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BDNF Val66Met Polymorphism and Stressful Life Events in Melancholic Childhood-Onset Depression

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Abstract

Brain-derived neurotrophic factor (*BDNF*) polymorphisms have been examined for their contribution to depression with equivocal results. More homogeneous phenotypes might be used to improve our understanding of genetic liability to depression. The aim of our study was to 1) test for association between *BDNF* Val66Met polymorphism and childhood onset melancholic depression and 2) to examine the interactive effects of stressful life events (SLE) and the Val66Met polymorphism on the risk of childhood onset melancholic depression.

Materials and Methods—583 depressed probands were involved in this study (162 of the melancholic subtype). Diagnoses were derived via the Interview Schedule for Children and Adolescents - Diagnostic Version and life event data were collected by means of an Intake General Information Sheet

Results—27.8% of the participants met criteria for melancholy. In the melancholic group the proportion of the females was higher (53.1%), though there were more males in the overall depressed sample. We detected no significant differences in genotype or allele frequency between the melancholic and the non-melancholic depressed group. *BDNF* Val66Met polymorphism and stressful life event interaction was not significantly associated with the melancholy outcome.

Conclusion—In our study, females are more prone to develop the early-onset melancholic phenotype.

To our knowledge, this is the first study to investigate the differentiating effect of the genotype and the G×E interaction on melancholic phenotype in a large sample of depressed young patients.

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No conflict of interest was reported.

We didn't find association between the melancolic subtype of major depression and the *BDNF* genotype and stressful life event interaction in this sample, which is representative to the Hungarian clinic-referred population of depressed youths.

Keywords

children, melancholic depression; homogeneous phenotype; brain-derived neurotrophic factor; extrafamilial life events

INTRODUCTION

It is well documented that MDD is caused by numerous interacting genetic and non-genetic factors (e.g. Ebmeier et al., 2006). Indeed, there is fairly consistent evidence that childhood onset depression (COD) has familial determinants (Rice et al., 2002). For example, in a large twin study the hereditability for MDD was 29% in males and 42% in females, respectively (Kendler et al., 2006).

Furthermore, numerous candidate genes have been studied as potential risk factors for COD (Rice, 2010), including the *BDNF* locus. *BDNF* Val66Met is a single nucleotide polymorphism (SNP) of nucleotide 196 in exon 5, resulting in a Val/Met amino acid change in codon 66, affecting the pro-BDNF sequence, with no functional effect on the mature BDNF, but causing changes in its cellular transport and secretion. The encoded protein is a neurotrophin, playing a role in hippocampal dendritic morphology and synaptic function. It has been implicated in depression, evidenced by decreased hippocampal volume and hippocampal and serum BDNF levels associated with the disease. (Savitz and Drevets, 2009; Srijan et al., 2008, Cardoner et al. 2013). The presence of the Val66Met Met allele has been associated with inefficient secretion of BDNF regardless of gender (Egan et al., 2003; Ozan et al., 2010) and decreased serum BDNF levels were found in patients with depression (Ozan et al., 2010).

In a sample of adults with a history of childhood onset mood disorder (COMD) (Strauss et al., 2004) the *BDNF* Val66Met-$(GT)_n$ two marker Val/short (<170 bp) haplotype was associated with COMD, but no significant association was found between the examined *BDNF* polymorphisms and childhood-onset mood disorder by allelic or genotypic analysis. In another study, the same authors examined a sample of 258 Hungarian trios including juvenile probands with COMD and found the *BDNF* Val66Met Val allele to be associated with the disorder (Strauss et al., 2005). Importantly, the present study is performed on a subset of the same Hungarian sample.

Noteworthy, a meta-analysis of Chen et al. (2008) did not confirm the association between Val66Met polymorphism and depression. Also, in contrast to the often reported association between the *BDNF* polymorphism and depression, the meta-analysis of Verhagen et al. (2010) suggests only a gender-dependent role of the polymorphism in the development of depression, as significant association was found only in males.

One of the causes of the currently inconsistent findings could be that MDD as defined in DSM IV is a heterogeneous disorder with regard to etiology, symptoms and level of functioning and response to treatment (Domschke et al., 2010).

One of the clinical subtypes of MDD that showed distinct clinical (Kessler et al., 1997b) and biochemical (Maes et al., 1990) features was melancholic depression (Gold et al. 2002). Schotte et al. (1997) provided the validation through cluster analysis of melancholic and non-melancholic subtypes of unipolar depression.

