Meta-analysis of the COMT Val158Met polymorphism in major depressive disorder: the role of gender

Martina Klein, Michaela Schmoeger, Siegfried Kasper & Alexandra Schosser

ABSTRACT

Objectives: Many studies have reported an association of the COMT Val158Met polymorphism and major depressive disorder (MDD), although with conflicting results. The role of gender is a possible modulator. To overcome the problem of poor sample size detecting genes of small effect, we perform a meta-analysis of the current literature, investigating the influence of the COMT Val158Met polymorphism on the pathogenesis of MDD, with a major focus on the effect of gender.

Methods: Out of 977 retrieved articles, 21 included case–control studies allowed the analysis of 9005 patients with MDD and 12,095 controls. Allelic and genotypic pooled odds ratios (OR) were calculated for the total sample and gender-subgroups.

Results: In the absence of publication bias, allelic and genotypic analyses showed no significant association in the total sample, as well as in gender-specific subgroups. Sensitivity analysis did not alter the ORs.

Conclusions: The results imply a complex nature of the genotype/C2 phenotype interaction. Further studies of the COMT gene or the locus remain to be justified given the important positional and functional relevance and the plethora of gender-specific findings. A possible way to further dissect this topic is shifting the focus to gene-based or genome-wide analyses of intermediate phenotypes.

ARTICLE HISTORY

Received 26 March 2015
Revised 29 June 2015
Accepted 11 August 2015

KEYWORDS

Meta-analysis; COMT; Val158Met; gender; major depressive disorder

Introduction

Major depressive disorder (MDD) is a common psychiatric disorder, being predicted to be the second leading cause of disability worldwide by 2020 (Murray and Lopez 1996). It is a heterogeneous disorder caused by a large number of genetic and environmental factors with complex interactions, each with a relatively small contribution (Ebmeier et al. 2006). The heritability – the contribution of genetic factors to the onset of MDD – has been estimated from twin studies at about 40% (Sullivan et al. 2000) and is higher in women than in men (Jansson et al. 2004; Kendler et al. 2006) pointing towards a genetic basis for gender differences.

Despite the large focus on the serotonergic system, the role of dopamine in the aetiology of MDD has already been described in 1965 (Schildkraut 1995), and since then the idea of disturbances in dopamine signalling as one of the main contributors to the pathology of MDD has been underlined in literature. Many symptoms of depression or changes in certain behavioural aspects like mood, motivation, attention, decision making or psychomotor speed are regulated by dopamine (Opmeer et al. 2010). In the prefrontal cortex, the inactivation of dopamine and thus the termination of action in the synapse are mainly regulated by extracellular degradation by catechol-O-methyltransferase, a major catecholamine-degrading enzyme encoded by a single gene on the chromosome 22q11.1.

The COMT gene

The COMT gene consists of six exons. Two promoter regions enable the production of two COMT isoforms, the membrane-bound (MB-COMT) and the 50 amino acids shorter soluble (S-COMT) form encoded by the COMT gene (Bertocci et al. 1991). Most of the human tissues express both the short and the long COMT transcripts except of the adult human brain, where only the long transcript has been found (Tenhunen et al. 1994; Hong et al. 1998) making it the predominant variant in the brain. MB-COMT is assumed to be more important in the prefrontal cortex and in the striatal neurones than in other brain regions. It is responsible for over 60% of dopamine degradation in the prefrontal cortex and 15% in the striatum (Karoum et al. 1994).
The activity of the COMT enzyme is influenced mainly by a functional single nucleotide polymorphism, a G to A substitution at codon 158 (rs4680) of the MB-COMT sequence (corresponding to position 108 of S-COMT) resulting in a valine to methionine exchange (Lachman et al. 1996). This single nucleotide polymorphism is broadly referred to as Val158Met (Lachman et al. 1996; Malhotra et al. 2002). A 3–4-fold reduction in enzyme activity and thermal stability is the consequence (Lachman et al. 1996), making this gene one of the most studied candidate genes in mental disorders. The alleles are co-dominantly causing a trimodal phenotype distribution (Floderus et al. 1981): high activity in Val/Val, intermediate in Val/Met and low in Met/Met genotype.

**COMT in depression**

Since genotyping became an accessible method and with the knowledge that the Val158Met polymorphism largely influences the COMT enzymatic activity, the hypothesis whether the high-activity Val allele and the resulting increased dopamine degradation determine the diagnosis of a depressive disorder was tested in several studies, although with contradictory results (Opmeer et al. 2010). Some studies found an association between the high-activity COMT Val allele, particularly the COMT Val/Val genotype and early-onset MDD in adults (Massat et al. 2005, 2011) and between the Val/Val genotype and depressive symptoms in children (Sheikh et al. 2013). On the contrary, other studies found that the presence of the low-activity Met allele was significantly associated with depression in adult-onset MDD (Ohara et al. 1998) and that symptoms of depression in pregnancy and post-partum-depression increase in carriers of the Met allele (Doornbos et al. 2009, Comasco et al. 2011). Predominantly, studies found no association of the Val158Met polymorphism with the diagnosis of MDD (Kunugi et al. 1997; Frisch et al. 1999; Cusin et al. 2002; Funke et al. 2005; Garriock et al. 2006; Serretti et al. 2006; Jabbi et al. 2007; Baune et al. 2008; Huuhka et al. 2008; Ising et al. 2009; Potter et al. 2009; Huang et al. 2010; Kocabas et al. 2010; Lewis et al. 2010; Muglia et al. 2010; Rietschel et al. 2010; Utge et al. 2010; Bosker et al. 2011; Demirkan et al. 2011; Shi et al. 2011; Soronen et al. 2011) or with scores on depression scales (Henderson et al. 2000; Anttila et al. 2008; Baekken et al. 2008; Wray et al. 2008; Illis et al. 2010; Luciano et al. 2010; Terracciano et al. 2010).

**COMT and gender**

As many conditions in human life, most of the psychiatric disorders show gender differences regarding incidence, clinical features, age of onset or outcome (Piccinelli and Wilkinson 2000; Harrison and Tunbridge 2008; Diflorio and Jones 2010; Essau et al. 2010; McLean et al. 2011; Ochoa et al. 2012). The influence of sex hormones, sex chromosome genes and epigenetic mechanisms such as DNA methylation and chromatin modifications (Kaminsky et al. 2006) as well as influences of autosomal genes have been postulated to result in noteworthy sexual dimorphism (Harrison and Tunbridge 2008).

The sexually dimorphic effect of COMT was already ascribed to oestrogenic regulation in 1971 by Cohn and Axelrod (1971). One of the possible mechanisms has been described by Xie et al. (1999) – the oestrogen-modulated regulation of COMT transcription by interaction of the oestrogen receptor complex with a response element in the COMT promoter region, where oestrogen can inhibit COMT gene transcription, although it seems unlikely to be the only mechanism responsible for gender-based dimorphism.

