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| Study name | Results | Level of evidence | Number of participants |
| Ribeiro et al., 2007 | BDNF Val66Met SNP showed a significant association with the diagnosis of MDD (p=0.005) for a single marker association test between MDD and control group | Level 3b | N=278 cases  N=320 controls |
| Val/Val homozygous individuals were 70% more likely to be depressed (OR = 1.7, 95% CI 1.17-2.47) | Level 3b | N=278 cases  N=320 controls |
| Jessen et al., 2009 | There was no Val66Met effect on hippocampal volume in either group | Level 3b | N=79 cases  N=84 controls |
| Bilateral hippocampal volumes of MDD patients were significantly smaller than those of the controls | Level 3b | N=79 cases  N=84 controls |
| Liu et al., 2009 | There were no significant associations of rs6265, rs10835210 and rs2030324 SNPs with MDD | Level 3b | N=315 individuals (105 trios) |
| Pairwise analysis revealed substantial linkage disequilibrium among three SNPs | Level 3b | N=315 individuals (105 trios) |
| Analysis by multiple-marker transmission disequilibrium test (TDT) indicated that there was no association between the haplotypes and MDD | Level 3b | N=315 individuals (105 trios) |
| SNPs rs6265, rs10835210 and rs2030324 of the BDNF gene are unlikely to play a critical role in the pathogenesis of MDD, at least in Chinese Han patients | Level 3b | N=315 individuals (105 trios) |
| Zhang et al., 2010 | There was a significant effect of a two-locus BDNF/GSK3B interaction with MDD (GSK3B rs6782799 and BDNF rs7124442) (corrected p = 0.011) | Level 3b | N=447 cases  N=432 controls |
| Three-locus interaction (GSK3B rs6782799, BDNF rs6265 and BDNF rs7124442) was significant as well (corrected p = 0.019) | Level 3b | N=447 cases  N=432 controls |
| Combination of two risk alleles showed an OR of 4.00 (95% CI 2.05-7.79) | Level 3b | N=447 cases  N=432 controls |
| Combination of three risk alleles gave the largest OR of 4.46 (95% CI 2.15-9.24) | Level 3b | N=447 cases  N=432 controls |
| Kanellopoulos et al., 2011 | Elderly BDNF Val/Val homozygotes with MDD had significantly higher right hippocampal volumes compared with non-depressed Val/Val controls | Level 3b | N=33 cases  N=23 controls |
| There was no difference between the depressed and non-depressed Met carriers | Level 3b | N=33 cases  N=23 controls |
| Depressed Met carriers had an earlier age of onset of depressive illness than Val/Val homozygotes | Level 3b | N=33 cases  N=23 controls |
| Val/Val homozygosity may mediate a BDNF-based neuroprotective role against pathophysiological processes in adults with late-onset depression | Level 3b | N=33 cases  N=23 controls |
| Suchanek et al., 2011 | No association between the C-281A polymorphism and recurrent MDD | Level 3b | N=116 cases  N=218 controls |
| There was a significant association between Val66Met and MDD | Level 3b | N=116 cases  N=218 controls |
| The Val/Val genotype was more frequent in MDD patients compared to the control group, both in total analysis and after stratification by sex | Level 3b | N=116 cases  N=218 controls |
| The Val allele is connected to a higher risk of recurrent MDD development in men, rather than in women | Level 3b | N=116 cases  N=218 controls |
| Correspondence analysis has shown that the co-presence of genotypes Val/Val and C/C is connected with a higher risk of recurrent MDD development (odds ratio [OR]=2.05, p<0.01) compared to other genotype combinations | Level 3b | N=116 cases  N=218 controls |
| Chi et al., 2011 | There was no significant difference in the distribution of BDNF Val66Met in cases vs. controls | Level 3b | N=198 cases  N=106 controls  HapMap database for ethnicity comparison |
|  | There was however a significant difference in the distribution of Val66Met according to ethnicity |  | N=198 cases  N=106 controls  HapMap database for ethnicity comparison |
| Cole et al., 2011 | No significant difference between 5-HTTLPR Short allele carriers and Long/Long homozygotes in the healthy controls | Level 3b | N=84 cases  N=111 controls |
|  | No significant difference between BDNF Met allele carriers and Val/Val homozygotes in the group of healthy individuals | Level 3b | N=84 cases  N=111 controls |
