Interaction of early environment, gender and genes of monoamine neurotransmission in the aetiology of depression in a large population-based Finnish birth cohort

Emma S Nyman,1,2,3 Sonja Sulkava,1,2,4 Pia Soronen,1,2 Jouko Miettunen,5,6 Anu Loukola,1,2 Virpi Leppä,1,2,3 Matti Joukamaa,7,8 Pirjo Mäki,5 Marjo-Riitta Järvelin,9,10,11 Nelson Freimer,12 Leena Peltonen,1,2,3,13,14 Juha Veijola,5,6 Tiina Paunio1,2,4

ABSTRACT

Objectives: Depression is a worldwide leading cause of morbidity and disability. Genetic studies have recently begun to elucidate its molecular aetiology. The authors investigated candidate genes of monoamine neurotransmission and early environmental risk factors for depressiveness in the genetically isolated population-based Northern Finland Birth Cohort 1966 (12 058 live births).

Design: The authors ascertained and subdivided the study sample (n=5225) based on measures of early development and of social environment, and examined candidate genes of monoamine neurotransmission, many of which have shown prior evidence of a gene—environment interaction for affective disorders, namely SLC6A4, TPH2, COMT, MAOA and the dopamine receptor genes DRD1—DRD5.

Results and conclusion: The authors observed no major genetic effects of the analysed variants on depressiveness. However, when measures of early development and of social environment were considered, some evidence of interaction was observed. Allelic variants of COMT interacted with high early developmental risk (p=0.005 for rs2239393 and p=0.02 for rs4680) so that the association with depression was detected only in individuals at high early developmental risk group (p=0.0046 and β=0.056 for rs5993883—rs2239393—rs4680 risk haplotype CGG including Val158), particularly in males (p=0.0053 and β=0.083 for the haplotype CGG). Rs4274224 from DRD2 interacted with gender (p=0.017) showing a significant association with depressiveness in males (p=0.0006 and β=0.0023; p=0.00005 and β=0.069 for rs4648318—rs4274224 haplotype GG). The results support the role of genes of monoamine neurotransmission in the aetiology of depression conditional on environmental risk and sex, but not direct major effects of monoaminergic genes in this unselected population.

INTRODUCTION

Depression is a major cause of morbidity worldwide, with major depression affecting 5—7% of the population annually and 16% over a lifetime.1 Although a genetic component in the aetiology of major depression is evident with a 40—50% heritability,2 the predisposing genetic background has so far remained largely undefined, and recent findings from genome-wide association studies also point to a complex underlying architecture.3 Depressed patients frequently exhibit comorbidities such as anxiety and alcohol abuse,4 and certain personality types5—7 have been associated with depression proneness.
Environmental risk factors, in particular stressors influencing during development, are considered to have a significant impact on the development and course of depression. It is likely that many of the genetic risk factors for depression interact with the early developmental environment, but recapture of these interactions has remained a challenge for aetiological studies of depression. Although the interplay between genes and environment has been investigated with respect to several psychiatric disorders, including depression, this vast subject still remains largely unexplored. On the other hand, addressing the effects of genes and environment on psychiatric morbidity enables us to examine the two main constituents in their aetiology. Therefore, we wanted to include the environmental dimension in our study in order also to explore gene—environment interactions (G×E).

According to the monoamine hypothesis, depression is caused by underactivity in brain monoamines, such as dopamine, serotonin and norepinephrine. Recent results of neuroimaging studies have provided further support for this theory. The most solid evidence from candidate gene studies has perhaps been obtained for the interaction of the SLC6A4 gene for serotonin transporter and stressful early and current life events, including positive results from a recent review and meta-analysis of all studies to date, although there are also contradicting results. Other robust genetic findings have been obtained on the COMT gene for catechol-O-methyltransferase, an enzyme catabolising catecholamines such as dopamine and norepinephrine, which has been implicated in depression in conjunction with stress, and on the MAOA gene for monoamine oxidase A, an enzyme-oxidising neurotransmitter and dietary monoamines such as serotonin, norepinephrine and dopamine, which has been associated with depression in interaction with severity of maltreatment in childhood. Furthermore, the TPH2 gene for tryptophan hydroxylase 2, which is the brain-specific form of the key enzyme in serotonin synthesis, has been implicated to interact with stress on disorders of cognitive control and emotional regulation, including depression. Within the dopamine transmission, the DRD2 gene for dopamine receptor D2 has been associated with depressiveness and anxiety, combined with an effect of parenting in childhood, and the DRD4 gene for dopamine receptor D4 has been associated with an increased risk for obesity in women with seasonal affective disorder. Thus, genes from the monoamine neurotransmission system are among the most thoroughly studied in psychiatric genetics and in particular in the aetiology of mood disorders, and have provided perhaps the most robust evidence so far for interaction with various types of risk environments, including childhood environment.