A number of clinical studies reported a lower COMT activity in women than in men (Floderus et al. 1981; Boudikova et al. 1990; Chen et al. 2004) and in psychiatric research, studies show a significant association between gender-associated differences in psychiatric phenotypes according to COMT genotype. For instance, the functional Val(158)Met polymorphism in COMT is associated with obsessive–compulsive disorder in men (Pooley et al. 2007), with anxiety phenotypes in women (Eley et al. 2003; Enoch et al. 2003; Stein et al. 2005), and has a greater impact on cognitive function in boys than in girls (Barnett et al. 2007).

When considering gender as a covariate, there are more results pointing toward a significant role of the COMT Val158Met polymorphism in the aetiology of major depression. In a large population-based study, Aberg et al. (2011) found that depressed individuals displayed a higher frequency of Met/Met and Met/Val genotypes compared to controls. This association was found among men only. Further, depressed men homozygous for the Val-allele, had a higher motivation level than depressed men with a Met-variant.

In a study by Baekken et al. (2008), the Met/Met genotype and Met allele were significantly less common among depressed men compared to controls. The COMT Val allele was found to be associated with higher pre electro-convulsive therapy (ECT) severity of depression and better treatment response to ECT – these findings were restricted to the female subgroup (Domschke et al. 2010).

Nyman et al. (2011) examined aetiological factors for the development of depression in a large Finnish birth cohort. An association of the COMT genotype (rs4680) with depression was detected particularly in male
individuals at high developmental risk (low birth weight, late motor development, late development of speech).

In suicide research, one of the major contributors to mortality in depression, several gender-specific results occur: for male suicide attempters, there was a significant difference in COMT Val158Met genotype distributions and allele frequencies compared to controls. The Val/Val genotype and Val carrier status were more frequent in suicide attempters than in control subjects (Lee and Kim 2011). Another study found opposite results in suicide completers, the high activity Val/Val genotype being significantly less common in male suicide completers, suggesting a protective factor against suicide in males (Ono et al. 2004).

Animal studies show further evidence towards sexual dimorphism in COMT function (Gogos et al. 1998): dopamine levels of the frontal cortex of COMT knockout mice are increased almost threefold in male COMT –/– mice (and twofold in +/– mice) compared to wild-type mice, this effect has not been found in female knockout mice, where the tissue dopamine levels remained unchanged. This effect may occur presumably because of sex-specific compensatory mechanisms (Harrison and Tunbridge 2008).

The results of these multiple studies imply the importance of including gender as a covariate in analyses examining genetic influences on personality, behaviour and more broadly mental states including its pathologies.

**Aim of the study**

Many studies have reported on an association of the Val158Met polymorphism and psychiatric disorders including MDD, although with conflicting results. The role of gender has been postulated to be a possible modulator, although with the extent of its effect not yet been fully elucidated.

Due to the large sample sizes needed to detect genes of small effect as implicated in aetiology of psychiatric disorders such as MDD, the majority of genetic studies published so far are without doubt statistically underpowered. Therefore, we perform a meta-analysis of the current literature, investigating the influence of the COMT Val158Met polymorphism on the pathogenesis of MDD, with a major focus on the effect of gender as well.

**Materials and methods**

**Search strategy**

The literature research was conducted in the PubMed database for genetic association case–control studies on COMT Val 158 Met polymorphism published before 25 March 2014, using a broad definition of keywords to minimise the search bias. The following search terms were applied: “(depression OR depressive disorder OR depressed) AND (COMT OR rs4680 OR catechol-o-methyltransferase OR candidate gene*)”; “genome-wide AND depress*”; “(Val158Met OR rs4680) AND (depress* OR mood disorder* OR major depress*)”. All retrieved abstracts were reviewed to identify studies which examined the relationship between COMT and depression. After retrieving potentially relevant studies, references cited in these publications were reviewed to identify further publications not obtained by PubMed.

**Inclusion criteria**

Based on this literature research, genetic association studies examining the COMT Val158Met polymorphism were included if they were case-control studies investigating adult (>18 years) unrelated patients with MDD and healthy control subjects, where the case status was defined as having a current diagnosis of MDD, diagnosed by a trained professional in an established psychiatric interview fulfilling standard diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders) for MDD. In the majority of studies, the control-status was established as absence of any psychopathology. In some studies, the screening process of the healthy control subjects was not described explicitly (Kunugi et al. 1997; Arias et al. 2006; Serretti et al. 2006; Huuhka et al. 2008; Illi et al. 2010; Rietschel et al. 2010) which was not considered an exclusion criterion. The comorbidity with an anxiety disorder as a secondary diagnosis in some MDD cases was present in one study (Bosker et al. 2011). This was not considered an exclusion criterion and was examined in the sensitivity analysis.

Different age groups of patients were included (adults, geriatric patients), children and youth were not included in this analysis.

Studies were excluded if: (1) the cases were selected solely by a self-report questionnaire assessing symptoms of depression or reporting on sub-syndromal forms of depression or depression-related phenotypes such as personality traits as well as pure postpartum depression patients, (2) study participants were related, (3) the case or control group contained also bipolar patients or other primary Axis I comorbidity, (4) the data were used in another study on the same polymorphism, (5) the study used others than Caucasian subjects, and (6) was written in another language than English or German.


**Data extraction**

After identifying potentially relevant studies reporting on a case-control design and assessment of COMT rs4680, the full versions of all articles were obtained. In case more diagnoses were examined in one study, only the data on MDD was used.

For each study, the following information was extracted: first author, year of publication, diagnostic system (DSM-III, DSM-IV, ICD-10) and diagnostic tools for determining case status, sample size, ethnicity, gender and mean age of cases and controls, rs4680 allele and genotype frequencies stratified by gender. In case that not all data were published for a study fulfilling the inclusion and exclusion criteria, the authors were contacted to provide the unpublished data (mainly genotype distributions by gender). All contacted authors replied to our requests; however, not all unpublished data were retrievable.

**Statistical analysis**

Meta-analysis was performed for case-control studies reporting on COMT Val158Met polymorphism in MDD in adult Caucasian subjects fulfilling all inclusion and none of the exclusion criteria. Allele frequencies and genotype distribution were extracted for cases and controls. The present meta-analysis includes an overall analysis including all available data and subgroup analyses by gender. Overall, the total sample as well as females and males separately were analysed for both allelic and genotypic associations.

The allelic association of the Val allele with the risk of MDD, relative to the Met allele (OR Val vs. Met) was analysed. Furthermore, genotypic ORs were calculated separately for the homozygous Val/Val genotype with the Met/Met genotype as reference, as well as for heterozygous Val/Met genotype, with the Met/Met and the Val/Val genotype as reference. The odds ratios (OR) were pooled according to the methods of DerSimonian and Laird (1986). The significance of the pooled OR was determined by z-test, the degree of heterogeneity was quantified with the I² statistics (Higgins and Thompson 2002) which describes the proportion of total variation in study estimates due to heterogeneity. Case–control studies were analysed by random effects meta-analysis in case that at least moderate heterogeneity occurred (I² > 30%), and fixed effects meta-analysis in absence of heterogeneity.