A promising attempt has been made currently to determine the nosological status and diagnostic strategies to melancholia (Parker and Paterson, 2014). Furthermore several biological markers have been suggested to identify this putative endophenotype. The preliminary results of Bracht et al., (2013) suggest that the melancholic subtype of MDD is characterized by white matter microstructure alterations of the medial forebrain bundle compared to healthy controls, while it did not differ between the controls and the overall MDD sample. Though some studies claim that psychomotor retardation is a feature of depression (Widlöcher et al., 1983, Dantchev 1998), some authors suggested that psychomotor retardation allows determining putative endophenotypes such as melancholy (Bennabi et al., 2013, Parker et al., 1996). Preliminary evidence suggests that genetic factors may discriminate melancholic and non-melancholic depression in a putatively interesting preliminary study of Quinn et al., (2012) with low sample size. The authors (Quinn et al. 2012) found that the *BDNF* rs6265 Met allele predisposes non-melancholic depression and the interaction of the *BDNF* rs6265 Met allele and SLE predicts non-melancholia over main effects. Furthermore, in a current study of Patas et al. (2014) investigating the association between serum brain-derived neurotrophic factor and plasma interleukin-6 in major depressive disorder, plasma interleukin-6 was found to be a positive predictor of BDNF only in the melancholic sample. According to Harkness et al. (2006) subjects with severe melancholic depression are more sensitive to stress, with episodes being influenced by more minor stressors than those of non-melancholic patients.

Indeed, the role of stressful life events has been proven in depression (Kessler et al., 1997a) and several studies showed the effect of gene by environment (G×E) interaction on mood disorders. In a study of Bukh et al. (2009) the Met allele of the *BDNF* Val66Met polymorphism was independently associated with the presence of SLEs prior to the onset of depression and in a paper of Elzinga et al. (2011) *BDNF* Met allele carriers were found to be sensitive to early SLEs. Kim et al. (2007) found significant interaction of stressful life events and *BDNF* Met/Met and Val/Met genotypes on the risk of depression. In a study of Chen et al. (2012) on a sample of 780 pairs of ethnic Han Chinese adolescent twins, authors found that the BDNF Val allele modulates the influence of environmental stress on depression. Interaction between BDNF Val66Met polymorphism and environmental stress on depression was found even when separating pure environmental factors from the environmental factors under partial genetic control and adopting a prospective longitudinal design (Chen et al. 2013). In a study of Hosang et al. (2014) the Met allele of BDNF significantly moderates the relationship between life stress and depression, the association being stronger for an interaction with stressful life events and weaker for interaction of BDNF Val66Met with childhood adversity. In the study of Brown et al (2014) the Met

alleles of BDNF Val66Met a significant gene–environment interaction was found between recent life events and adult onsets of depression, though BDNF did not significantly influence the effect of childhood maltreatment on chronic depression.

To improve our knowledge about the potential genetic contributors to the melancholic type of depression, we examined whether an effect of the *BDNF* Val66Met polymorphism and its interaction with stressful life events could differentiate juvenile melancholic and non-melancholic patients.

We hypothesized that:

- **a.** Melancholic and non-melancholic depressed probands are characterized by different *BDNF* Val66Met genotype and allele distributions.
- **b.** Past exposure to stressful life events interacts with the *BDNF* Val66Met polymorphism to predict a melancholic depression phenotype.

MATERIALS AND METHODS

The data derive from a multidisciplinary Program Project studying risk factors for COMD, conducted in Hungary. The sample includes 583 depressed probands, recruited from 23 mental health facilities across the country, including 7 child and adolescent psychiatry inpatient units. Screening of probands was performed from 01.11.1999 to 01.07.2005. Signed consent from the parents and assent from the children were obtained from all subjects in accordance with the Hungarian National Health and the Regional Human Investigation Review Board guidelines.

Inclusion criteria were the following: DSM IV diagnosis of MDD with the onset of the first episode by age 14.9 and being free of mental retardation and major systemic medical disorders. The diagnostic procedure included the semi-structured Interview Schedule for Children and Adolescents - Diagnostic Version (ISCA-D) (Sherrill et al., 2000). Ratings were obtained both for current and past symptoms of DSM IV Axis I diagnoses and major DSM-III disorders (e.g. depression with melancholic features). The diagnostic assessment for the participants enrolled in this study has been described in detail previously (Kapornai et al., 2007; Kiss et al., 2007; Liu et al., 2006). Importantly, to establish depressive episodes and symptoms, we performed two independent semi-structured diagnostic interviews during the intake procedure rated by trained clinicians, and subsequently evaluated by Best-Estimate Diagnostic Procedure (Maziade et al., 1992).

