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"A melancholy…compounded of many simples, extracted from many objects": heritability of affective temperaments suggests their role as endophenotypes for depression

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Background: Depression shows a moderate average heritability of 37-42% [1], which in case of severe, recurrent, hospitalized samples may be as high as 75% [2]. In spite of this, efforts to identify genes and variants contributing to the emergence of mood disorders and their subtypes are far from effective. One potential contributor to the failure of such studies is heterogeneity of depression which warrants identifying and using clinically relevant intermediate phenotypes in the genetic research of depression. This may also aid diagnosis and identifying potential biomarkers for predictive models. The affective temperamental model proposed by Akiskal [3] suggests that the five affective temperament types are strongly related to affective disorders and especially in their marked or dominant manifestation may be considered high-risk states or subclinical manifestations of mood disorders. Considering their strong genetic and biological background, high heritability in family studies, and their stability throughout the lifespan, affective temperaments may prove to be relevant endophenotypes in the genetic research of depression. The aim of the current study was to investigate the genetic determinants and heritability of affective temperaments based on a GWAS approach.

Methods: We used genetic and phenotypic data from the NewMood project. 775 subjects aged between 18-60 years recruited in Budapest, Hungary provided genetic samples and completed a detailed questionnaire pack including the TEMPS-A (Temperament Evaluation of Memphis, Pisa, Paris and San Diego) scale. A genome-wide association analysis was performed in the first step with the five affective temperaments as outcome variables. During all analyses age, gender, the top 10 principal components of the genome, and the other 4 phenotypes were added in the model as covariates. In the next step, summary statistics derived from the GWAS analyses were used to estimate the heritability, i.e. the genetic variance explained by the different affective temperaments. We performed LD score regression using LDPred2 [4] to estimate the heritability from the beta values and effect size in case of all 5 affective temperament phenotypes.

Results: Only part of our results is reported here. We identified one SNP, rs3798978 with a genome-wide significance ($p = 4.44x10-8$) for anxious temperament and several variants with suggestive significances for all five temperaments. The highest estimated heritability ($h2 = 0.5224$) was observed in case of the depressive temperament, and similarly high heritability was observed in case of the hyperthymic temperament ($h2 = 0.4956$). Anxious and cyclothymic temperament showed almost the same heritability (cyclothymic $h2 = 0.1651$, anxious $h2 = 0.1663$), whereas for the irritable temperament, we got a negative heritability estimation ($h2 = -0.0567$), which means that all of the phenotypic variance is explained by environmental factors.

Conclusion: Our results investigating the genetic background and heritability of affective temperaments yielded remarkably high values for the depressive and hyperthymic temperaments where 52% and 50% of phenotypic variances are explained by the genetic background. Considering the 37-42% heritability of depression estimated in family studies, our SNP-based findings may suggest that these temperaments may indeed be clinically relevant endophenotypes and the contributing variants may be considered as potential markers in predictive models.

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Conflict of interest

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The involvement of Nrf2 in depression: systematic review of preclinical studies

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Introduction: Increased levels of pro-inflammatory cytokines and decreased antioxidant defenses are likely to be linked to the development of depressive symptoms [1]. Nrf2 plays an important role in cellular defense against oxidative stress and binds to ARE, which is located in the promoter region of several phase II antioxidant enzymes and associated stress-responsive enzymes. Reduced Keap1-Nrf2 signaling is implicated in the pathogenesis of mood disorders such as Major Depressive Disorder (MDD) [2].

Objective: The aim of this research was to systematically evaluate the in vitro and in vivo evidence of the involvement of Nrf2 in depression.

Methods: The current study comprised a systematic review performed on PubMed database for articles published until March 8, 2022. The following query was used "((keap1 nrf2) OR (NRF2) OR (NRF-2) OR (Nuclear factor erythroid-derived 2 like 2) OR (NF-E2-related factor 2) OR (nuclear factor erythroid 2-related factor 2) OR (nuclear factor erythroid 2-related)". Papers which evaluated NRF2 in animals and/or cell lines with depression and on English language were included in the review. Research addressing other diseases/topics, systematic reviews, studies that didn't address Nrf2 were excluded. Quality assessment was evaluated according to the criteria proposed by Koch et al., 2022 [3].

Results: The key criteria were satisfied by 57 of the 203 possibly relevant abstracts found through the Pubmed search. Twelve studies were eliminated after careful examination of the full-text papers. As a result, this systematic review comprised 45 papers. This is the first study to look at the Nrf2 system's role in depression. Here we present the following key Findings: (i) When presented with inflammatory settings, Nrf2 is lowered; (ii) When faced with depression states, Nrf2 is decreased; (iii) When an anti-inflammatory or antidepressant medicine is taken, Nrf2 levels increase; and (iv) Nrf2 levels are largely affected in the hippocampus and/or prefrontal cortex.

Discussion: The levels of Nrf2 tend to decrease when animals are exposed to oxidative stress or were exposed to a depressive behavior, confirming that this protein is involved in the depressive phenotype. When animals were treated with antidepressants or anti-inflammatory drugs, Nrf2 levels tend to increase, since antidepressants decrease inflammation and oxidative stress. In addition, IL-10 and BDNF were key elements because they were positively influenced by Nrf2 levels, protecting against oxidative stress through Keap1/Nrf2. Finally, it is not possible to determine precisely where Nrf2 is expressed (prefrontal cortex, hippocampus, or both), which requires further investigation.

Conclusion: Nrf2 may be a possible therapeutic target in depression because pharmacological stimulation of Nrf2 may play a critical role in controlling hypoxia and reactive oxygen species during depression, as well as decreasing the inflammation that is associated with some depression phenotypes. Further studies on clinical samples should evaluated Nrf2 to address its putative effect in depression and antidepressant response.

