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Depression and anxiety in relation to catechol-O-methyltransferase Val¹⁵⁸Met genotype in the general population: The Nord-Trøndelag Health Study (HUNT)

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Abstract

Background: The catechol-O-methyltransferase (COMT) gene contains a functional polymorphism, Val158Met, which has been linked to anxiety and depression, but previous results are not conclusive. The aim of the present study was to examine the relationship between the Val158Met COMT gene polymorphism and anxiety and depression measured by the Hospital Anxiety and Depression Scale (HADS) in the general adult population.

Methods: In the Nord-Trøndelag Health Study (HUNT) the association between the Val158Met polymorphism and anxiety and depression was evaluated in a random sample of 5531 individuals. Two different cut off scores (≥ 8 and ≥ 11) were used to identify cases with anxiety (HADS-A) and depression (HADS-D), whereas controls had HADS-A < 8 and HADS-D < 8 .

Results: The COMT genotype distribution was similar between controls and individuals in the groups with anxiety and depression using cut-off scores of ≥ 8 . When utilizing the alternative cut-off score HADS-D ≥ 11 , Met/Met genotype and Met allele were less common among men with depression compared to the controls (genotype: $p = 0.017$, allele: $p = 0.006$). In the multivariate analysis, adjusting for age and heart disease, depression (HADS-D ≥ 11) was less likely among men with the Met/Met genotype than among men with the Val/Val genotype (OR = 0.37, 95% CI = 0.18–0.76).

Conclusion: In this population-based study, no clear association between the Val158Met polymorphism and depression and anxiety was revealed. The Met/Met genotype was less likely among men with depression defined as HADS-D ≥ 11 , but this may be an incidental finding.

Background

The catechol-O-methyltransferase (COMT) gene located on chromosome 22q11.2 contains a common functional polymorphism at codon 158. This polymorphism has been subject to a large number of studies, due to the COMT enzyme's important role in the metabolism of catecholamines (1). A substitution of valine (Val) by methionine (Met) at codon 158 affects the activity of the COMT enzyme, and individuals with the Val/Val genotype have a 3–4-times higher enzyme activity than those with the Met/Met genotype [1]. Since the alleles are co-dominant, heterozygous individuals (Val/Met) show an enzyme activity halfway between the homozygous genotypes.

The Val158Met polymorphism has been linked to a broad range of psychiatric disorders including anxiety and mood disorders [2]. Although anxiety and depression both are influenced by several genes in combination with environmental factors, association studies with large samples of subjects are appropriate for searching susceptibility genes with minor effects on these disorders [3]. A large European multicenter study including 1512 participants reported an association between the Val/Val genotype and major depression with early onset [3], but conflicting results have been found in other studies with fewer participants [4]. Similarly, inconsistent findings have also been reported in studies evaluating the relationship between the Val158Met polymorphism and anxiety [5-7]. Ethnic heterogeneity and gender specificity may have influenced on the inconclusive results [8].

Most of the previous studies evaluating the relationship between the Val158Met polymorphism and anxiety and/or mood disorders have been case-control studies. In such studies undiagnosed- and untreated cases with depression and/or anxiety may have been missed. Generalization of the results should therefore be done with caution. Because population-based studies have the potential to intercept undiagnosed- and untreated cases [9], the influence of the Val158Met polymorphism on anxiety and depression should also be evaluated in the general population.

To the best of our knowledge, this is the first population-based study evaluating the relationship between the Val158Met polymorphism and anxiety and depression measured by the Hospital Anxiety and Depression Scale (HADS). The dimensional structure of HADS has been found stable across age-groups [9], and the HADS questionnaire is widely used to measure anxiety and depression in somatic and psychiatric patients as well as in the general population [10]. Previous studies on HADS have shown good reliability and validity compared to other symptom scales of depression and anxiety [10-15].

In the present study, we examined the relationship between the Val158Met polymorphism and anxiety and depression measured by HADS in a population-based cohort of 5531 subjects.