| No significant difference in normalized hippocampal volumes between 5-HTTLPR di-allelic and tri-allelic classifications or between the BDNF Val66Met genotypes in MDD patients | Level 3b | N=84 cases  N=111 controls |
| Xiao et al., 2011 | Corticotropin-releasing hormone receptor 1 (CRHR1) (rs1876828, rs242941) and BDNF (rs6265) alleles were found to have no association with the risk of recurrent MDD (p=0.1952, 0.0822, 0.4078, respectively) | Level 3b | N=181 cases  N=186 controls |
| Evinova et al., 2012 | No difference between MDD patients and healthy controls regarding the BDNF G196A polymorphism | Level 3b | N=134 cases  N=143 controls |
| Carballedo et al., 2012 | Met allele had smaller fractional anisotropy (FA) in the uncinate fasciculus compared to those patients homozygous for Val allele and compared to healthy subjects carrying the Met allele | Level 3b | N=37 cases  N=42 controls |
| A significant three-way interaction was detected between the cingulum (dorsal, rostral, and parahippocampal regions), brain hemisphere and BDNF genotype | Level 3b | N=37 cases  N=42 controls |
| Larger fractional anisotropy was detectable in the left rostral cingulum for Met allele carriers when compared to Val/Val homozygotes | Level 3b | N=37 cases  N=42 controls |
| Met allele of the BDNF polymorphism seems to render subjects more vulnerable to neurophysiological circuitry dysfunctions associated with the uncinate fasciculus, a tract known to be related to negative emotional-cognitive processing bias, declarative memory problems and self-awareness | Level 3b | N=37 cases  N=42 controls |
| Murphy et al., 2012 | MRI and subsequent tract-based spatial statistics yielded an interactive effect between NTRK2 and depression diagnosis, maximally affecting the cingulum | Level 3b | N=45 cases  N=45 controls |
| MDD patients homozygous for the A allele of NTRK2 showed significantly reduced fractional anisotropy compared with depressed patients with at least one copy of the G allele or control subjects with either the A/A or G carrier genotypes in the left and right corona radiata, left uncinate fasciculus, left inferior fronto-occipital fasciculus, left cerebral peduncle, posterior thalamic radiation, and middle cerebral peduncle | Level 3b | N=45 cases  N=45 controls |
| Significantly smaller gray matter volume was seen in frontal lobe regions in patients homozygous for the A allele | Level 3b | N=45 cases  N=45 controls |
| There was no significant effect of BDNF Val66Met polymorphism or early life adversity (ELA) on white matter diffusion | Level 3b | N=45 cases  N=45 controls |
| Carballedo et al., 2013 | There was no significant association of Val66Met genotype with a diagnosis of MDD | Level 3b | N=62 cases  N=71 controls |
|  | Met allele carriers with a history of early life adversity had significantly lower hippocampal volumes | Level 3b | N=62 cases  N=71 controls |
|  | Met allele carriers without a history of early life adversity have larger hippocampal volumes than participants that are Val homozygotes | Level 3b | N=62 cases  N=71 controls |
| Cardoner et al., 2013 | Gray matter volume reduction in the left hippocampus was observed in Met carriers, while there was a volume increase in the right orbitofrontal cortex. This decrease was inversely correlated to days to remission, while a significant negative correlation between left hippocampal volume and days to remission was found in the Val/Val genotype | Level 3b | N=37 cases |
| Lan et al., 2014 | There was an interaction between diagnosis and allele (F=4.23, df=1, 94, p=0.042), such that Met allele carriers had 17.4% lower binding potential (BP(F)) than non-Met carriers in the control group (t=2.6, df=96, p=0.010), but not in the MDD group (t=-0.4, df=96, p=0.58) | Level 3b | N=50 cases  N=50 controls |
| In MDD, the effect of the BDNF Val66Met polymorphism is not detectable, which may be possibly due to a ceiling effect of over-expression of 5-HT1A receptors in mood disorders | Level 3b | N=50 cases  N=50 controls |
| Frodl et al., 2014 | Patients with MDD had significantly smaller cornu ammonis 4/dentate gyrus (CA4/DG) and cornu ammonis 2/3 (CA2/3) volumes compared to healthy controls | Level 3b | N=38 cases  N=44 controls |
| There was a significant interactive effect of BDNF allele and childhood adversity on CA2/3 and CA4/DG volumes | Level 3b | N=38 cases  N=44 controls |
