremensky, Vanio Mitev & Radka Kaneva (2017) Investigation of candidate genes reveals significant statistical epistasis between *DISC1* and *TPH2* in Bulgarian affective disorder patients, Biotechnology & Biotechnological Equipment, 31:6, 1178-1183, DOI: 10.1080/13102818.2017.1382391

To link to this article: https://doi.org/10.1080/13102818.2017.1382391

Published online: 25 Sep 2017.

BIOTECHNOLOGY & BIOTECHNOLOGICAL EQUIPMENT, 2017
VOL. 31, NO. 6, 1178–1183
https://doi.org/10.1080/13102818.2017.1382391

Taylor & Francis
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ARTICLE; MEDICAL BIOTECHNOLOGY

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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.

ARTICLE HISTORY
Received 2 May 2017
Accepted 18 September 2017

KEYWORDS
rs6675281; rs1872824; interaction

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

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(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 HTTPR.

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 *NDE1* 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			Plink 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					
	rs6675281=CC * rs4290270=AA							−2.64	0.07	0.02	A2	0.04
DISC1	rs6675281	1	*TPH2*	rs1872824	12	0.005	A1					
	rs6675281=CC * rs1872824=AA							−2.56	0.08	0.03	A1	0.05
	rs6675281=C * rs1872824=A							−1.43	0.24	0.005*	A1	0.04
DISC1	rs6675281	1	*TPH2*	rs1872824	12	0.005	A2					
	rs6675281=CC * rs1872824=AA							−2.61	0.07	0.02	A2	0.05
	rs6675281=C * rs1872824=A							−1.43	0.24	0.004*	A2	0.03
DISC1	rs821616	1	*TPH2*	rs1386483	12	0.02	A2					
	rs821616=A * rs1386483= G							−1.61	0.20	0.008*	A2	0.02
DISC1	rs980989	1	*CLOCK*	rs3805154	4	0.03	A2					
	rs980989=G * rs3805154=C							−1.03	0.36	0.02	A2	0.03
DISC1	rs980989	1	*BDNF*	rs16917237	11	0.02	A2					
	rs980989=G * rs16917237=G							−0.82	0.44	0.03	A2	0.02
CLOCK	rs3805154	4	*BDNF*	rs16917237	11	0.04	A1					
	rs3805154=C * rs16917237=G							−1.03	0.36	0.03	A1	0.03
CLOCK	rs3805154	4	*BDNF*	rs16917237	11	0.03	A2					
	rs3805154=C * rs16917237=G							−0.92	0.40	0.04	A2	0.02
CRH	rs12721510	8	*ANK3*	rs9804190	10	0.03	A1					
	rs12721510= C * rs9804190=C							−1.55	0.21	0.02	A1	0.02
CRH	rs12721510	8	*ANK3*	rs9804190	10	0.04	A2					
	rs12721510= C * rs9804190=C							−1.45	0.23	0.02	A2	0.02
SLC6A4	5-HTTLPR	17	*TPH2*	rs1386483	12	NS	A1					
	5-HTTLPR =LL * rs1386483= GA							−3.14	0.04	0.01	A1	
	5-HTTLPR =LL * rs1386483= GG							−2.89	0.06	0.02	A1	0.04
SLC6A4	5-HTTLPR	17	*TPH2*	rs1386483	12	0.04	A2					
	5-HTTLPR =LL * rs1386483= GA							−3.08	0.05	0.01	A2	
	5-HTTLPR =LL * rs1386483= GG							−3.11	0.05	0.01	A2	0.03

AS, affection status; Chr, chromosome; R^2, maximum pseudo R^2.
* Statistical significance surviving Bonferroni correction.

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

Locus 1			Locus 2			Plink 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*	rs1386483	12	0.02	A2	1.71	5.54	0.02	A2	0.02
rs6675281 = C * rs1386483 = G												
DISC1	rs821577	1	*CRH*	rs12721510	8	0.03	A1	2.63	13.91	0.04	A1	0.02
rs821577 = GG * rs12721510 = CC												
DISC1	rs821577	1	*CRH*	rs12721510	8	0.03	A2	2.64	14.0	0.04	A2	0.02
rs821577 = GG * rs12721510 = CC												

AD, affective disorder; AS, affection status; Chr, chromosome; R^2, maximum pseudo R^2.
* Statistical significance surviving Bonferroni correction.
Note: The *p*-values presented are unadjusted for the multiple testing.

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].

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.

Funding

This study was supported by the Science Fund, Medical University of Sofia [grant number 10/2009], [grant number 56-D/2011], [grant number 33/2011]; the National Science Fund, Ministry of Education and Science, infrastructure [grant number DFNI B 02/6-2014], [grant number DUNK01-2/2009].

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