We chose to include these candidate genes of monoamine neurotransmission showing prior evidence of gene—environment interaction, including SLC6A4, TPH2, COMT, MAOA, as well as the dopamine receptor genes DRD1—DRD5, in our study on the aetiology of depression with a particular focus on their interaction with available markers reflecting measures of early development and of social environment. The study was performed in a sample of 5225 individuals from a large Finnish isolated population cohort. As gender is an important confounder for depression and at least some of the genetic liability is gender-specific, we also examined gene—gender interactions in this sample.

**METHODS**

**Setting**

We utilised the genetically isolated Northern Finland Birth Cohort (NFBC 1966) to investigate the effects of candidate genes and environmental risk factors during the development on depressiveness. We subdivided the study sample based on measures of early development arising from the fetal growth environment and neurodevelopmental measures of early development as well as from stressful early and current life events, and measures of social environment. We examined interactions of these measures with candidate genes of the monoamine neurotransmitter systems, which have prior evidence of gene—environment interactions on affective disorders, namely SLC6A4, TPH2, COMT, MAOA and the dopamine receptor genes DRD1—DRD5.
Early environment, gender and genes in depression

Study subjects
The Northern Finland Birth Cohort 1966 (NFBC 1966) is a longitudinal 1-year birth cohort from an unselected population (N=12,058 live births) comprising inhabitants of the two northernmost provinces of Finland. Data collection was begun during the antenatal period, and follow-up studies were performed at the ages of 1, 14 and 31 years. The cohort study was approved by the Ethical Committee of Oulu University Faculty of Medicine, and written informed consent was obtained from all participants.

In 1997, for the 31-year follow-up study all alive cohort members with a known address (N=11,540) were sent a postal questionnaire surveying lifestyle, social status and health (76% participated), including the Hopkins Symptom Check List-25 (HSCL) and items on self-reported lifetime depression diagnosis (eg, ‘Has your doctor ever diagnosed a depressive disorder?’). Additionally, cohort members who lived in Northern Finland or had moved to the Helsinki area (N=8,465) were invited to a clinical examination (71% participated) with another questionnaire to be filled in later and sent to the research group (61% participated). It included, among others, a validated Finnish translation of Cloninger’s Temperament and Character Inventory (TCI) questionnaire.

Current depressive symptoms were assessed by the HSCL questionnaire, a 25-item shortened version of an originally 90-item questionnaire. HSCL contains 15-item depression and 10-item anxiety subscales assessing presence and intensity of depressive and anxiety symptoms during the previous week. Answers are scored on a scale from 1 (not bothered) to 4 (extremely bothered). The HSCL total score is the sum of items divided by the number of items answered. We used mainly HSCL total score, as symptoms of depression and anxiety are known to overlap significantly. In the post hoc analyses, in order to better understand the original association signals, the separate HSCL subscales for depressive and anxiety symptoms were also taken into consideration. In addition to current depressive symptoms (HSCL score) and lifetime (diagnosed) depression, we used the TCI temperament trait Harm avoidance and its subcomponents as a measure of proneness to depression.