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Role of genetic polymorphisms on neuroplasticity pathways in a cohort of Portuguese patients with Major Depressive Disorder

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Background: Growing evidence suggests the implication of brain plasticity in antidepressant drug (AD) efficacy. Several authors have been pointing out the role of the BDNF-TrkB signaling pathway, including the downstream kinases Akt and ERK, and the mTOR pathway in neuroplasticity [1-3]. Furthermore, the prediction of AD response phenotypes of depressed patients treated with AD drugs remains a challenge for clinicians. Although previous studies have suggested that genetic variants may play a key role in the mechanism of Treatment Resistance Depression and Relapse, attempts to identify risk polymorphisms within genes with putative interest in AD response, had a limited success.
Objectives: The aim of the present study was to evaluate the role of genetic polymorphisms within BDNF, NTRK2, NGFR, CREB1, GSK3B, AKT, MAPK1, MTOR, PTEN, ARC and SYN1 in AD treatment phenotypes, including Treatment Resistant Depression (TRD) and relapse, in a cohort of Portuguese MDD patients.
Methods: We genotyped 26 polymorphisms in the referred genes in 80 major depressive disorder (MDD) patients followed at Hospital Magalhães Lemos, Portugal, within a period of 27 months. Genomic DNA was extracted from peripheral blood according to standard laboratory procedures, with a commercial kit. Polymorphisms genotyping analysis was carried out using Sequenom MassARRAY platform. Odds ratio (OR) and 95% confidence interval (CI) were calculated as a measure of association between genotypes and risk of developing a specific phenotype. Kaplan-Meier survival curves were used to evaluate correlation between genotypes and time to remission and relapse and were compared by log-rank statistical test.
Results: Statistically significant differences were found in genotype frequencies among TRD and non-TRD participants for the BDNF gene polymorphism rs6265, for the PTEN polymorphism rs12569998, and for the SYN1 polymorphism rs1142636. Furthermore, statistically significant differences were found in genotype frequencies between relapsed and non-relapsed participants for the MAPK1 gene polymorphism rs6928 and the GSK3B gene polymorphism rs6438552. Moreover, it was observed an association of rs6928 MAPK1 polymorphism with the time to relapse($p=0.022$). The remaining polymorphisms were not associated with any phenotypes.
Discussion: Statistically significant differences were found in genotype frequencies among TRD and non-TRD participants for the BDNF gene polymorphism rs6265, for the PTEN polymorphism rs12569998, and for the SYN1 polymorphism rs1142636. Given the importance that each of these molecules has in neurotrophic/neuroplasticity pathways we hypothesised that TRD phenotype is correlated with alterations in the neuroplasticity molecules, what may impair the reestablishment of synaptic plasticity in neuronal networks upon AD treatment. Furthermore, MAPK1 rs6928 and GSK3B rs6438552 gene polymorphisms were associated with relapse. Given the fact that MAPK1 activation is altered after stress and corticosterone exposure, and that Wnt1-GSK3β signalling in the hippocampus is markedly involved in the pathophysiology of depression induced by chronic stress, it is possible that these genetic variations can contribute to relapse upon remission.
Conclusions: In conclusion our results suggest distinct molecular events contributing to relapse and TRD. While the genotypic effect of PTEN polymorphism rs12569998, SYN1 polymorphism rs1142636, and BDNF rs6265 polymorphism may contribute to a TRD phenotype, MAPK1 and GSK3B may have a role in a relapse predisposed phenotype.
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E. Munch: from broken childhood to anxiety and mental illness

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The artwork of E. Munch are often used as an example of the association between creativity and mental illnesses. His most famous painting, The Scream, is an example of his autobiography: "I was walking along the road with two friends – the sun was setting – suddenly the sky turned blood red – I paused, feeling exhausted, and leaned on the fence – there was blood and tongues of fire above the blue-black fjord and the city – my friends walked on, and I stood there trembling with anxiety – and I sensed an infinite scream passing through nature" 1.Munch recognized how he was affected by mental illness: "My father was temperamentally nervous and obsessively religious—to the point of psychoneurosis. From him I inherited the seeds of madness. When the artist showed one copy of " The Scream" in a student union gathering, a medical student shouted: " Painted by a mad man". Mr. Munch wrote this sentence in the corner of his painting. The work of Munch represents a recollection of his life: "I don't paint what I see but what I saw."Traumatized by the death of his mother when he was only five -year old [The Dead Mother, Death and a Child]2, Munch remained scarred throughout his life 1,2. In the first stage of childhood psychological development, trust versus mistrust is the rule 3. Munch as a child never successfully developed trust, he never felt safe and secure in the world. His mother suddenly became unavailable physically and emotionally and his father was withdrawn and distant.The emotions of frozen time, disbelief, and trauma of a child expressed in his painting [Death and the Child] 2 were actually his own emotions . Death continued to haunt Munch, his sister died when he was around 14 the scene of illness in [The Sick Child] 2 shows this clearly: a pale, frail girl looking for help while an adult person, next to her ,in a silent breakdown despair. This vivid image kept haunting him throughout his life. Most of the time, Munch painted children without their parents, as if he was remembering his own family: The children were alone. When the father appeared in a painting [Worker and Child]2, he was wearing a black band of mourning on his arm indicating that the girl in the painting has probably lost her mom as Munch did.The feeling of mistrust has affected Munch's relationships with women and is clearly seen in various paintings of love and relations. The broken- hearted man in [Separation] 2 is probably Munch himself and the woman who is moving away is a shadow of his mom. When unhappy or uncomfortable, children tend to scream. Perhaps Munch did the sam: Scream! [The Scream]2.
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