The publication bias was evaluated by visual inspection of the funnel plot (Egger et al. 1997). To evaluate the influence of individual studies on the pooled OR, sensitivity analyses were performed by removing studies not reporting on Hardy–Weinberg equilibrium (HWE; Frisch et al. 1999; Illi et al. 2010) or deviating from HWE (Kocabas et al. 2010), studies not explicitly reporting on the screening process of healthy controls (Kunugi et al. 1997; Arias et al. 2006; Serretti et al. 2006; Huuhka et al. 2008; Illi et al. 2010; Rietschel et al. 2010), studies not reporting on screening for psychiatric comorbidities (Kunugi et al. 1997; Frisch et al. 1999; Serretti et al. 2006; Illi et al. 2010) or the presence of comorbidity-secondary anxiety disorder in one study (Bosker et al. 2011). Furthermore, a sensitivity analysis was conducted excluding studies which examined late life depression (Pan et al. 2009), major depression mixed with dysthymia (Demirkan et al. 2011), patients receiving ECT (Huuhka et al. 2008) or suicidal patients (Calati et al. 2011), to rule out potential bias due to different aetiology of depression or more severe manifestation. The OR and 95% confidence interval were recalculated. Cochrane Review Manager Version 5.1 was used for all statistical analyses. \( P < 0.05 \) (two-tailed) were considered statistically significant.

**Results**

The literature search resulted in 977 articles fulfilling the search criteria of which 58 described case–control studies on COMT Val158Met in unrelated adult subjects. We excluded 34 studies for different reasons described in detail in Figure 1. A total of 24 studies fulfilled all inclusion and none of the exclusion criteria. The raw data for further analysis of three studies were not retrievable after contacting the authors (Cusin et al. 2002; Muglia et al. 2010; Shi et al. 2011), resulting in 21 studies included in the final meta-analysis (Figure 1). For 15 out of 21 included studies, gender-specific data was provided by the authors. One study consisted of two samples, which were analysed separately (Frisch et al. 1999); hence, reported results include 22 samples of 21 studies with a final sample size of 9005 patients with MDD and 12,095 controls (Table 1).

**Heterogeneity between studies**

Heterogeneity in meta-analyses indicates, that included studies differ considerably in one or several important aspects, which may have caused differences in results and affected their comparability (Tak et al. 2010). In the majority of our meta-analytic tests, no significant heterogeneity was observed. Merely in the Val/Met vs. Met/Met condition heterogeneity was found in the total sample (\( I^2 = 42\%, \ P = 0.03, \ df = 19 \)) and the female subgroup (\( I^2 = 55\%, \ P = 0.004, \ df = 15 \)). Results of heterogeneity tests are shown in Table 2.
Publication bias

If trials with statistically significant results are more likely to be published, the so-called publication bias arises. In meta-analyses, this may lead to inflated effect estimates in the hypothesised direction (Tak et al. 2010). A funnel plot – a scatter graph plotting a trial's effect estimate against a measure of prediction (standard error of the effect size SE) – was used to assess publication bias. After visual inspection, the funnel plot shown in Figure 2 is symmetric showing no evidence of publication bias.

Association of COMT Val158Met and MDD

The results of the different tests for association of the genetic polymorphism and risk for MDD in the total sample and the gender subgroups are shown in Table 2 and Supplementary Tables 1–12 (available online at http://dx.doi.org/10.3109/15622975.2015.1083615). If no heterogeneity was observed, fixed effects model was applied, in case of observed heterogeneity, random effects model was used.

In all allelic (Val vs. Met) and genotypic (Val/Val vs. Met/Met, Val/Met vs. Val/Val; Val/Met vs. Met/Met) association analyses neither fixed nor random pooled OR were significant both in the total sample, as well as in females or males.

Sensitivity analyses

To evaluate the influence of individual studies on the results of the meta-analytic tests, sensitivity analysis (selectively excluding studies and recalculating the pooled OR) was conducted. Sensitivity analysis was performed with respect to Hardy–Weinberg equilibrium (HWE) deviations, screening of controls, comorbidity and severity of depression. Studies reporting on genotype frequencies deviating significantly from HWE (Kocabas et al. 2010) or not explicitly stating results of HWE analyses (Frisch et al. 1999; Illi et al. 2010) were removed. Furthermore, studies were removed if the control subjects were not screened for depression (Rietschel et al. 2010) or if screening for depression in controls was not reported (Kunugi et al. 1997; Arias et al. 2006; Serretti et al. 2006; Huuhka et al. 2008; Illi et al. 2010). Moreover, studies allowing comorbidity (Bosker et al. 2011) or not explicitly stating the screening process for comorbidities (Kunugi et al. 1997; Frisch et al. 1999; Serretti et al. 2006; Illi et al. 2010;) were excluded. Finally, a sensitivity analysis was performed excluding studies which examined late life depression (Pan et al. 2009), major depression mixed with dysthymia (Demirkan et al. 2011) or patients with severe depression – patients who underwent ECT (Huuhka et al. 2008) or attempted suicide (Calati et al. 2011). Excluding these studies did not substantially alter the ORs as reported above (data not shown).

Discussion

In the present study, we aimed at elucidating an association between the COMT Val158Met functional polymorphism and MDD with a special focus on the role of gender as a moderator. Given the large sample sizes required to assess even small effects of polymorphisms, a meta-analysis represents a crucial technique. As far as we know, this is the largest meta-analysis to date that investigates the role of COMT Val158Met in the aetiology of MDD, and the first one to examine the effect of gender as a variable on a meta-analytic level. Some of the strengths of our study are the wide definition of search terms used to minimise search bias, a conservative approach in study inclusion enhancing the homogeneity of the sample, the acquisition of unpublished (especially gender-specific) data from included studies to
enhance the power and a high level of data transparency, a quality criterion as suggested by Huf et al. (2011). We analysed data from 9005 patients with MDD and 12095 controls from 21 studies (22 samples from 21 studies). Our results showed no association of the Val158Met polymorphism of the COMT gene with MDD, which is in line with a previously published smaller meta-analysis (Lopez-Leon et al. 2008) that included six studies. Even though there is a growing body of evidence for a sexual dimorphism in MDD due to COMT polymorphisms, the subgroup-analyses according to gender did not show an association on allelic or genotypic level. A simple explanation of the relationship between COMT genotype and MDD seems to be unlikely, as underlined by our results. The precise mechanism of action of a genotype × phenotype interaction is complex and not fully clear, but published studies point towards multiple possible contributors, outline directions for further research and help to interpret the lack of association in our study despite of multiple positive findings in the literature.

One possible explanation for the lack of association could be the rather broad definition of the MDD diagnosis with a variety of symptoms making one SNP
unlikely to play a major role. The study by Kocabas et al. (2010) examined a more homogenous population of depressive patients (treatment resistant depression). Even though the association between MDD and COMT did not withstand the correction for multiple testing, a significant association of treatment response in treatment resistant depression has been found. Breaking down into symptoms or intermediate phenotypes could enable an even more homogeneous sample of markers to be examined. Supporting this assumption, there are several studies showing significant associations between intermediate phenotypes or their neural correlates relevant for depressive disorder and COMT Val158Met.