The depressed group was divided into two groups on the basis of the presence of melancholic subtype. Melancholic subtype of depression was estimated by ISCA-D, on the basis of the criteria for melancholic features of the DSM IV. The differentiating symptoms were pervasive, nonreactive anhedonia, distinct quality of depressed mood, depression worse in the morning, early morning awakening, marked psychomotor retardation or agitation, anorexia, weight loss and excessive and inappropriate guilt. 135 subjects met criteria for melancholic depression in the current time-frame, and 44 subjects had such features during a past episode. There were overlaps between the two groups given that some

subjects had melancholy in both time frames. Thus, 162 subjects met criteria for melancholic depression in at least one time frame.

583 depressed probands were included in the analysis. The mean age of depressed subjects at first interview was 11.72 (SD=2.01) years. The melancholic group (N=162) had a mean age of 11.71 (SD=2.01) and the non-melancholic group (N=421) had a mean age of 11.76 (SD=2.01). The distribution by gender was 55.6% male (n=324) in the total depressed group, 46.9% male (n=76) in the melancholic group and 58.9% male (n=248) in the non-melancholic group.

Life events were abstracted from a pre-coded demographic data sheet, the Intake General Information Sheet (GIS), completed by clinicians as part of the intake psychiatric interview, using parents as informants. The assessment procedure has been described in detail previously (Mayer et al., 2009). On the basis of the study of Mayer et al. (2009), 22 of the 26 stressful life events were separated into five clinically meaningful groups: “Parental health”, “Death of close relatives”, “Sociodemographic” and “Intrafamilial”. Miscellaneous events formed the fifth group containing items reflecting extrafamilial life events and abuse.

In the present study, a continuous weighted total score reflecting the number of stressful life events was also computed from the 26 items. Both the total and the grouped scores of stressful life event items were weighted by age (age in years at the intake ISCA-D interview).

Laboratory Methods

The *BDNF* rs6265 single nucleotide polymorphism (SNP), also known as Val66Met, was genotyped using the Applied Biosystems TaqMan pre-designed assay C__11592758_10 (Foster City, CA). For each reaction, 20 ng genomic DNA was amplified as per manufacturer’s directions in a total volume of 10 ml in an MJ Research thermocycler (Bio-Rad Laboratories, Hercules, CA). Each genotyping plate was analyzed post-amplification on the ABI Prism 7000 Sequence Detection System (software v1.2.3) using the allelic discrimination option. Allele calls were made manually.

Statistical Analysis

Data analysis was performed using the software package SPSS Statistics version 17. Group characteristics were investigated with independent samples t-test and Chi-square test. Fisher’s exact test was applied to compare allele frequencies and the Chi-square test of statistical significance set at $p < 0.05$ was used to compare genotype frequencies among the non-melancholic and melancholic subgroups. Logistic regression models were used to examine total weighted and grouped weighted life event scores and *BDNF* Val66Met genotypes. We applied these models in the total melancholic group. Main effects and possible interactions were tested by likelihood ratio test (stepwise regression). In the first model (Model 1) the main effects of total weighted life event score and Val66Met genotypes were tested. Secondly we included the interaction term of (total weighted life event scores and Val66Met genotypes). In the second model (Model 2) the genotype and the main effects of grouped life events scores were tested, later adding the interaction terms between grouped

life event scores and Val66Met genotypes. Main effects of stressful life events were analyzed continuously, as continuous score yields more information than dichotomous, providing more sensitive results.

Effect size was counted for the genotype-by-melancholia interaction and power analysis was performed, using GPower (Faul et al, 2007). For the power calculation of the logistic regression analysis the POWER procedure in SAS 9.4 was used.

RESULTS

In this sample of depressed youths, 27.78% met criteria for melancholic depression. The mean age at interview did not differ significantly between the melancholic and non-melancholic subgroups (t=−0.28, p(2-tailed)=0.78), while there was a statistically significant difference (t=−0.262, p(2-tailed)=.01) in gender. Further characteristics of the total sample and the subsamples can be found in Table 1 (here we provided an unweighted sum of life events).

Comparing the total and grouped stressful life event scores did not reveal any significant difference between the two patient groups. A non-significant difference (t=1.759, df=1, *p*=.079) was found in the intrafamilial stressful life event scores (M=17.33 in the non-melancholic and 15.62 in the melancholic group, respectively). Table 2 shows the frequency of each life event and the life event grouping, together with the relative p-values.

In both melancholic and non-melancholic depressed groups the homozygous Val/Val genotype had the highest occurrence. The homozygous Met/Met genotype was the least common in both groups. Table 3 gives the genotype and allele frequencies in the total depressed group and the subgroups. The genotypes were in Hardy-Weinberg equilibrium, both in the total depressed group and in the subgroups.