The subjects (n=5,225; 2,509 males, 2,716 females; 45% of the 31-year follow-up study sample or 43% of the original study sample) were divided into high- and low-risk groups based on the available information reflecting measures of early neurodevelopment and of social environment (table 1). The markers for the measure of high early developmental risk included (1) low birth weight (<2500 g), considered to reflect suboptimal growth environment during fetal life and to increase risk for somatic and psychiatric diseases such as depression in adulthood; (2) late motor development as reflected by first standing later than at the age of 10 months; and (3) late development of speech, defined by no words at the age of 1 year. If two of these risk indicators were present, the subject was classified as having experienced a high-risk environment for early brain development. The markers for the measure of high social risk environment included the occurrence of two or more of the following five indicators for high-risk social environment during pregnancy and early childhood: (1) unwanted pregnancy (rated by mothers of the cohort members at the sixth or seventh month of pregnancy), (2) low socio-economic status, shown to be linked with depression in the offspring in earlier studies, as defined by father’s occupation at birth (no occupation, unskilled worker, or farmer with area under cultivation under 8 hectares), (3) single parenthood at birth, (4) low level of education of mother (less than 9 years of primary school) and (5) low level of information retrieval by the mother related to pregnancy and childcare. There was no significant drop-out in either of the high-risk groups, as 43% and 41% of the individuals of high early developmental and social risk groups, and 47% and 46% of those of the respective low-risk groups, were available for study.

Genotyping methods
We investigated genes relevant within the context of the monoamine hypothesis of depression: SLC6A4, TPH2, COMT, MAOA and the dopamine receptor genes DRD1—DRD5 (table 2). The genotyping was performed at the Broad Institute (Cambridge, MA) on the HumanCNV370-duo chip (Illumina, San Diego, California) platform according to the manufacturer’s instructions. The analysed SNPs included HapMap tag SNPs and were relatively evenly spaced to cover the genes and flanking regions.

Statistical analysis
LD structures were determined using HAPLOVIEW. Interaction and association/correlation analyses using linear and logistic regression with permutation were performed using PLINK Software Package Version 1.04, in a stepwise manner to maximise our ability to detect associations and to minimise multiple testing. First, analyses were primarily performed to identify genetic risk variants for current depressive symptoms (HSCL score) interacting with measures of early development (G×EDev) and of social environment (G×ESoc). For variants giving significant evidence of interaction, we also performed analyses separately in subgroups at high and low risk, respectively. As gender is an important confounder for depression, and at least some of the genetic liability is gender-specific, we also examined gene–gender interactions (GxSex). For variants showing significant evidence of gene–gender interaction, we also performed analyses separately in males and females. In order to achieve a more complete view of the effects of the examined genes on depressive symptoms in the cohort, we also examined their influence on the gender-adjusted HSCL score in the complete sample regardless of gender.
Early environment, gender and genes in depression

<table>
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<th>N</th>
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<th>Depression diagnosis</th>
<th>Measure of early development†</th>
<th>Measure of social environment‡</th>
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<td>269 (10%)</td>
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<td>5225</td>
<td>438 (8%)</td>
<td>215 (4%)</td>
<td>422 (8%)</td>
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</table>

*There is prior support for using the Hopkins Symptom Check List score 1.75 as a cut-off when aiming to identify clinical depression. †Defined by the presence of two out of three possible indicators for high early developmental risk: low birth weight, late motor development and late development of speech. ‡Defined by the presence of two out of five possible indicators for high social risk environment: unwanted pregnancy, low socio-economic status, single parenthood, low level of education of mother and low activity for information retrieval by the mother. For further details, see text. §Not defined.

of environmental effectors. Finally, we tested for gene–environment correlations ($r_{GED}$, and $r_{GSoc}$) and associations of the risk environments with the HSCL score (PASW Statistics 18, linear regression model). Second, haplotype analyses were performed when two SNPs located at physically close vicinity had given association signals of $p<0.05$ when analysed separately. Third, genetic variants and haplotypes which had been identified in the previous analyses were analysed post hoc with respect to HSCL subscales (depressive and anxiety symptoms), depression diagnosis and TCI temperament Harm avoidance. We report pointwise empirical $p$ values generated by PLINK’s max(T) permutation (10 000 permutations) throughout the manuscript, and state explicitly where corrected empirical $p$ values are reported. SNPs with Hardy–Weinberg Equilibrium $p$ values $<0.05$ were excluded from all analyses.

RESULTS

Gene–environment and gene–gender interaction and association analyses in relation to the HSCL score

We examined the effects of nine candidate genes of monoamine neurotransmission on current depressive symptoms (HSCL score) in a longitudinal population-based NFBC 1966 cohort. In particular, we searched for evidence of interaction of variants in these genes with two measures of early growth, one with indicators for potentially disturbed neurobehavioural development (measure of early development) and the other with risk factors from social environment for normal emotional development (measure of social environment). The results are presented in table 2 in which nominal $p$ values are reported.