Antypa et al. (2013) observed that clinical phenotypes such as depression severity, the diagnosis of depression or behavioural endophenotypes were less reliably associated with COMT genetic variation, which might contribute to the negative findings of our study. A more pronounced gene effect was seen in emotion processing systems and antidepressant efficacy, pointing towards a more biological model of action of this gene–phenotype interaction. Specifically, the Met allele was associated with increased activity in limbic areas and prefrontal cortex and was also more likely to show a better response to antidepressant treatment, compared to the Val allele.

In a fMRI study by Swart et al. (2011), COMT Met homozygotes reported more difficulties in verbalising their feelings and the Met allele was associated with attenuated brain activation in posterior cingulate gyrus, supporting the hypothesis that the Met allele modulates neural activation in regions associated with emotional awareness. Similarly, Williams et al. (2010) showed in an fMRI study, that a larger number of Met alleles predicted a hypersensitivity toward negative information and an attenuated processing of positive cues. These patterns of activation had correlates in self-reported negativity bias (perceiving and expecting negative events and outcomes) reflecting risk for depressive disorders. These effects were more apparent for females.

In a study by Weiss et al. (2007), Val homozogyosity, as compared to Met homozogyosity, was associated with better and faster recognition of negative facial expressions such as anger and sadness.

Underlining the complexity of the issue, contradictory results were found: Wichers et al. (2008) examined the experience of reward in daily life as a relevant factor in the development of depression, finding significantly increased ability to experience reward in everyday life with increased number of Met alleles.

A consistent COMT-by-sex interaction effect on affect-related personality traits was found by Chen et al. (2011), where males with the Val/Val Genotype showed significantly higher negative emotionality and significantly lower positive emotionality scores compared with Met/Met Males. Females, however, showed an opposite but non-significant pattern.

In a recent fMRI study, Domschke et al. (2012) examined neural activation correlates of emotional face processing as a neural underpinning for depression and anxiety-related intermediate phenotypes and the influence of COMT Val158Met variant with significant and gender-specific results: the more active Val158 variant increased predominantly left-sided amygdala activity in response to fearful/angry facial stimuli (allele-dose effect) and the influence of the Val allele was strictly female-specific, providing further support for the gender-specific effects of COMT Val158Met on emotional processing.

Kempton et al. (2009) also reported on a significant effect of gender on brain activation in an affective processing task with Val/Val carriers showing larger signal magnitude in limbic and paralimbic regions compared to Met/Met carriers, particularly in females.

Another contributor to the diversity of findings might be the gene × gene interaction as well as the role of haplotypes and epigenetic mechanisms strengthening the association between MDD and genes.

Doornbos et al. (2009) reported on a significant role of COMT in the development of peripartal depression, this effect was even stronger in combination with a MAO-A variant. Mandelli et al. (2007) described a significant influence of the COMT Met allele on higher depression scores after adverse life events, which was more pronounced in the presence of the short allele of the serotonin transporter protein gene (SERTPR). Hatzimanolis et al. (2013) found two polymorphisms (rs2020917, rs737865) in the MB-COMT promoter region.
being significantly associated with female depressive symptomatology. Funke et al. (2005) reported on a significant association between rs2097603 (COMT promoter region) and MDD. A high-risk haplotype of the Val allele of rs4680 with the A allele of rs165599 was significantly predictive of differences in neuroticism and risk for several anxiety disorders and major depression in females but not in males (Hettema et al. 2008). Nackley et al. (2006) described certain haplotypes in COMT exhibiting the largest difference in COMT enzymatic activity due to a reduced amount of translated protein not to an altered amount of COMT mRNA. The effect of COMT on depression might also be masked by epigenetic processes such as the genotype-dependent methylation of the COMT Val158 allele modulating lifetime stress perception (Ursini et al. 2011), a significant contributor to the development of depressive states.

Considering the complexity of mental disorders including MDD, the neurochemical pathways involved and the genetic underpinnings, it is not surprising that the interrelation between genetic markers and mental states interacts with other biological factors altering the final effect. Studies examining COMT’s effect on frontal lobe function demonstrate that the relationship between genotype and phenotype, such as emotion regulation networks via the prefrontal cortex, illustrates a similar phenomenon. Winterer et al. (2004) suggested an inverted U-shaped model of the relationship between dopamine levels and prefrontal cortex (PFC) function with both super- and sub-optimal PFC dopamine levels impairing cognitive function and thus the presentation of symptoms. COMT activity influences the position of a given individual on this inverted U curve. This phenomenon highlights the difficulty to differentially assess the function of any individual SNP or partially explains the conflicting results regarding COMT.

It is important to view this study in the scope of its limitations. In general, the results of a meta-analysis always depend on the quality of each included study. By setting conservative inclusion criteria we aimed at solving this issue, nevertheless, between-study heterogeneity (variability between studies) was still partially present. Possible sources of heterogeneity are various clinical and methodological factors in the conducting of the studies, e.g. screening of the healthy participants, assessing comorbid disorders, differences in interviewing styles, etc. In case of heterogeneity, we used random-effects meta-analyses as a more conservative method with a wider confidence interval. Performing sensitivity analysis and sequentially excluding separate studies to check for the effect of suspected divergences in the conducting was used to further dissect this question. No clear confounding factors were found.

Population stratification could still be a problem due to unknown heterogeneity even though we tried to minimise this risk by including Caucasian samples only. It is known, that even among European countries, allelic frequencies differ remarkably (Palmatier et al. 1999) but a more pronounced selection of participants could lead to loss of power. In the future, single well-powered studies on distinct populations could overcome this problem.

To enable comparisons between ethnic groups and further generalizability of results, future research should also take inclusion of other ethnic groups into account.

To obtain a homogeneous and thus comparable sample, we considered comorbid Axis I disorders an exclusion criterion except in one case (Bosker et al. 2011) with anxiety disorders (comorbidity between depression and anxiety-spectrum disorders is highly prevalent and points towards a possibly shared pathogenesis (van Veen et al. 2012)). The role of the comorbidity as a confounder was assessed in sensitivity analysis excluding studies not explicitly reporting on screening for comorbidities and exclusion of one study with comorbid anxiety disorders, showing no effect on the OR. An overall exclusion of comorbid patients seems partially problematic regarding the high level of occurrence. This issue can be solved or minimised by addressing common pathological pathways or shared phenotypes.

For the purpose of maximising the power, we did not focus on other COMT polymorphisms or gene × gene interactions and concentrated on Val158Met, the best studied polymorphism in the COMT gene. This might be considered a limitation.

In conclusion, our meta-analysis did not show an association between COMT Val158Met and MDD in the overall analysis as well as in the gender-specific subgroups.

Further study of the COMT gene or the locus remains to be justified given the important positional and functional relevance and the plethora of gender-specific findings. A possible way to further dissect this topic is shifting the focus to gene-based or genome-wide analyses of intermediate phenotypes related to the disease of interest, which provide a homogeneous dimensional measure, can be defined more precisely and are considered to be more closely related to genotype (Gottesman and Gould 2003).