Testing our first hypothesis, the allele frequency was not significantly different across the two diagnostic groups (*Fisher's exact: p*=.121). The Val/Val genotype frequency did not differ significantly (χ^2=2.80, df=2, *p*=.*25*) between the melancholic and the non-melancholic group. Because of the low rate of Met/Met genotype, genotypes were dichotomized on the basis of the presence of the Met allele. There was a trend for the non-melancholic depressed youth toward a slightly higher rate of Met-containing genotype, although not statistically significant (*Fisher's exact: p*=.112).

The effect size (W) for our genotype-by-melancholia interaction was 0.12, power on such an effect size with 2 degrees of freedom was .74.

Examining our second hypothesis, in the total melancholic group with the Model 1 of the logistic regression, described in the Statistical analysis section, taking Met-containing genotypes as reference category, we did not find either significant main effect, or significant interaction effect of the total stressful life events and the BDNF polymorphism on the melancholy outcome. When we applied Model 2 (again Met-containing genotype was taken as reference category) to examine life event groups separately, neither of the events contributed significantly to the model.

Main effects and interactions of BDNF Met-containing genotypes, total stressful life events and stressful life event groups as predictors in the model of melancholic depression are displayed in Table 4.

For the logistic regression analysis, power was 0.31 for life events, .56 for presence of a Met allele, and .06 for life events-by-genotype interaction.

DISCUSSION

Even today, gene variants associated with MDD vulnerability have not been clearly identified (Lopizzo et al, 2015). Given that MDD as defined by the DSM IV is a complex disorder, finding susceptibility genes may be facilitated by using alternative, more homogenous depression phenotypes.

However, even other factors than genetic vulnerability and diagnostic procedure must be considered to explain the development of MDD (Hosang et al, 2014).

Despite the clinical utility and validity of the melancholic phenotype of depression, a debate has been ongoing about the relevance of the subtype, suggesting that further research is needed (Hadzi-Pavlovic et al., 2012) to define its biological features.

Consequently, we studied the contribution of the *BDNF* polymorphism and its interaction with SLE to early onset melancholic depression. To our knowledge this is the first study to investigate the differentiating effect of the genotype and the G×E interaction on melancholic phenotype in a large sample of depressed young patients, which was representative of the Hungarian population.

The frequency of melancholia in our sample was in the range of the previously reported prevalences of 20% to nearly 50% in juvenile samples (Ambrosini et al., 2002, Kolvin et al., 1991, Ryan et al., 1987). The ratio of females was significantly higher in the melancholic than in the non-melancholic group ($t=-0.262$, $p(2\text{-tailed})=.01$), suggesting that females are more prone to develop the early-onset melancholic phenotype.

The current literature establishes that girls show more depressive symptoms than boys (Wade et al.,2002, Hankin et al., 2007), however there is some inconsistency in the findings (Chen et al., 2012), that is may be due to metodological, age and ethnic differences in the sample populations. Although in a preliminary study of Quinn et al (2012) and in the study of Guo et al (2015), no significant differences were found for the melancholic, non-melancholic and control groups for gender or age, the difference compared to our findings may be due to their focus on the adult population in addition to a smaller sample size that decreases the chances of finding significant difference.

Our result may represent an interesting suggestion for future research since the presence of the subtype might influence treatment response (Rush et al., 2008) and complications. According to a study of Gold et al, 2002 common medical complications of different subtypes of depression may occur because of different underlying mechanisms.

In the genotypic and allelic association analysis we found elevated Val/Val genotype frequency in the melancholic group. Our analysis however could not be used to discriminate between the melancholic and non-melancholic groups. The calculated effect-size and the power analysis performed for our genotype-by-melancholia interaction suggests that small to medium effects would have been detected if present.

Our results partly correlate with the study of Quinn et al. (2012), showing that no significant relationship was revealed between BDNF genotype and groups.

However, they found that the gene by environment interaction effect is expected to provide a better prediction for melancholic depression. The explanation for the different but not contradictory results is that we examined biological features discriminating melancholic vs. non-melancholic phenotype within a depressed sample, while Quinn et al. (2012) compared the melancholic and non-melancholic group of patients to healthy controls. Power analysis for the logistic regression analysis suggests that our sample was adequate to detect main effects of life events or genotype if they were medium to large, but could only detect interaction effects if they were quite large. Given the complexity of Model 2 of our life event groups, the particular model would only be able to detect large effects, being a limitation to our study.

