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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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