Acknowledgments

We thank all authors we contacted in the process of obtaining the necessary data for this meta-analysis for their replies and sharing their data with us.
Statement of interest

Martina Klein, Michaela Schmoeger and Alexander Schosser declare no conflict of interest. Siegfried Kasper has received grant/research support from Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Lundbeck, Organon, Pfizer, Sepraco and Servier; he has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Merck Sharp and Dose (MSD), Novartis, Organon, Pfizer, Schwabe, Sepraco, and Servier; and he has served on speakers’ bureaus for Angelini, AOP Orphan Pharmaceuticals AG, AstraZeneca, Bristol-Myers-Squibb, Eli Lilly, Janssen, Lundbeck, Neuropharm, Pfizer, Pierre Fabre, Schwabe, Sepraco, and Servier, Wyeth.

References

Aberg E, Fandino-Losada A, Sjoholm LK, Forsell Y, Lavebratt C. 2011. The functional Val158Met polymorphism in catechol-O-methyltransferase (COMT) is associated with depression and motivation in men from a Swedish population-based study. J Affect Disord. 133:516–521.

Arias B, Serretti A, Lorenzi C, Gasto C, Catalan R, Fananas L. 2006. Analysis of COMT gene (Val 158 Met polymorphism) in the clinical response to SSRIs in depressive patients of European origin. J Affect Disord. 90:251–256.

Baekken PM, Skorpen F, Stordal E, Zwart JA, Hagen K. 2008. Depression and anxiety in relation to catechol-O-methyltransferase Val158Met genotype in the general population: the Nord-Trondelag Health Study (HUNT). BMC Psychiatry. 8:48.

Barnett JH, Heron J, Ring SM, Golding J, Goldman D, Xu K, Jones PB. 2007. Gender-specific effects of the catechol-O-methyltransferase Val108/158Met polymorphism on cognitive function in children. Am J Psychiatry. 164:142–149.

Baune BT, Hohoff C, Berger K, Neumann A, Mortensen S, Roehrs T, et al. 2008. Association of the COMT val158met variant with antidepressant treatment response in major depression. Neuropsychopharmacology. 33:924–932.

Bertocci B, Miggiano V, Da Prada M, Organo, Pfizer, Sepraco and Servier; he has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Merck Sharp and Dome (MSD), Novartis, Organon, Pfizer, Schwabe, Sepraco, and Servier; and he has served on speakers’ bureaus for Angelini, AOP Orphan Pharmaceuticals AG, AstraZeneca, Bristol-Myers-Squibb, Eli Lilly, Janssen, Lundbeck, Neuropharm, Pfizer, Pierre Fabre, Schwabe, Sepraco, and Servier, Wyeth.

References

Aberg E, Fandino-Losada A, Sjoholm LK, Forsell Y, Lavebratt C. 2011. The functional Val158Met polymorphism in catechol-O-methyltransferase (COMT) is associated with depression and motivation in men from a Swedish population-based study. J Affect Disord. 133:516–521.

Anttila S, Huuhka K, Huuhka I, Illi A, Rontu R, Leinonen E, Lehtimaki T. 2008. Catechol-O-methyltransferase (COMT) polymorphisms predict treatment response in electroconvulsive therapy. Pharmacogenomics J. 8:113–116.

Antypa N, Drago A, Serretti A. 2013. The role of COMT gene variants in depression: bridging neuropsychological, behavioral and clinical phenotypes. Neurosci Biobehav Rev. 37:1597–1610.

Aragas N, Wang KS, Pan Y. 2011. Genome-wide association analysis of gender differences in major depressive disorder in the Netherlands NEDSA and NTR population-based samples. J Affect Disord. 133:516–521.

Arias B, Serretti A, Lorenzi C, Gasto C, Catalan R, Fananas L. 2006. Analysis of COMT gene (Val 158 Met polymorphism) in the clinical response to SSRIs in depressive patients of European origin. J Affect Disord. 90:251–256.

Baekken PM, Skorpen F, Stordal E, Zwart JA, Hagen K. 2008. Depression and anxiety in relation to catechol-O-methyltransferase Val158Met genotype in the general population: the Nord-Trondelag Health Study (HUNT). BMC Psychiatry. 8:48.

Barnett JH, Heron J, Ring SM, Golding J, Goldman D, Xu K, Jones PB. 2007. Gender-specific effects of the catechol-O-methyltransferase Val108/158Met polymorphism on cognitive function in children. Am J Psychiatry. 164:142–149.

Baune BT, Hohoff C, Berger K, Neumann A, Mortensen S, Roehrs T, et al. 2008. Association of the COMT val158met variant with antidepressant treatment response in major depression. Neuropsychopharmacology. 33:924–932.

Bertocci B, Miggiano V, Da Prada M, Dembic Z, Lahm HW, Malherbe P. 1991. Human catechol-O-methyltransferase: cloning and expression of the membrane-associated form. Proc Natl Acad Sci USA. 88:1416–1420.

Boomsma DI, Willemsen G, Sullivan PF, Heutink P, Meijer P, Sondervan D, et al. 2008. Genome-wide association of major depression: description of samples for the GAIN Major Depressive Disorder Study: NTR and NESDA biobank projects. Eur J Hum Genet. 16:335–342.

Bosker FJ, Hartman CA, Nolte IM, Prins BP, Terpstra P, Posthuma D, et al. 2011. Poor replication of candidate genes for major depressive disorder using genome-wide association data. Mol Psychiatry. 16:516–532.

Boudikova B, Szumlanski C, Maida B, Weinshilboum R. 1990. Human liver catechol-O-methyltransferase pharmacogenetics. Clin Pharmacol Ther. 48:381–389.

Calati R, Porcelli S, Giegling I, Hartmann AM, Moller HJ, De Ronchi D, et al. 2011. Catechol-O-methyltransferase gene modulation on suicidal behavior and personality traits: review, meta-analysis and association study. J Psychiatr Res. 45:309–321.

Chen C, Chen C, Moyzis R, Dong Q, He Q, Zhu B, et al. 2011. Sex modulates the associations between the COMT gene and personality traits. Neuropsychopharmacology. 36:1593–1598.

Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, et al. 2004. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. Am J Hum Genet. 75:807–821.

Chiesa A, Lia L, Alberti S, Lee SJ, Han C, Patkar AA, et al. 2014. Lack of influence of rs4680 (COMT) and rs6276 (DRD2) on diagnosis and clinical outcomes in patients with major depression. Int J Psychiatry Clin Pract. 18:97–102.

Cohn CK, Axelrod J. 1971. The effect of estradiol on catechol-O-methyltransferase activity in rat liver. Life Sci 10:1351–1354.

Comasco E, Sylven SM, Papadopoulos FC, Sundstrom-Poromaa I, Oreland L, Skalkidou A. 2011. Postpartum depression symptoms: a case-control study on monoaminergic functional polymorphisms and environmental stressors. Psychiatr Genet. 21:19–28.

Conway CC, Hammen C, Brennan PA, Lind PA, Najman JM. 2010. Interaction of chronic stress with serotonin transporter and catechol-O-methyltransferase polymorphisms in predicting youth depression. Depress Anxiety. 27:737–745.

Cross-Disorder Group of the Psychiatric Genomics Consortium. 2013. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet. 381:1371–1379.