Though sample size would ideally be larger, this study has several metodological strengths. We note that our melancholic group is a well-defined subgroup within the depressed patients, thanks to the diagnoses established through a very rigorous procedure, described in the Materials and Methods section, using clinician-administered semi-structured interviews to obtain the optimal collection of biographical and contextual information. Life events were measured by researcher-administered questionnaires. Since the parents were the ones providing information about their children’s stressful life events, we had limited information about some of them e.g. teasing by peers, and this lack of additional data may have influenced the scores.

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REFERENCES

Ambrosini PJ, Bennett DS, Cleland CM, Haslam N. Taxonicity of adolescent melancholia: A categorical or dimensional construct. J Psychiat Res. 2002; 36:247–256. [PubMed: 12191629]

American Psychiatric Association (APA). Diagnostic and Statistical manual of mental disorders. 3rd ed.. Washington DC: APA; 1987.

American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders. 4th ed.. Washington DC: APA; 1994.

Bennabi D, Vandel P, Papaxanthis C, Pozzo T, Haffen E. Psychomotor Retardation in Depression: A Systematic Review of Diagnostic, Pathophysiologic, and Therapeutic Implications. Biomed Res Int. 2013; 2013:158746. [PubMed: 24286073]

Bracht T, Horn H, Strik W, Federspiel A, Schnell S, Höfle O, Stegmayer K, Wiest R, Dierks T, Müller TJ, Walther S. White matter microstructure alterations of the medial forebrain bundle in melancholic depression. J Affect Disord. 2014; 155:186–193. [PubMed: 24252169]

Brown GW, Craig TKJ, Harris TO, Herbert J, Hodgson K, Tansey KE, Uher R. Functional polymorphism in the brain-derived neurotrophic factor gene interacts with stressful life events but not childhood maltreatment in the etiology of depression. Depress Anxiety. 2014; 31:326–334. [PubMed: 24338983]

Bukh JD, Bock C, Vinberg M, Werge T, Gether U, Vedel Kessing L. Interaction between genetic polymorphisms and stressful life events in first episode depression. J Affect Disord. 2009; 119(1–3):107–115. [PubMed: 19339052]

Cardoner N, Soria V, Gratacos M, Hernandez-Ribas R, Pujol J, et al. Val66met BDNF genotypes in melancholic depression: effects on brain structure and treatment outcome. Depress Anxiety. 2013; 30:225–233. [PubMed: 23165919]

Chen L, Lawlor DA, Lewis SJ, Yuan W, Abdollahi MR, Timpson NJ, Day IN, Ebrahim S, Smith GD, Shugart YY. Genetic association study of BDNF in depression: Finding from two cohort studies and a meta-analysis. Am J Med Genet (Neuropsychiatr Genet). 2008; 147:814–821.

Chen J, Li X, McGue M. Interacting effect of BDNF Val66Met polymorphism and stressful life events on adolescent depression. Genes, Brain and Behavior. 2012; 11:958–965.

Chen J, Li X, McGue M. The interacting effect of the BDNF Val66Met polymorphism and stressful life events on adolescent depression is not an artifact of gene-environment correlation: evidence from a longitudinal twin study. J Child Psychol Psychiatry. 2013; 54(10):1066–1073. [PubMed: 23848344]

Dantchev N, Widlöcher DJ. The measurement of retardation in depression. J Clin Psychiatry. 1998; 59(Suppl 14):19–25. [PubMed: 9818627]

Domschke K, Lawford B, Laje G, Berger K, Young R, Morris P, Deckert J, Arolt V, McMahon FJ, Baune BT. Brain-derived neurotrophic factor (BDNF) gene: no major impact on antidepressant treatment response. Int. J. Neuropsychop. 2010; 13:93–101.

Elzinga BM, Molendijk ML, Oude Voshaar RC, Bus BA, Prickaerts J, Spinhoven P, Penninx BJ. The impact of childhood abuse and recent stress on serum brain-derived neurotrophic factor and the moderating role of BDNF Val66Met. Psychopharmacology (Berl,). 2011; 214(1):319–328. [PubMed: 20703451]

Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods. 2007; 39:175–191. [PubMed: 17695343]

Gold PW, Gabry KE, Yasuda MR, Chrousos GP. Divergent endocrine abnormalities in melancholic and atypical depression: clinical and pathophysiologic implications. Endocrin Metab Clin. 2002; 31(1):37–62.

Guo CC, Nguyen VT, Hyett MP, Parker GB, Breakspear MJ. Out-of-sync: disrupted neural activity in emotional circuitry during film viewing in melancholic depression. Sci Rep. 2015; 5:11605. [PubMed: 26112251]

Hadzi-Pavlovic D, Boyce P. Melancholia. Curr Opin Psychiatr. 2012; 25(1):14–18.