Out of the 69 genetic variants examined, none gave a statistically significant association signal with depression or for an interaction with measures of early development or of social environment, which would survive correction for multiple testing. We observed nominal evidence for association with the HSCL score ($p<0.05$) in the complete sample in the cases of rs1487275 in $TPH2$, ($p=0.049$, $\beta=0.008$), rs4646316 in $COMT$ ($p=0.026$, $\beta=0.012$), rs4274224 and rs4581480 in $DRD2$ ($p=0.022$, $\beta=0.011$; and $p=0.009$, $\beta=0.022$, respectively), and rs13106539 in $DRD5$ ($p=0.044$, $\beta=0.008$). Three variants of $COMT$ and one of $DRD3$ showed some evidence of interaction ($p<0.05$) with high early developmental risk with respect to the HSCL score ($p=0.028$ for rs737866, $p=0.005$ for rs2239393 and $p=0.020$ from rs4680 from $COMT$, and rs9825563, $p=0.045$ from $DRD3$). All of these were associated with the HSCL score in individuals of the high-risk group ($p=0.036$, $\beta=0.0414$ for $rs737866$; $p=0.008$, $\beta=0.0440$ for $rs2239393$; $p=0.042$, $\beta=0.0320$ for rs4680; and $p=0.022$, $\beta=0.0396$ for rs9825563, respectively). None of the variants gave any evidence of interaction with the measure of social environment in relation to the HSCL score. Five of the genetic variants showed some evidence of interaction with gender ($p<0.05$), including rs737866 and rs5993883 in $COMT$ and rs4274224 in $DRD2$. Out of these, only rs4274224 was associated at $p<0.05$ with one of the genders ($p=0.0006$, $\beta=0.023$ in males). The evidence for gene–environment correlations ($r_{GE}$) was observed only nominally about rs1906451 from $TPH2$ ($p=0.035$), rs265973 from $DRD1$ ($p=0.047$) and rs9825563 from $DRD3$ ($p=0.028$). Despite a priori evidence for the role of the markers which indicate a high developmental risk for psychiatric health and well-being, namely low birth weight and late motor or verbal development, there was no correlation between these markers and the HSCL score in the present sample ($p=0.131$), whereas the social high-risk environment correlated significantly with the score ($p=0.00001$).

Although none of the association findings of these primary analyses survived correction for multiple testing, post hoc association analyses in gender groups led to a finding close to statistical significance, even when taking into account the amount of multiple testing performed ($p=0.0006$ for males with rs4274224 in $DRD2$). Furthermore, as there was an accumulation of association signals within two highly plausible candidate genes, $DRD2$ and $COMT$, we proceeded to perform haplotype analyses on these genes in order to better characterise the allelic variants which yielded the observed suggestive associations, and to obtain
### Table 2

Interaction (G×E) and correlation (rGE) between genetic variants of genes of monoamine neurotransmission and measures of early development (G×E<sub>Dev</sub>, rG<sub>Dev</sub>) and of social environment (G×E<sub>Soc</sub>, rG<sub>Soc</sub>)<sup>†</sup> and gender (G×Sex) on current depressive symptoms (Hopkins Symptom Check List score), and genetic association with Hopkins Symptom Check List score in the complete study sample from the NFBC 1966 (All).

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<th>Gene name</th>
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<th>SNP</th>
<th>Position/bp</th>
<th>Minor allele</th>
<th>MAF&lt;sup&gt;‡&lt;/sup&gt;</th>
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<th>P (G×E&lt;sub&gt;Soc&lt;/sub&gt;)</th>
<th>P (G×Sex)</th>
<th>P (All)</th>
<th>P (rG&lt;sub&gt;Dev&lt;/sub&gt;)</th>
<th>P (rG&lt;sub&gt;Soc&lt;/sub&gt;)</th>
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The analyses were performed using PLINK's linear and logistic regression models and interaction analysis. Empirical p values based on max(T) permutation are reported, with p values <0.05 shown in bold.
*Defined by the presence of two out of three possible indicators for high early developmental risk: low birth weight, late motor development and late development of speech.
†Defined by the presence of two out of five possible indicators for high social risk environment: unwanted pregnancy, low socio-economic status, single parenthood, low level of education of mother and low activity for information retrieval by the mother.
‡Minor allele frequency.
§p=0.0364 (β=0.0414).
¶p=0.008 (β=0.0440).
**p=0.042 (β=0.0320).
††p=0.022 (β=−0.0396) in individuals at high risk group.
§§p>0.05 in both genders.
¶¶p=0.0006 (β=0.023) in males.
***p=0.008.
††††β=−0.012.
†††β=0.011.
§§§β=0.022.
¶¶¶=0.0.
Early environment, gender and genes in depression