Cusin C, Serretti A, Lattuada E, Lilli R, Lorenzi C, Smeraldi E. 2002. Association study of MAOA-A, COMT, 5-HT2A, DRD2, and DRD4 polymorphisms with illness time course in mood disorders. Am J Med Genet. 114:380–390.

Dao DT, Mahon PB, Cai X, Kovacsics CE, Blackwell RA, Arad M, et al. 2010. Mood disorder susceptibility gene CACNA1C modifies mood-related behaviors in mice and interacts with sex to influence behavior in mice and diagnosis in humans. Biol Psychiatry. 68:801–810.

Demirkan A, Penninx BW, Hek K, Wray NR, Amin N, Aulchenko YS, et al. 2011. Genetic risk profiles for depression and anxiety in adult and elderly cohorts. Mol Psychiatry. 16:773–783.

DerSimonian R, Laird N. 1986. Meta-analysis in clinical trials. Control Clin Trials. 7:177–188.

Difiorio A, Jones I. 2010. Is sex important? Gender differences in bipolar disorder. Int Rev Psychiatry. 22:437–452.

Domschke K, Baune BT, Havlik L, Stuhrmann A, Suslow T, Kugel H, et al. 2012. Catechol-O-methyltransferase gene variation: impact on amygdala response to aversive stimuli. Neuroimage. 60:2222–2229.

Domschke K, Zavorotnyy M, Diemer J, Nitsche S, Hohoff C, Baune BT, et al. 2010. COMT val158met influence on electroconvulsive therapy response in major depression. Am J Med Genet B Neuropsychiatr Genet. 153B:286–290.
Doornbos B, Dijck-Brouwer DA, Kema IP, Tanke MA, van Goor SA, Muskiet FA, Korf J. 2009. The development of peripartum depressive symptoms is associated with gene polymorphisms of MAOA, 5-HTT and COMT. Prog Neuropsychopharmacol Biol Psychiatry. 33:1250–1254.

Ebele KP, Donaghey C, Steele JD. 2006. Recent developments and current controversies in depression. Lancet. 367:153–167.

Egger M, Davey Smith G, Schneider M, Minder C. 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ. 315:629–634.

Eley TC, Tahir E, Angleitner A, Harriss K, McClain J, Plomin R, et al. 2003. Association analysis of MAOA and COMT with neuroticism assessed by peers. Am J Med Genet B Neuropsychiatr Genet. 120B:90–96.

Enoch MA, Xu K, Ferro E, Harris CR, Goldman D. 2003. Genetic origins of anxiety in women: a role for a functional catechol-o-methyltransferase polymorphism. Psychiatr Genet. 13:33–41.

Essau CA, Lewinsohn PM, Seeley JR, Sasagawa S. 2010. Gender differences in the developmental course of depression. J Affect Disord. 127:185–190.

Floderus Y, Ross SB, Wetterberg L. 1981. Erythrocyte catechol-o-methyltransferase activity in a Swedish population. Clin Genet. 19:389–392.

Frisch A, Postlinick D, Rockah R, Michaelovsky E, Postlinick S, Birman E, et al. 1999. Association of unipolar major depressive disorder with genes of the serotonergic and dopaminergic pathways. Mol Psychiatry. 4:389–392.

Funke B, Malhotra AK, Finn CT, Plocik AM, Lake SL, Lencz T, et al. 2005. COMT genetic variation confers risk for psychotic and affective disorders: a case control study. Behav Brain Funct. 1:19

Garrick HA, Delgado P, Kling MA, Carpenter LL, Burke M, Burke WJ, et al. 2006. Number of risk genotypes is a risk factor for major depressive disorder: a case control study. Behav Brain Funct. 2:24.

Gogos JA, Morgan M, Luine V, Santha M, Ogawa S, Pfaff D, Karayiorgou M. 1998. Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. Proc Natl Acad Sci USA. 95:9991–9996.

Gottesman II, Gould TD. 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry. 160:636–645.

Haefelf GJ, Eastman M, Grigorenko EL. 2012. Using a cognitive endophenotype to identify risk genes for depression. Neurosci Lett. 510:10–13.

Harrison PJ, Tunbridge EM. 2008. Catechol-O-methyltransferase (COMT): a gene contributing to sex differences in brain function, and to sexual dimorphism in the predisposition to psychiatric disorders. Neuropsychopharmacology. 33:3037–3045.

Hatzimanolis AVS, Mandelli L, Vaiopoulos C, Nearchou FA, Stefanis CN, Serretti A, Stefanis NC. 2013. Potential role of membrane-bound COMT gene polymorphisms in female depression vulnerability. Journal of Affective Disorders. 148:316–322.

Henderson AS, Korten AE, Jorm AF, Jacomb PA, Christensen H, Rodgers B, et al. 2000. COMT and DRD3 polymorphisms, environmental exposures, and personality traits related to common mental disorders. Am J Med Genet. 96:102–107.

Hettema JM, An SS, Bukszar J, van den Oord EJ, Neale MC, Kendler KS, Chen X. 2008. Catechol-O-methyltransferase contributes to genetic susceptibility shared among anxiety spectrum phenotypes. Biol Psychiatry. 64:302–310.

Higgins JP, Thompson SG. 2002. Quantifying heterogeneity in a meta-analysis. Stat Med. 21:1539–1558.

Hong J, Shu-Leong H, Tao X, Lap-Ping Y. 1998. Distribution of catechol-o-methyltransferase expression in human central nervous system. Neuroreport. 9:2861–2864.

Huang J, Perlis RH, Lee PH, Rush AJ, Fava M, Sachs GS, et al. 2010. Cross-disorder genomewide analysis of schizophrenia, bipolar disorder, and depression. Am J Psychiatry. 167:1254–1263.

Huf W, Kalcher K, Pail G, Friedrich ME, Filizmoser P, Kasper S. 2011. Meta-analysis: fact or fiction? How to interpret meta-analyses. World J Biol Psychiatry. 12:188–200.

Huhuoka K, Anttila S, Huhuoka M, Hietala J, Huhtala H, Mononen N, et al. 2008. Dopamine 2 receptor C957T and catechol-o-methyltransferase Val158Met polymorphisms are associated with treatment response in electroconvulsive therapy. Neurosci Lett. 448:79–83.

Illi A, Setala-Solikelli E, Kampman O, Viikki M, Nuolivirta T, Poutanen O, et al. 2010. Catechol-O-methyltransferase val108/158met genotype, major depressive disorder and response to selective serotonin reuptake inhibitors in major depressive disorder. Psychiatry Res. 176:85–87.

Ising M, Lucae S, Binder EB, Bettecken T, Uhr M, Ripke S, et al. 2009. A genomewide association study points to multiple loci that predict antidepressant drug treatment outcome in depression. Arch Gen Psychiatry. 66:966–975.

Jabbi M, Kema IP, van der Pompe G, te Meeran GJ, Ormel J, den Boer JA. 2007. Catechol-o-methyltransferase polymorphism and susceptibility to major depressive disorder modulates psychological stress response. Psychiatr Genet. 17:183–193.