Methods

Study population

Between August 1995 and June 1997, all inhabitants aged 20 years or older in Nord-Trøndelag County were invited to participate in the Nord-Trøndelag Health Study (HUNT). In brief, two questionnaires including more than 200 health related questions were administered to the participants. The population in Nord-Trøndelag County was ethnically homogenous (less than 3% of subjects were of non-Caucasian ethnicity), making it suitable for epidemiological genetic research [16].

Out of 92,936 invited individuals, a total of 65,291 subjects (70%) answered the first questionnaire and participated in a health examination. The first questionnaire included questions about e.g. vascular diseases, smoking, and physical activity [16]. The health examination included measurements of height, weight, and blood pressure, and blood samples measuring e.g. cholesterol were collected [16].

Details of the non-participants are described elsewhere [17]. Blood samples were collected from 62,664 of the study population whenever they attended, and stored at HUNT 2 Biobank [16]. In 2002, all surviving participants (n = 61,426) were asked for permission to use the blood samples in genetic analyses. Over 98% (n = 60,241) accepted this [16]. Analyses on the Val158Met polymorphism have been carried out on 5,531 participants, of whom 4513 (82%) were selected completely at random. The first 1018 (18%) subjects were randomly selected among an older group who did not have self-reported diabetes mellitus [18]. This group was generated in connection with a planned genetic study on diabetes that needed age-matched controls to a diabetic population. As a consequence, the prevalence of self-reported diabetes mellitus was somewhat lower among individuals with known genotype than among those without COMT data available (1.3% versus 3.2%, $p < 0.001$).

Genotyping

DNA for genotyping was extracted from peripheral blood leukocytes from EDTA whole blood or blood clots, stored in the HUNT 2 Biobank, manually with the use of Puregene kit (Gentra Systems Inc., Minneapolis, MN) or with the Autopure LS (Gentra Systems Inc., Minneapolis, MN). The laboratory technicians were blinded for other HUNT data. Genotypes of the COMT Val158Met polymorphism were determined using a LightCycler Real Time PCR machine (Roche Diagnostics Scandinavia AB, Bromma,

Sweeden) [19]. PCR-technique was carried out in 20 μ L reagent on a LightCycler System by using 2 μ L genomic DNA and LightCycler-FastStart DNA Master Hybridization Probes kit (Roche Diagnostics, Bromma, Sweeden). Details on PCR primers and hybridization probes used have been published elsewhere [17]. Based on melting-curve profiles, the genotypes of the participants were classified as Val/Val, Val/Met or Met/Met.

Anxiety and depression

HADS is a self-assessment scale containing 14 questions developed to detect states of anxiety and depression, specifically designed for non-psychiatric hospital departments [20]. To each question there are four possible response options which are scored from 0 to 3 points depending on the severity of the symptoms. There are seven questions related to depressive symptoms (HADS-D subscale) and seven questions concerning anxiety symptoms (HADS-A subscale). Based on empirical knowledge a clinically significant anxiety disorder is defined by a HADS-A score of ≥ 8 , while depressive disorder is defined by HADS-D ≥ 8 . These limits are found to give the optimal balance between sensitivity and specificity [11]. Based on HADS-A and HADS-D scores, the participants were classified into one of five groups: 1) No disorder (controls): both HADS-A < 8 and HADS-D < 8 ; 2) Anxiety disorder: HADS-A ≥ 8 ; 3) Depressive disorder: HADS-D ≥ 8 ; 4) Combined disorder: both HADS-A ≥ 8 and HADS-D ≥ 8 ; and 5) Unclassified. This last group consisted of subjects with insufficient HADS score data. Some had total HADS scores but unavailable subscale scores, while others only had valid HADS-A or HADS-D score. To increase the specificity [9] and with intention identify individuals with moderate or severe disorder, analyses using cut-off score ≥ 11 were also performed, recommended for the first time 25 years ago [21]. Analyses were performed for men and women separately because previous studies have reported a gender difference regarding anxiety and the Val158Met polymorphism [8].