Haplotype analysis of COMT and DRD2 variants in relation to the HSCL score

We performed 2-SNP and 3-SNP haplotype analyses combining rs2239393 and rs4680 from COMT and their neighbouring variants using the sliding window approach. Evidence of association was observed for the rs5993883–rs2239393 haplotype spanning a region from the space between LD blocks 1 and 2 to block 2 of COMT (supplementary figure 1) (p=0.0049, β=0.055), for the rs2239393–rs4680 haplotype in block 2 (p=0.0072, β=0.044) and the rs5993883–rs2239393–rs4680 haplotype CGG (p=0.0046, β=0.055) in the high early developmental risk group, in agreement with analyses using single variants (table 3). As rs5993883 from the haplotype had also given evidence of interaction with gender (table 2), we further examined haplotype association in males and females of the high-risk group separately. We found that the haplotypes increased the risk for depressive symptoms in males, but not in females (p=0.004, β=0.083 for rs5993883–rs2239393 haplotype CG; p=0.0037, β=0.072 for rs2239393–rs4680 haplotype GG; and p=0.0053, β=0.083 for rs5993883–rs2239393–rs4680 haplotype CGG) (table 3). As is evident from the β-values, each of the haplotypes accounts for more variance in depression than any individual constituent SNP.

Haplotype analysis of rs4274224 and rs4581480 from DRD2, which gave evidence suggestive of an association with the HSCL score in the complete sample, and of their neighbouring variants, gave evidence of an association of rs4648318–rs2742242 haplotype spanning from block 2 to block 3 of DRD2 (p=0.0007, β=0.041), rs4274224–rs4581480 haplotype in block 3 (p=0.0069, β=0.022), and rs4581480–rs7131056 haplotype spanning from block 3 to block 4 (p=0.0071, β=0.029) with the HSCL score. The 3-SNP haplotypes rs4648318–rs4274224–rs4581480 haplotype GGG (p=0.0027, β=0.052) and rs4274224–rs4581480–rs7131056 haplotype GGA (p=0.0081, β=0.021) gave evidence of an association in agreement with the findings from the 2-SNP haplotypes as well as the single variants (table 4). As one of the variants contained within these haplotypes, namely rs4274224, also gave evidence of interaction with gender as well as an association with the HSCL score in males, we also examined the association in males alone. The association signal became stronger for all of the risk haplotypes, being strongest for rs4648318–rs4274224 haplotype GG (p=0.0005, β=0.069). Similarly as for the COMT haplotypes, the β-values imply that each of the DRD2 haplotypes accounts for more variance in depression than any individual constituent SNP.

Haplotype analysis of COMT and DRD2 variants in relation to other neurobehavioural traits

Encouraged by the findings of the haplotype analyses, we tested for associations of haplotypes rs5993883–rs2239393
in COMT and rs4648318—rs4274224 in DRD2, as well as the single variant rs737866 in COMT with other traits related to depression, including the HSCL depression and anxiety subscales, depression diagnosis and TCI temperament trait harm avoidance (table 5). In both genes, it is evident that the association with HSCl stems mainly from the subscale which reflects symptoms of depression and not that reflecting anxiety (with HSCl depression subscale, p=0.018, β=0.075 for COMT haplotype CG and p=0.0015, β=0.060 for DRD2 haplotype GG; with HSCl anxiety subscale, p=0.288, β=0.02 and p=0.02 and β=0.033, respectively). We did not detect any evidence of an association with depression diagnosis or with Harm avoidance or its subcomponents.