|  | Met carriers without childhood adversity had larger and with childhood adversity smaller CA4/DG and CA2/3 volumes than Val/Val homozygotes | Level 3b | N=38 cases  N=44 controls |
| Stress seems relevant for gene interaction effects on hippocampal volume reductions, in particular for the subfield CA2/3 and the dentate gyrus | Level 3b | N=38 cases  N=44 controls |
| Rimay et al., 2015 | Results showed that 27.8% of the participants fulfilled the criteria for melancholy, and the proportion of females amongst them was higher (53.1%) | Level 3b | N=583 cases |
|  | There was no significant difference in BDNF genotype or allele frequency between the melancholic and the non-melancholic depressed group (27,8% vs 72,2%) | Level 3b | N=583 cases |
|  | BDNF Val66Met and stressful life events (SLE) interaction was not significantly linked with melancholy (as an outcome) | Level 3b | N=583 cases |
| Legge et al., 2015 | It was found that Met carriers showed significantly reduced caudal middle frontal thickness in both groups | Level 3b | N=79 cases  N=74 controls |
| Significant interaction effects were found in the anterior cingulate cortex (ACC) and rostral middle frontal regions, where in the MDD group Met carriers showed the greatest reduction in surface area | Level 3b | N=79 cases  N=74 controls |
| Phillips et al., 2015 | There was some evidence for norepinephrine and serotonin-related genes being involved in MDD (C allele-carriers for both the NET-182 T/C (rs2242446) and 5-HT1A-1019C/G (rs6295) polymorphisms had smaller hippocampal volumes relative to other genotypes | Level 3b | N=26 cases  N=27 controls |
| For the 5-HTTLPR (rs25531) polymorphism, there was a significant diagnosis with genotype interaction effect on hippocampal volume. Among the trMDD group, homozygosity for the 5-HTTLPR short (S) allele was associated with smaller hippocampal volume | Level 3b | N=26 cases  N=27 controls |
| There was no association between the 5-HT2A, COMT, and BDNF SNPs and hippocampal volume | Level 3b | N=26 cases  N=27 controls |
| Yang et al., 2016 | A significant gene-environment interaction of negative life events, BDNF Val66Met and a PRKCG SNP, significantly influencing MDD risk | Level 3b | N=406 cases  N=391 controls |
| Sun et al., 2016 | BDNF Val66Met showed no correlation with MDD | Level 3b | N=459 cases  N=412 controls |
| When interaction with BDNF was modelled, for individuals with BDNF (rs6265), genotype GG, cases in the heterozygous group had even higher odds of MDD than those in the combined homozygous group of 5-HTTLPR polymorphism, suggesting that there may be significant interactions between the 5-HTT gene and BDNF gene in relation to MDD | Level 3b | N=459 cases  N=412 controls |
| Voegeli et al., 2016 | NTRK2 rs1439050 was significantly associated with antidepressant-worsening suicidal ideation | Level 3b | N=78 cases  N=312 controls |
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| Kostic et al., 2016 | Compared to controls, the high-frequency susceptibility polymorphism (hfSP) group MDD patients showed thinning of the middle frontal cortex bilaterally, left frontal pole, and right lateral occipital cortex and smaller hippocampal volume bilaterally | Level 3b | N=77 cases  N=66 controls |
| Both hfSP and low-frequency susceptibility polymorphism (lfSP) controls and MDD patients showed thinning of the left inferior parietal cortex and reduced WM integrity of the corpus callosum | Level 3b | N=77 cases  N=66 controls |
| Compared to patients, hfSP controls showed greater integrity of the fronto-occipital cortices and corpus callosum | Level 3b | N=77 cases  N=66 controls |
| It was affirmed that cortical prefrontal and occipital damage of MDD patients is modulated by the polymorphism accumulation, while damage to the parietal cortex and corpus callosum seems to be independent of genetic accumulation | Level 3b | N=77 cases  N=66 controls |
| Colle et al., 2017 | Plasma BDNF levels were significantly and linearly associated with respective BDNF Val66Met genotypes where the Met/Met genotype carriers had lower plasma BDNF levels than the Val/Met and Val/Val carriers (1,525.9 ± 1,183.3 pg/mL vs. ValMet: 1,248.7 ± 1,081.8 vs. MetMet: 1,004.9 ± 952.8; p = 0.04) | Level 3b | N=328 cases |