Ethics

The study was approved by the Regional Committee of Ethics, by the Norwegian Data Inspectorate and by the Directorate for Health and Social Affairs.

Statistical analyses

Baseline data were compared between genotype status with analyses of variance (one-way ANOVA) for continuous variables and with Pearson's chi-square test for categorical variables. Blood pressure values were compared with the non-parametric Mann-Whitney U test because of a skewed distribution of the data [18].

Gender comparisons for each genotype regarding HADS-A scores and HADS-D scores as continuous variables were

performed with Mann-Whitney U because of skewed data. Spearman's correlation analyses were conducted to correlate scores of HADS-A and HADS-D with genotypes.

Chi-square test was used to evaluate dichotomous variables of HADS-A and HADS-D. Binary multivariate logistic regression was used to estimate odds ratios (OR) for the association between genotype and each of the two HADS subscales, i.e. depression and anxiety disorder (dependent variable). Potential confounding was evaluated by adjusting for sex, age (5-year categories) and ischemic heart disease. The precision for the OR was estimated with 95% confidence interval (CI).

Two-tailed estimations of significance were used, and the level of significance was set at $p < 0.05$.

Overall, our sample of 5,531 had more than 90% power to detect a 3% difference in prevalence of anxiety and depression between genotypes with 95 percent certainty.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 14.0 (SPSS Inc, Chicago, IL).

Results

The genotype distribution among the 5,531 individuals was in Hardy-Weinberg equilibrium. Demographic data of the different genotype groups are shown in Table 1. No significant difference in gender, age, education level, body mass index, cholesterol level, smoking status, level of physical activity, diabetes-, stroke- or headache prevalence was found between the genotype groups. However, individuals with Val/Val genotype had lower prevalence of myocardial infarction (2.3% versus 3.6%, $p < 0.05$) and ischemic heart disease (myocardial infarction and/or angina pectoris) (5.7% versus 7.7%, $p = 0.02$) compared to those with the other genotypes (Table 1). The individuals with known genotype were significantly older and had, consequently, higher blood pressure and cholesterol level, higher prevalence of ischemic heart disease and chronic musculoskeletal pain, and had lower physical activity level than those with unknown COMT genotype (Table 1).

Mean HADS-D and HADS-A scores related to genotype are displayed in Figure 1 and in Figure 2, respectively. As demonstrated, the genotype distribution of the scores tended to differ by gender, most prominent for HADS-A. However, no significant correlations between genotypes and scores of HADS-A and HADS-D were found for men or women.

The distribution of genotypes and alleles of the Val158Met polymorphism by gender failed to detect a dif-

Table 1: COMT genotypes related to sex, mean age, education > 12 years, mean systolic and diastolic blood pressure, and several factors associated with hypertension.

Characteristics	No COMT genotyping (n = 60,072)	Met/Met (n = 1769)	Val/Met (n = 2726)	Val/Val (n = 1036)
Sex, female (%)	53.1	53.7	54.3	56.1
Age, mean (SD)	49.2 (17.3) ¹	50.7 (17.9)	50.7 (18.0)	50.2 (17.7)
Education > 12 years (%)	19	18	18	18
Median systolic blood pressure (mmHg)	134 ¹	136.5	136	136
Median diastolic blood pressure (mmHg)	79 ¹	80	80	80
Body mass index, kg/m ² (SD)	26.4 (4.1)	26.4 (4.1)	26.3 (4.1)	26.3 (4.2)
Cholesterol, mmol (SD)	5.89 (1.26) ¹	5.96 (1.30)	5.96 (1.30)	6.02 (1.33)
Current smoking (%)	28.2	27.9	28.4	29.6
High level of physical activity (%)	15.8 ¹	13.9	14.1	14.8
Diabetes mellitus (%)	3.2 ¹	1.3	1.3	1.1
Myocardial infarction (%)	3.3	3.8	3.4	2.3 ²
Angina pectoris (%)	5.0 ¹	6.7	5.8	5.1
Stroke (%)	1.9	2.1	1.8	1.8
Headache (%)	38.6	39.7	40.0	37.9
Chronic musculoskeletal pain (%)	46.3 ¹	46.4	50.5	48.6