### DISCUSSION

We investigated genetic and environmental risk factors for depression in a genetically isolated Finnish birth cohort by assessing the relative impacts of monoaminergic candidate genes for depression in groups of contrasting (high and low) early developmental and social risk. We did not observe any robust genetic effects of the analysed variants on depressiveness. However, when measures of early development and social environment were considered, some signals for association were observed, although none of them survive correction for multiple testing. Our study sample provided modest evidence of an interaction of COMT with the measure of high early developmental risk, particularly in males, and a contribution of an allelic variant of DRD2 to genetic risk for depressiveness particularly in males (table 2).

The COMT gene encoding for catechol-O-methyltransferase enzyme is among the most investigated genes in psychiatric genetics. The enzyme degrades catecholamine neurotransmitters such as dopamine, norepinephrine and epinephrine by catalysing the transfer of a methyl group from Sadenosylmethionine to the catecholamines. Its enzymatic activity varies according to a G-to-A transition at codon 158 in the COMT gene, resulting in a valine-to-methionine substitution (Val158Met) on the protein level. The enzyme encoded by the Val158 allele has a three- to four-fold higher activity than that encoded by the Met158 allele. Here, we found an association of the haplotype comprising rs5993883 between LD blocks 1 and 2 of COMT, as well as rs2239393 and rs4680, which are two variants in virtually complete linkage disequilibrium in block 2, with depressive symptoms in high-developmental-risk males (p=0.0053). The high-risk haplotype included the high-activity variant Val158 of COMT, the allele G of rs4680. This allele has repeatedly been found to be associated with a poor response to pharmacological treatment of depression, and a European multicentre study identified an association between that allele and early-onset major depression. The Val158 allele has already been found earlier to associate with cognitive deficits including poor performance in tasks related to higher-order components of processing and perseverative errors, less efficient physiological responses in the prefrontal cortex, and even schizophrenia based on a meta-analysis, although the effect was not significant when studies with allele frequencies deviating from the Hardy–Weinberg equilibrium were excluded.

In our study we observed evidence for an interaction between COMT and a measure of early developmental risk on depressive symptoms. This interaction could not be explained through gene–environment correlations. Nor were we able to detect a significant correlation of the measure of early developmental risk with depressive symptoms, despite prior evidence for the role of its markers, which were low birth weight and late motor or verbal development, in decreased psychiatric health and well-being, including depression. This finding may reflect the presence of other environmental risk indicators which were not examined in our study. However, they may also reflect individual variability in response to the risk environment and presence of genetic factors (such as the COMT haplotype containing Met158) that may relate to resilience, adaptive changes in regulation of emotion reactivity and successful coping with stress. The observed risk also seemed to arise from an aggregate of the environmental indicators, as none of the risk items separately gave evidence of G×E with the risk...
variants from \textit{COMT} or \textit{DRD3} (data not shown). This could reflect a cumulative nature of these environmental influences, such that the effect of one marker may be weak, but the accumulated effect of multiple markers, together with genetic susceptibility, would be strong enough to increase the risk for a deviant development of emotional regulation and thus depressiveness.\textsuperscript{39} There is some prior evidence of interaction of \textit{COMT} with a risk environment on psychosis, antisocial behaviour and dissociation. A study on children with ADHD showed a gene–environment interaction between the Val/Val genotype and low birth weight on early-onset antisocial behaviour,\textsuperscript{40} and the Val158 allele was also found to associate with cannabis use and psychotic symptoms\textsuperscript{41} and with increasing levels of dissociation in those exposed to higher levels of childhood trauma.\textsuperscript{42} Interestingly, a recent report\textsuperscript{43} revealed an impact of that polymorphism on gender-related patterns of regulation of emotions (activation in limbic and paralimbic regions) in line with findings of the present study.

Another main finding of the present study, and statistically the strongest one, was observed in the dopamine receptor D2 gene \textit{DRD2}, where a haplotype comprising the intronic variants rs4648318 in LD block 2 and rs4274224 in block 3 was found to associate with depressive symptoms particularly in males, regardless of their early environment (p = 0.00005). Dopamine receptors have key roles in a variety of processes in the vertebrate central nervous system, and dysfunction in dopaminergic neurotransmission may therefore predispose to a variety of neuropsychiatric disorders. Among the receptor genes, \textit{DRD2} has attracted the most attention and has been implied to have a role in the aetiology of several psychiatric disorders. However, there are only a few previous reports on unipolar depression, including positive,\textsuperscript{44} nominal\textsuperscript{45} and negative\textsuperscript{46} \textsuperscript{47} findings, and for results on depression conditional on risk environment.\textsuperscript{44} \textsuperscript{46} \textsuperscript{48}