|  | Age of onset (AOO), MDD duration and number of previous episodes were associated with Val66Met genotype for plasma BDNF levels | Level 3b | N=328 cases |
|  | In Met/Met and Val/Met genotypes, plasma BDNF levels were negatively correlated with AOO and showed positive correlation with MDD duration and number of previous episodes (not so for Val/Val genotype) | Level 3b | N=328 cases |
| Caldieraro et al., 2018 | The Met allele was significantly associated with higher BDNF and lower TNF-alpha levels vs. higher TNF-alpha levels and lower BDNF levels in Val/Val homozygotes | Level 3b | N=73 cases |
| Low serum level of BDNF and high level of inflammatory markers may be influenced by the Val66Met SNP | Level 3b | N=73 cases |
| Deflesselle et al., 2018 | TrkB rs2289656 CC genotype was associated with higher suicide risk | Level 3b | N=624 cases |
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| Aldoghachi et al., 2019 | BDNF Val66Met in the Malaysian population increases the odds of developing MDD by 2.05 fold (95% CI = 1.48-3.65) | Level 3b | N=300 cases  N=300 controls |
| 206 randomly selected cases as well as 206 randomly selected controls underwent ELISA-based plasma BDNF assessment and a significant decrease in plasma BDNF levels of MDD cases as versus controls (p<0.0001) was observed | Level 3b | N=300 cases  N=300 controls |
| No evidence of the effect of the Val66Met genotype on the plasma BDNF level | Level 3b | N=300 cases  N=300 controls |
| Froud et al., 2019 | The control group had a significantly higher dietary quality than the participants with MDD (t = 2.435, p = 0.016) | Level 3b | N=187 cases  N=55 controls |
| A logistic regression model (age, sex, serum BDNF levels, dietary quality and depression) concluded that lower dietary quality, and surprisingly, higher BDNF levels, were associated with increased depression risk (p = 0.037 and p < 0.001, respectively) | Level 3b | N=187 cases  N=55 controls |
| Neither seasonality (at time of patient and control recruitment) nor the BDNF Val66Met polymorphism was associated with BDNF levels | Level 3b | N=187 cases  N=55 controls |
| No evidence of interaction between the Val66Met polymorphism, serum BDNF, dietary quality and depression was demonstrated | Level 3b | N=187 cases  N=55 controls |
| Higher dietary quality was associated with decreased depression incidence and severity | Level 3b | N=187 cases  N=55 controls |
| Val66Met polymorphism appeared not to predict serum BDNF levels, depression incidence or modify the relationship between dietary quality and BDNF | Level 3b | N=187 cases  N=55 controls |
| Ferrer et al., 2019 | Significant associations between neurocognitive performance and two BDNF SNPs (including rs908867 and rs925946) were found | Level 3b | N=64 cases  N=70 controls |
| The association effect between neurocognitive performance BDNF SNPs rs908867 and rs925946 was significantly mediated by methylation values at (specific) promoter I sites | Level 3b | N=64 cases  N=70 controls |
| Significant associations between neurocognitive results and methylation status as well as its interactions with MDD diagnosis, sex, and childhood trauma questionnaire (CTQ) scores were found | Level 3b | N=64 cases  N=70 controls |
| Shen et al., 2020 | There was a diagnosis-by-genotype interaction of MDD, Val66Met and the rostral anterior cingulate cortical thickness | Level 3b | N=105 cases  N=111 controls |
|  | MDD-Met carriers had comparably reduced rACC thickness | Level 3b | N=105 cases  N=111 controls |
| Schröter et al., 2020 | No significant difference in BDNF genotype or allelic frequencies between MDD, (BD) and control groups | Level 3b | N=49 cases  N=57 controls |
| Zhang et al., 2020a | No significant association of investigated geno- and haplotype frequencies with MDD | Level 3b | N=105 cases  N=154 controls |
| Losenkov et al., 2020 | There was no association of Val66Met with diagnosis | Level 3b | N=138 cases  N=94 controls |
|  | However, depression severity was significantly associated with Val66Met status | Level 3b | N=138 cases  N=94 controls |
| Costache et al., 2021 | The multiple investigated SNPs, including Val66Met did not have an association with MDD | Level 3b | N=82 cases  N=286 controls |