1. Genotyped versus not genotyped: $p < 0.003$.
 2. Val/Val versus other genotypes: $p = 0.046$.
 Heart disease (myocardial infarction and/or angina pectoris):
 Val/Val versus other genotypes: $p = 0.02$ Genotyped versus not genotyped: $p < 0.02$

ference between controls and subjects with anxiety and depression using the cut-off score ≥ 8 for HADS-A and HADS-D. When utilizing the alternative cut-off score ≥ 11 , the Met/Met genotype and Met allele were less common among men with depression compared to the controls (genotype: 18.3% versus 33.9%, $p = 0.017$; allele: 46.5% versus 58.1%, $p = 0.006$) (Table 2). In the multivariate

analysis, adjusting for age and heart diseases, HADS-D ≥ 11 was less likely among men with the Met/Met genotype than among men with the Val/Val genotype (OR = 0.37, 95% CI = 0.18–0.76). For women, this tendency was less clear (OR = 0.89, 95% CI 0.48–1.63). However, for both genders combined, depression was less common for the Met/Met genotype (OR = 0.60, 95% CI = 0.38–0.95).

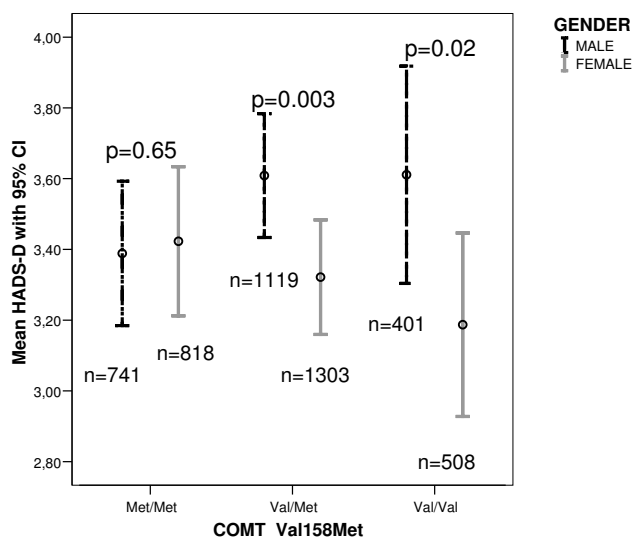


Figure 1
Mean HADS-D scores with 95% confidence interval related to COMT genotype in men and women. Numbers of participants are given. Gender comparison for each genotype was performed with Mann-Whitney U test.

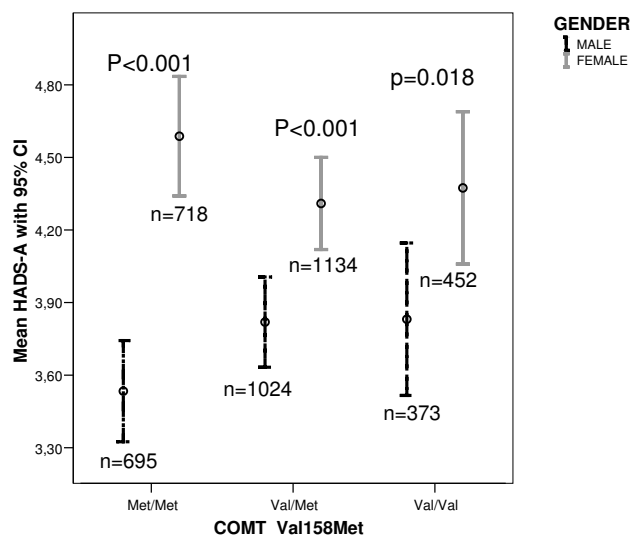


Figure 2
Mean HADS-A scores with 95% confidence interval related to COMT genotype in men and women. Numbers of participants are given. Gender comparison for each genotype was performed with Mann-Whitney U test.