Hankin BL, Mermelstein R, Roesch L. Sex differences in adolescent depression: stress exposure and reactivity models. Child Dev. 2007; 78:279–295. [PubMed: 17328705]

Harkness KL, Monroe SM. Severe melancholic depression is more vulnerable than non-melancholic depression to minor precipitating life events. J Affect Disord. 2006; 91:257–263. [PubMed: 16476487]

Hosang GM, Shiles C, Tansey KE, McGuffin P, Uher R. Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis. BMC Med. 2014; 12:7. [PubMed: 24433458]

Hyett MP, Parker GB, Proudfoot J, Fletcher K. Examining age effects on prototype melancholic symptoms as a strategy for refining definition of melancholia. J Affect Disord. 2008; 109:193–197. [PubMed: 18162189]

Joyce PR, Mulder RT, Luty SE, McKenzie JM, Rae AM. A differential response to nortriptyline and fluoxetine in melancholic depression: the importance of age and gender. Acta Psychiatr Scand. 2003; 108:20–23. [PubMed: 12807373]

Kapornai K, Gentzler AL, Tepper P, Kiss E, Mayer L, Tamas Z, Kovacs M, Vetro A. Early developmental characteristics and features of major depressive disorder among child psychiatric patients in Hungary. J Affect Disord. 2007; 100(1–3):91–101. [PubMed: 17113651]

Kendler KS, Gatz M, Gardner CO, Pedersen NL. A Swedish national twin study of lifetime major depression. Am J Psychiatry. 2006; 163(1):109–114. [PubMed: 16390897]

Kessler RC. The effects of stressful life events on depression. Annu Rev Psychol. 1997a; 48:191–214. [PubMed: 9046559]

Kessler RC. The diagnostic validity of melancholic major depression in a population-based sample of female twins. Arch Gen Psychiat. 1997b; 54:299–304. [PubMed: 9107145]

Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Kim YH, Yoon JS. Interactions between life stressors and susceptibility genes (5-HTTLPR and BDNF) on depression in Korean elders. Biol Psychiat. 2007; 62(5):423–428. [PubMed: 17482146]

Kiss E, Gentzler AM, George C, Kapornai K, Tamas Z, Kovacs M, Vetro A. Factors influencing mother-child reports of depressive symptoms and agreement among clinically referred depressed youngsters in Hungary. J Affect Disord. 2007; 100:143–151. [PubMed: 17125844]

Kolvin I, Barrett LM, Bhate SR, Berney TP, Famuyiwa OO, Fundudis T, et al. Issues in the diagnosis and classification of childhood depression. Brit J Psychiat. 1991; 159(Suppl 11):9–11.

Liu X, Gentzler AL, Tepper P, Kiss E, Kothencne VO, Tamas Z, Vetro A, Kovacs M. Clinical Features of Depressed Children and Adolescents with Various Forms of Suicidality. J Clin Psychiat. 2006; 67(9):1442–1450.

Lopizzo N, Bocchio Chiavetto L, Cattane N, Plazzotta G, Tarazi FI, Pariante CM, Riva MA, Cattaneo A. Gene-environment interaction in major depression: focus on experience-dependent biological systems. Front Psychiatry 8. 2015; 6:68.

Maes M, Maes L, Schotte C, Vandewoude M, Martin M, D'Hondt P, et al. Clinical subtypes of unipolar depression: Part III, Quantitative differences in various biological markers between the cluster-analytically generated nonvital and vital depression classes. Psychiat Res. 1990; 34:59–75.

Mayer L, Lopez-Duran NL, Kovacs M, George C, Baji I, Kapornai K, Kiss E, Vetro A. Stressful Life Events in a Clinical Sample of Depressed Children in Hungary. J Affect Disord. 2009; 115(1–2): 207–214. [PubMed: 18845343]

Maziade M, Roy MA, Fournier JP, Cliche D, Merette C, Caron C, Garneau Y, Montgrain N, Shriqui C, Dion C. Reliability of best-estimate diagnosis in genetic linkage studies of major psychoses: results from the Quebec pedigree studies. Am J Psychiat. 1992; 149:1674–1686. [PubMed: 1443244]

Michopoulos I, Zervas IM, Pantelis C, Tsaltas E, Papakosta VM, Boufidou F, Nikolaou C, Papageorgiou C, Soldatos CR, Lykouras L. Neuropsychological and hypothalamic–pituitary-axis function in female patients with melancholic and non-melancholic depression. Eur Arch Psy Clin N. 2008; 258:217–225.

Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res. 1988; 16(3):1215. [PubMed: 3344216]

Parker, G.; Hadzi-Pavlovic, D. Melancholia: A Disorder of Movement and Mood. New York: Cambridge University Press; 1996.

Parker G, Paterson A. Melancholia: definition and management. Curr Opin Psychiatry. 2014; 27(1):1–6. [PubMed: 24270479]

Patas K, Penninx BW, Bus BA, Vogelzangs N, Molendijk ML, Elzinga BM, Bosker FJ, Oude Voshaar RC. Association between serum brain-derived neurotrophic factor and plasma interleukin-6 in major depressive disorder with melancholic features. Brain Behav Immun. 2014; 36:71–79. [PubMed: 24140302]

Quinn CR, Dobson-Stone C, Outhred T, Harris A, Kemp AH. The contribution of BDNF and 5-HTT polymorphisms and early life stress to the heterogeneity of major depressive disorder: a preliminary study. Aust N Z J Psychiatry. 2012; 46:55–63. [PubMed: 22247094]

Rice F, Harold G, Thapar A. Assessing the effects of age, sex, and shared environment on the genetic aetiology of depression in childhood and adolescence. Journal of Child Psychology and Psychiatry and Allied Disciplines. 2002; 43(8):1039–1051.

Rice F. Genetics of childhood and adolescent depression: insights into etiological heterogeneity and challenges for future genomic research. Genome Med. 2010; 2(9):68. [PubMed: 20860851]

Ryan ND, Puig-Antich J, Ambrosini P, Rabinovich H, Robinson D, Nelson B, et al. The clinical picture of major depression in children and adolescents. Arch Gen Psychiat. 1987; 44(10):854–861. [PubMed: 3662742]

Rush AJ, Wisniewski SR, Warden D, Luther JF, Davis LL, Fava M, Nierenberg AA, Trivedi MH. Selecting among second-step antidepressant medication monotherapies: predictive value of clinical demographic or first-step treatment features. Arch Gen Psychiat. 2008; 65(8):870–880. [PubMed: 18678792]

SAS Institute Inc. Cary, NC, USA:

Savitz JB, Drevets WC. Imaging Phenotypes of Major Depressive Disorder: Genetic Correlates. Neuroscience. 2009; 164(1):300–330. [PubMed: 19358877]

Sen S, Duman R, Sanacora G. Serum BDNF, Depression and Anti-Depressant Medications: Meta-Analyses and Implications. Biol Psychiatry 15. 2008; 64(6):527–532.

Sherrill JT, Kovacs M. Interview schedule for children and adolescents (ISCA). J Am Acad Child Adolesc Psych. 2000; 39(1):67–75.

Strauss J, Barr CL, George CJ, King N, Shaikh S, Devlin B, Kovacs M, Kennedy JL. Association study of brain-derived neurotrophic factor in adults with a history of childhood onset mood disorder. Am J Med Gen (Neuropsychiatric Genetics). 2004; 131:16–19.

Strauss J, Barr CL, George CJ, Devlin B, Vetro A, Kiss E, Baji I, King N, Shaikh S, Lanktree M, Kovacs M, Kennedy JL. the International Consortium for Childhood-Onset Mood Disorders. Brain-derived neurotrophic factor variants are associated with childhood-onset mood disorder: confirmation in a Hungarian sample. Mol Psychiatr. 2005; 10:861–867.

Schotte CK, Maes M, Cluydts R, Cosyns P. Cluster analytic validation of the DSM melancholic depression: the threshold model: integration of quantitative and qualitative distinctions between unipolar depressive subtypes. Psychiat Res. 1997; 71(3):181–195.

Verhagen M, Meij vd A, Deurzen v PAM, Janzing JGE, Arias-Vásquez A, Buitelaar JK, Franke B. Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity. Mol Psychiatr. 2010; 15:260–271.

Wade TJ, Cairney J, Pevalin DJ. Emergence of gender differences in depression during adolescence: national panel results from three countries. J Am Acad Child Adolesc. 2002; 41:190–198.