Jansson M, Gatz M, Berg S, Johansson B, Malmberg B, McClean GE, et al. 2004. Gender differences in heritability of depressive symptoms in the elderly. Psychol Med. 34:471–479.

Kaminsky Z, Wang SC, Petronis A. 2006. Complex disease, gender and epigenetics. Ann Med. 38:530–544.

Karoum F, Chrapusta SJ, Egan MF. 1994. 3-Methoxytryptamine is the major metabolite of released dopamine in the rat frontal cortex: reassessment of the effects of antipsychotics on the dynamics of dopamine release and metabolism in the frontal cortex, nucleus accumbens, and striatum by a simple two pool model. J Neurochem. 63:972–979.

Kempton MJ, Haldane M, Mogia J, Cristodoulou T, Powell J, Collier D, et al. 2009. The effects of gender and COMT Val158Met polymorphism on fearful facial affect recognition: a fMRI study. Int J Neuropsychopharmacol. 12:371–381.

Kendler KS, Gatz M, Gardner CO, Pedersen NL. 2006. A Swedish national twin study of lifetime major depression. Am J Psychiatry. 163:109–114.

Kocabas NA, Faghel C, Barreto M, Kasper S, Linotte S, Mendlewicz J, et al. 2010. The impact of catechol-O-methyltransferase SNPs and haplotypes on treatment response phenotypes in major depressive disorder: a case-control association study. Int Clin Psychopharmacol. 25:218–227.

Kunugi H, Vallada HP, Hoda F, Kirov G, Gill M, Altvichon KJ, et al. 1997. No evidence for an association of affective disorders
with high- or low-activity allele of catechol-o-methyltransferase gene. Biol Psychiatry. 42:282–285.

Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinsilboum RM. 1996. Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics. 6:243–250.

Lee HY, Kim YK. 2011. Gender effect of catechol-O-methyltransferase Val158Met polymorphism on suicidal behavior. Neuropsychobiology. 63:177–182.

Lee PH, Perlis RH, Jung JY, Byrne EM, Rueckert E, Sibuiran R, Haddad S, Mayerfeld CE, Heath AC, Pergadia ML, et al. 2012. Multi-locus genome-wide association analysis supports the role of glutamatergic synaptic transmission in the etiology of major depressive disorder. Transl Psychiatry. 2:e184.

Lewis CM, Ng MY, Butler AW, Cohen-Woods S, Uher R, Pirlo K, et al. 2010. Genome-wide association study of major recurrent depression in the U.K. population. Am J Psychiatry. 167:949–957.

Lopez-Leon S, Janssens AC, Gonzalez-Zuloeta Ladd AM, Del-Favero J, Claes SJ, Oostra BA, van Duijn CM. 2008. Meta-analyses of genetic studies on major depressive disorder. Mol Psychiatry. 13:772–785.

Luciano M, Houllihan LM, Harris SE, Gow AJ, Hayward C, Starr JM, Deary IJ. 2010. Association of existing and new candidate genes for anxiety, depression and personality traits in older people. Behav Genet. 40:518–532.

Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D. 2002. A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. Am J Psychiatry. 159:652–654.

Mandelli L, Serretti A, Marino E, Pirovano A, Calati R, Colombo C. 2007. Interaction between serotonin transporter gene, catechol-O-methyltransferase gene and stressful life events in mood disorders. Int J Neuropsychopharmacol. 10:437–447.

Massat I, Kocabas NA, Crisafulli C, Chiesa A, Calati R, Linotte S, et al. 2011. COMT and age at onset in mood disorders: a replication and extension study. Neurosci Lett. 498:218–221.

Massat I, Souery D, Del-Favero J, Nothen M, Blackwood D, Muir W, et al. 2005. Association between COMT (Val158Met) functional polymorphism and early onset in patients with major depressive disorder in a European multicenter genetic association study. Mol Psychiatry. 10:598–605.

McLean CP, Asnaani A, Litz BT, Hofmann SG. 2011. Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. J Psychiatr Res. 45:1027–1035.

Muglia P, Tozzi F, Galwey NW, Francks C, Upmanyu R, Kong XQ, et al. 2010. Genome-wide association study of recurrent major depressive disorder in two European case-control cohorts. Mol Psychiatry. 15:589–601.

Murray CJ, Lopez AD. 1996. Evidence-based health policy-Muglia P, Tozzi F, Galwey NW, Francks C, Upmanyu R, Kong XQ, McLean CP, Asnaani A, Litz BT, Hofmann SG. 2011. Gender differences in schizophrenia and first-episode psychosis: a comprehensive literature review. Schizophr Res Treatment. 2012:916198

Ohara K, Nagai M, Suzuki Y, Ohara K. 1998. Low activity allele of catechol-o-methyltransferase gene and Japanese unipolar depression. Neuroreport. 9:1305–1308.

Ono H, Shirakawa O, Nushida H, Ueno Y, Maeda K. 2004. Association between catechol-O-methyltransferase functional polymorphism and male suicide completers. Neuropsychopharmacology. 29:1374–1377.

Opmeer EM, Kortekaas R, Aleman A. 2010. Depression and the role of genes involved in dopamine metabolism and signalling. Prog Neurobiol. 92:112–133.

Opmeer EM, Kortekaas R, van Tol MJ, van der Wee NJ, Woudstra S, van Buchem MA, et al. 2013. Influence of COMT val158met genotype on the depressed brain during emotional processing and working memory. PLoS One. 8:e73290

Palmatier MA, Kang AM, Kidd KK. 1999. Global variation in the frequencies of functionally different catechol-O-methyltransferase alleles. Biol Psychiatry. 46:557–567.

Pan CC, McQuoid DR, Taylor WD, Payne ME, Ashley-Koch A, Steffens DC. 2009. Association analysis of the COMT/MTHFR genes and geriatric depression: an MRI study of the putamen. Int J Geriatr Psychiatry. 24:847–855.

Piccinelli M, Wilkinson G. 2000. Gender differences in depression. Critical review. Br J Psychiatry. 177:486–492.

Pooley EC, Fineberg N, Harrison PJ. 2007. The met(158) allele of catechol-O-methyltransferase (COMT) is associated with obsessive-compulsive disorder in men: case-control study and meta-analysis. Mol Psychiatry. 12:556–561.

Potter GG, Taylor WD, McQuoid DR, Steffens DC, Welsh-Bohmer KA, Krishnan KR. 2009. The COMT Val158Met polymorphism and cognition in depressed and nondepressed older adults. Int J Geriatr Psychiatry. 24:1127–1133.

Rebeck TRSH, Sammeld MD, Lin H, Tran TV, Gracia CR, Freeman EW. 2010. Effect of hormone metabolism genotypes on steroid hormone levels and menopausal symptoms in a prospective population-based cohort of women experiencing the menopausal transition. Menopause. 17:1026–1034.

Rietschel M, Mattheisen M, Frank J, Treutlein J, Degenhardt F, Breuer R, et al. 2010. Genome-wide association-, replication-, and neuroimaging study implicates HOMER1 in the etiology of major depression. Biol Psychiatry. 68:578–585.