Table 2: Distribution of HADS-score related to genotype of COMT in men and women.

	No.	Met/Met %	Val/Met No.	Val/Met %	Val/Val No.	Val/Val %
Genotypes						
Men						
Controls (HADS-D < 8 + HADS-A < 8)	579	33.9	829	48.5	301	17.6
HADS-D ≥ 8	71	30.2	122	51.9	42	17.9
HADS-D ≥ 11 ¹	13	18.3	40	56.3	18	25.4
HADS-A ≥ 8	70	29.7	123	52.1	43	18.2
HADS-A ≥ 11	16	25.0	39	60.9	9	14.1
Combined (HADS-D ≥ 8+HADS-A ≥ 8)	30	30.9	53	54.6	14	14.4
Unclassified (incomplete data)	29	29.5	226	51.6	83	18.9
Women						
Controls (HADS-D < 8 + HADS-A < 8)	549	30.6	889	49.5	358	19.9
HADS-D ≥ 8	96	35.2	132	48.4	45	16.5
HADS-D ≥ 11 ¹	27	32.9	37	45.1	18	22.0
HADS-A ≥ 8	125	34.2	175	47.8	66	18.0
HADS-A ≥ 11	46	37.4	53	43.1	24	19.5
Combined (HADS-D ≥ 8+HADS-A ≥ 8)	47	37.3	55	43.7	24	19.0
Unclassified (incomplete data)	227	32.4	338	48.2	136	19.4
Alleles						
Men						
Controls	1987	58.1	1431	41.9		
HADS-D ≥ 8	264	56.2	206	43.8		
HADS-D ≥ 11 ²	66	46.5	76	53.5		
HADS-A ≥ 8	263	55.7	209	44.3		
HADS-A ≥ 11	71	55.5	57	44.5		
Combined (HADS-D ≥ 8+HADS-A ≥ 8)	113	58.2	81	41.8		
Unclassified (incomplete data)	484	55.3	392	44.7		
Women						
Controls	1987	55.3	1605	44.7		
HADS-D ≥ 8	324	59.3	222	40.7		
HADS-D ≥ 11 ²	91	55.5	73	44.5		
HADS-A ≥ 8	425	58.1	307	41.9		
HADS-A ≥ 11	145	58.9	101	41.1		
Combined (HADS-D ≥ 8+HADS-A ≥ 8)	49	59.1	103	40.9		
Unclassified (incomplete data)	792	56.5	610	43.5		

1. Male cases with HADS-D ≥ 11 versus male controls: p = 0.01.
 2. Male cases with HADS-D ≥ 11 versus male controls: p = 0.006

Discussion

This is the first population-based study evaluating the relationship between HADS and the Val158Met polymorphism. In a group of 5,531 unselected adults, no significant association was found with anxiety and depression using the cut-off score ≥ 8 for HADS-A and HADS-D.

When employing the alternative cut-off score ≥ 11, depression was less likely among men with the Met/Met genotype than among men with the Val/Val genotype. Val/Val individuals would be expected to have lower transsynaptic catecholamine levels, due to their high COMT enzyme activity. Such depletion of transsynaptic catecholamine neurotransmitters, like dopamine and noradrenaline, may very well influence susceptibility to depression in this genotype group [3]. Because this association was based on a very small number of cases, it may

be incidental, and therefore needs to be interpreted with some caution. Interestingly, however, an association between Val/Val genotype and major depression with early onset has been reported in a multicenter study of various European populations [3]. In contrast to these findings, Ohara et al. found higher frequencies of the Met allele in depressed Asian patients compared with a control group [4]. However, because differences in COMT genotype distribution between ethnic groups are considerable, a finding in one group might not be valid for other groups [23].