Widlöcher DJ. Psychomotor retardation: clinical, theoretical, and psychometric aspects. Psychiatr Clin North Am. 1983; 6(1):27–40. [PubMed: 6889173]

Table 1

Characteristics of the total depressed group (D) and the melancholic (MEL) and non-melancholic subjects (NMEL)

	D n=583	**MEL n=162**	**NMEL n=421**
Age of onset (years)	11.7 ± 2.0	11.7 ± 2.0	11.7 ± 2.0
Male/female	324/259	76/86	248/173
SLE (Mean ± SD)	6.07±2.86	5.84±3.03	6.15±2.78

Table 2

Frequency of stressful life events in the total depressed and the melancholic and non-melancholic groups and the p-values of the independent sample t-statistics testing the differences of the SLE scores between those with and without melancholy

Life event groups	Frequency in the melancholic group (N=162)		Frequency in the non-melancholic group (N=421)		
	N	%	N	%	p-value
Parental health events					
1. Medical hospitalization of biological mother due to somatic illness	49	30.2	155	36.8	0.59
2. Medical hospitalization of biological father	43	26.9	116	27.6	
3. Medical. hospitalization of stepparent	5	3.1	8	1.9	
4. Physical illness of biological mother	16	9.9	46	10.9	
5. Physical illness of biological father	18	11.2	33	7.8	
6. Physical illness of stepparent	0	0.0	1	0.2	
7. Psychiatric hospitalization of biological mother	31	19.1	63	15	
8. Psychiatric hospitalization of biological father	22	13.7	57	13.5	
9. Psychiatric hospitalization of stepparent	0	0.0	6	1.4	
Death of Close Relatives Events					
10. Death of a parent	10	6.2	17	4.0	0.63
11. Death of a close relative	107	66.0	286	67.9	
Sociodemographic Events					
12. Financial problem	40	24.7	134	31.8	0.40
13. Move	92	56.8	222	52.7	
14. Parent unemployed	73	45.3	203	48.2	
15. Natural disaster	4	2.5	13	3.1	
16. Loss of home	5	3.1	17	4	
Intra-familial Events					
17. Sibling birth	102	63.0	275	65.3	0.079
18. Sibling medical hospitalization	36	22.5	139	33.0	
19. Sibling psychiatric hospitalization	12	7.4	33	7.8	
20. Family arguments	78	48.1	225	53.4	

Life event groups	Frequency in the melancholic group (N=162)		Frequency in the non-melancholic group (N=421)		
	N	%	N	%	p-value
21. Foster-care of subject	0	0.0	4	1	
22. Divorce of biological parents	61	37.7	160	38.0	
Extrafamilial Events and Abuse					
23. Abuse	44	27.2	114	27.1	0.92
24. Teasing by peers	88	54.3	230	54.6	
25. Police contact	6	3.7	19	4.5	
26. Suspension from school	3	1.9	7	1.7	

Grouping is based on the study of Mayer et al. (2009)Ref. 24

Table 3

BDNF genotype distributions and allele frequencies in the depressed group and the melancholic and non-melancholic subgroups

	D n=583	MEL n=162	NMEL n=421
Genotype			
Met/Met	18 (3.1%)	4 (2.5%)	14 (3.3%)
Val/Met	167 (28.6%)	39 (24.1%)	128 (30.4%)
Val/Val	398 (68.3%)	119 (73.5%)	279 (66.3%)
Allele			
Val	963 (82.6%)	277 (85.5%)	686 (81.5%)
Met	203 (17.4%)	47 (14.5%)	156 (18.5%)

D: Depressed; MEL: Melancholic (either current or past); NMEL: Non-melancholic depressed

Table 4

Main effects and interactions of BDNF Met-containing genotypes, total stressful life events and stressful life event groups as predictors in the model of melancholic depression in males and females

Dependent variable	Models	Independent variables	OR	*p* value
Melancholy (Females)	Model 1	Met-containing genotypes	-	**.0789**
		Total stressful life events	-	.733
		Met-containing genotypes × Total stressful life events	-	.385
	Model 2	Met-containing genotypes	-	.391
		Parental health	-	.893
		Death of close relatives	-	.187
		Sociodemographic	-	.631
		Intrafamilial	-	.111
		Extrafamilial and Abuse	-	.871
		Met-containing genotypes × Parental health	-	.901
		Met-containing genotypes × Death of close relatives	-	.894
		Met-containing genotypes × Sociodemographic	-	.573
		Met-containing genotypes × Intrafamilial	-	.126
		Met-containing genotypes × Extrafamilial and Abuse	1.05	.021
Melancholy (Males)	Model 1.	Met-containing genotypes	-	.073
		Total stressful life events	-	.109
		Met-containing genotypes × Total stressful life events	-	.990
	Model 2.	Met-containing genotypes	-	.073
		Parental health	-	.485
		Death of close relatives	-	.074
		Sociodemographic	-	.485
		Intrafamilial	-	.195
		Extrafamilial and Abuse	-	.419
		Met-containing genotypes × Parental health	-	.995
		Met-containing genotypes × Death of close relatives	-	.964
		Met-containing genotypes × Sociodemographic	-	.888
		Met-containing genotypes × Intrafamilial	-	.706
		Met-containing genotypes × Extrafamilial and Abuse	-	.356