Rus MJ, Lachman HM, Kashdan T, Saito T, Bajmajakovic-Kacila S. 2000. Analysis of catechol-O-methyltransferase and 5-hydroxytryptamine transporter polymorphisms in patients at risk for suicide. Psychiatry Res. 93:73–78.

Schildkraut JJ. 1995. The catecholamine hypothesis of affective disorders: a review of supporting evidence. 1965. J Neuropsychiatry Clin Neurosci. 7:524–533. Discussion 523-4.

Schol-Gelok SJA, Tiemerer H, Liu F, Lopez-Leon S, Zorkoltseva IV, Axenovich TI, et al. 2010. A genome-wide screen for depression in two independent Dutch populations. Biol Psychiatry. 68:187–196.

Schosser A, Butler AW, Uher R, Ng MY, Cohen-Woods S, Caddick N, et al. 2013. Genome-wide association study of co-occurring anxiety in major depression. World J Biol Psychiatry. 14:611–621.

Seok JHCS, Lim HK, Lee SH, Kim J, Ham BJ. 2013. Effect of the COMT val158met polymorphism on white matter depression in a large population-based Finnish birth cohort. BMJ Open. 1:e000087.
connectivity in patients with major depressive disorder. Neurosci Lett. 545:35–39.
Serretoni R, Rotondo A, Lorenzi C, Smeraldi E, Cassano GB. 2006. Catechol-O-methyltransferase gene variants in mood disorders in the Italian population. Psychiatr Genet. 16:181–182.
Sheikh HI, Kryski KR, Smith HJ, Dougherty LR, Klein DN, Bufford SJ, et al. 2013. Catechol-O-methyltransferase gene val158met polymorphism and depressive symptoms during early childhood. Am J Med Genet B Neuropsychiatr Genet. 162B:245–252.
Shi J, Potash JB, Knowles JA, Weissman MM, Coryell W, Scheftner WA, et al. 2011. Genome-wide association study of recurrent early-onset major depressive disorder. Mol Psychiatry. 16:193–201.
Shyn SI, Shi J, Kraft JB, Potash JB, Knowles JA, Weissman MM, et al. 2011. Novel loci for major depression identified by genome-wide association study of Sequenced Treatment Alternatives to Relieve Depression and meta-analysis of three studies. Mol Psychiatry. 16:202–215.
Song GG, Kim JH, Lee YH. 2013. Genome-wide pathway analysis in major depressive disorder. J Mol Neurosci. 51:428–436.
Soronen P, Mantere O, Melartin T, Suominen K, Vuorilehto M, Ryttsala H, et al. 2011. P2RX7 gene is associated consistently with mood disorders and predicts clinical outcome in three clinical cohorts. Am J Med Genet B Neuropsychiatr Genet. 156B:435–447.
Stein MB, Fallin MD, Schork NJ, Gelernter J. 2005. COMT polymorphisms and anxiety-related personality traits. Neuropsychopharmacology. 30:2092–2102.
Sullivan PF, de Geus EJ, Willemsen G, James MR, Smit JH, Zandbelt T, et al. 2009. Genome-wide association for major depressive disorder: a possible role for the presynaptic protein piccolo. Mol Psychiatry. 14:359–375.
Sullivan PF, Neale MC, Kendler KS. 2000. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry. 157:1552–1562.
Swart M, Bruggeman R, Laroi F, Alizadeh BZ, Kema I, Kortekaas R, et al. 2011. COMT Val158Met polymorphism, verbalizing of emotion and activation of affective brain systems. Neuroimage. 55:338–344.
Tak LM, Meijer A, Manoharan A, de Jonge P, Rosmalen JG. 2010. More than the sum of its parts: meta-analysis and its potential to discover sources of heterogeneity in psychosomatic medicine. Psychosom Med. 72:253–265.
Tenhunen J, Salminen M, Lundstrom K, Kiviluoto T, Savolainen R, Ulmanen I. 1994. Genomic organization of the human catechol O-methyltransferase gene and its expression from two distinct promoters. Eur J Biochem. 223:1049–1059.
Terracciano A, Tanaka T, Sutin AR, Sanna S, Deiana B, Lai S, et al. 2010. Genome-wide association scan of trait depression. Biol Psychiatry. 68:811–817.
Ursini G, Bollati V, Fazio I, Porcelli A, Iacovelli L, Catalani A, et al. 2011. Stress-related methylation of the catechol-O-methyltransferase Val 158 allele predicts human prefrontal cognition and activity. J Neurosci. 31:6692–6698.
Utge S, Soronen P, Partonen T, Loukola A, Kronholm E, Pirkola S, et al. 2010. A population-based association study of candidate genes for depression and sleep disturbance. Am J Med Genet B Neuropsychiatr Genet. 153B:468–476.
van Veen T, Goeman JJ, Monajemi R, Wardenaar KJ, Hartman CA, Snieder H, et al. 2012. Different gene sets contribute to different symptom dimensions of depression and anxiety. Am J Med Genet B Neuropsychiatr Genet. 159B:519–528.
Wang X, Wang Z, Wu Y, Yuan Y, Hou Z, Hou G. 2013. Association analysis of the catechol-O-methyltransferase/methylenetetrahydrofolate reductase genes and cognition in late-onset depression. Psychiatry Clin Neurosci. 68:344–352.
Weiss EM, Stadelmann E, Kohler CG, Brensinger CM, Nolan KA, Oberacher H, et al. 2007. Differential effect of catechol-O-methyltransferase Val158Met genotype on emotional recognition abilities in healthy men and women. J Int Neuropsychol Soc. 13:881–887.
Wichers M, Aguilera M, Kenis G, Krabbe D, Myin-Germeyns I, Jacobs N, et al. 2008. The catechol-O-methyltransferase Val158Met polymorphism and experience of reward in the flow of daily life. Neuropsychopharmacology. 33:3030–3036.
Williams LM, Gatt JM, Grieve SM, Dobson-Stone C, Paul RH, Gordon E, Schofield PR. 2010. COMT Val(108/158)Met polymorphism effects on emotional brain function and negativity bias. Neuroimage. 53:918–925.
Winterer GWD. 2004. Genes, dopamine and cortical signal-to-noise ratio in schizophrenia. Trends Neurosci. 27:683–690.
Wong MLDC, Andreev V, Arcos-Burgos M, Licinio J. 2012. Prediction of susceptibility to major depression by a model of interactions of multiple functional genetic variants and environmental factors. Mol Psychiatry. 17:624–633.
Wray NR, James MR, Dumenil T, Handoko HY, Lind PA, Montgomery GW, Martin NG. 2008. Association study of candidate variants of COMT with neuroticism, anxiety and depression. Am J Med Genet B Neuropsychiatr Genet. 157B:1314–1318.
Wray NR, Pergadia ML, Blackwood DH, Penninx BW, Gordon SD, Nyholt DR, et al. 2012. Genome-wide association study of major depressive disorder: new results, meta-analysis, and lessons learned. Mol Psychiatry. 17:36–48.
Xie T, Ho SL, Ramsden D. 1999. Characterization and implications of estrogenic down-regulation of human catechol-O-methyltransferase gene transcription. Mol Pharmacol. 56:31–38.