Our failure to establish a significant association between anxiety and the Val158Met polymorphism is supported by previous research on various forms of anxiety [6,24], including a meta-analysis on panic disorder [8]. Conflicting results have been found in other studies. Most of these

reported an association between Val/Val genotype and anxiety and panic disorder [5,25-27], whereas Woo et al. showed a Met/Met genotype predominance in patients with panic disorder [7].

The strength of this study was that our sample was drawn from a large and unselected population, which consisted of ethnically homogenous Norwegian individuals. Because no information about ethnic backgrounds was available in our data file, the relatively few numbers of non-Caucasians subjects could not be excluded in the statistical analyses. Because the distribution of the two COMT alleles differs between different ethnic groups [23], the risk of bias caused by ethnical admixture could not be ruled out.

The fact that psychiatric questions were not the primary objectives of HUNT made interest-related bias less likely. Some research has indicated that people with psychiatric disorders are over-represented among non-responders in studies of the general population [28]. This could be a weakness, since 30% of invited individuals did not attend [16]. But according to a study on non-attendants, health related reasons for not attending were unlikely among individuals below 70 years of age [17]. Our sample of more than 4000 individuals should have sufficient power to detect a difference of clinical interest in prevalence of depression and anxiety between genotypes. Because of the large sample size, we had enough power to present separate analyses by gender.

HADS, used in many former studies of the HUNT population [20,29-31], has good reliability and validity compared with other symptom scales of depression and anxiety [10-15]. Several articles have stated its suitability in samples from the general population with the potential to intercept undiagnosed- and untreated cases with depression and/or anxiety [9,11,15]. Such cases may have been missed in previous case-control studies examining the relationship between the Val158Met polymorphism and anxiety and/or mood disorders [3-8,24,25,32,33]. In addition, diagnostic differences also exist, because most previous studies have selected cases according to DSM-IV or ICD-10 categories. However, the use of rigid diagnostic criteria may fail to capture a potential genetic predisposition, and more and more studies have taken this into account by also looking at psychological traits or intermediate phenotypes instead of standard diagnoses [34-36]. HADS based diagnoses of depression and anxiety disorder do not correspond exactly to any of the specific diagnoses of DSM-IV or ICD-10, but HADS includes certain ICD-10 features [11,20]. In particular, HADS-D focuses on anhedonia, by some viewed as a core symptom of depression [14], while the HADS-A subscale mainly captures features of generalized anxiety [21]. Recently, it has been suggested

that HADS-A covers two dimensions, i.e. negative affectivity and autonomic arousal [37]. A separate evaluation of these two dimensions was not possible, and as a consequence, we can not rule out a possible positive association between the Val158Met polymorphism and negative affectivity or autonomic arousal, respectively.

Our study could not confirm any clear association between the Val158Met polymorphism and anxiety or depression measured by HADS. However, a number of functional polymorphisms in- or close to the COMT gene have been described, and some recent studies have looked at multiple single nucleotide polymorphisms (SNPs) and different COMT haplotypes in relation to psychiatric phenotypes [38,39], and interaction between the COMT gene and other genes [26,33]. Due to lack of financial- and personnel resources we did not assess additional SNPs within the COMT gene or in other genes. As a consequence, we were unable to evaluate the influence of haplotypes of the COMT gene or possible interactions with other genes on HADS.

Conclusion

In this population-based study on 5531 unselected Norwegian adults no clear association between the Val158Met polymorphism and depression and anxiety was revealed. Among men the Met/Met genotype was associated with lower prevalence of depression when using a high cut-off score, but this may be an incidental finding.

Abbreviations

COMT: Catechol-O-methyltransferase; HUNT: "Helseundersøkelsen i Nord-Trøndelag" (The Nord-Trøndelag Health Study); Val: Valine; Met: Methionine; HADS: Hospital Anxiety and Depression Scale; HADS-A: Anxiety subscale of Hospital Anxiety and Depression Scale; HADS-D: Depression subscale of Hospital Anxiety and Depression Scale.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KH and PMB conceived of the study and performed the statistical analysis. FS, ES and J-AZ all participated in the design and drafted the manuscript. All authors read and approved the final manuscript.

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