Our varying results for males and females in general imply different mechanisms of mood regulation and possible gender-specific responses to environmental effectors. Gender differences in depression\textsuperscript{2} \textsuperscript{49} as well as in temperament traits\textsuperscript{49} have previously been reported in various populations, including the current one,\textsuperscript{50} and the prevalence of depression is higher in women.\textsuperscript{51} A true gender-specific effect of genetic variants on depressiveness would not be surprising, as there is evidence of gender differences in dopaminergic function\textsuperscript{52} that may be oestrogen-dependent.

It is noteworthy that despite previous reports of the 5-HTTLPR variant,\textsuperscript{13} we did not detect any evidence of an association for \textit{SLC6A4}. Similarly, a recent meta-analysis did not find any evidence of an association with depression alone, or in interaction with stressful life events,\textsuperscript{10} although a current review\textsuperscript{14} and a meta-analysis of all studies to date\textsuperscript{15} support the positive association findings and the role of 5-HTTLPR and stress in depression. The \textit{SLC6A4} SNPs included in our study tag the 5-HTTLPR well (D > 0.9), as determined using

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|l|l|l|}
\hline
\textbf{Group} & \textbf{Gender} & \textbf{HSCL (total)} & \textbf{HSCL (depression)} & \textbf{HSCL (anxiety)} & \textbf{Depression diagnosis} & \textbf{OR} & \textbf{p Value} \\
\hline
\textit{COMT} & High risk & Males & 0.0640 & 0.0054 & & & \\
& & Males & 0.0684 & 0.0005 & & & \\
& High risk & Males & 0.0640 & 0.0054 & & & \\
& & Males & 0.0684 & 0.0005 & & & \\
& All & Males & 0.0640 & 0.0054 & & & \\
 DRD2 & & & & & & & \\
& High risk & Males & 0.0440 & 0.0040 & & & \\
& & Males & 0.0756 & 0.0016 & & & \\
& All & Males & 0.0554 & 0.0015 & & & \\
\hline
\end{tabular}
\caption{Haplotype analysis of \textit{COMT} and \textit{DRD2} variants on other neurobehavioural traits in the NFBC1966 group.}
\end{table}
genotypes from a population-based Finnish Health 2000 study. Moreover, the LD measure thus obtained is conservative, since in the population under current study, LD has been shown to be stronger than in the general Finnish population, which was represented by the Health 2000 study sample.

We did not use the Bonferroni correction for multiple testing, owing to limitations of sample size and expected magnitude of gene effects in complex traits. Although none of the results from the primary analyses (table 2) survive conservative correction, a neurobiological a priori hypothesis based on previously published studies supports the validity of our most robust findings. It is, however, noteworthy that they were observed only when the sample was conditioned on measures of early development or of social environment, or gender. Still, the strongest association signal, obtained using DRD2’s rs4274224 with HSCL score in males (p=0.0006), remains close to statistical significance, even when taking into account the amount of multiple testing performed. The finding was further supported by results of our haplotype analysis containing rs4274224, which showed a statistically significant association with the HSCL score in males (p=0.00005).

There are some limitations in the present study. First, it is notable that depression as defined here did not necessarily signify a clinical diagnosis of major depression. Instead, it was defined based either on self-report or on the score from HSCL, which as a measure has its limitations. However, the prevalence of depressed mood was in the same range as in earlier reports. Second, there was a notable drop-out rate among the original material of all cohort members. About half of the original cohort members did not participate in this study. Finally, when the NFBC 1966 study was initiated, it was not possible to predict that an investigation such as the present one would one day be conducted. Therefore, we are limited by the original choice of variables to be collected, and the measures of early development or of social environment may only be indicators or markers of risk rather than risk factors themselves. It is also noteworthy that we did not detect any association of our measure of current depression with the measure of high early developmental risk, despite it being formulated based on previous reports of their effects on psychiatric health and well-being. However, the effect of genetic risk may be modulated by early life stress, even though the direct link between early life environment and current status would be too weak to be detected in our study sample. In addition, the size of the sample is sufficient to identify genetic variants of moderate impact. We also have both genders represented in almost equal amounts (48% males, 52% females), which is notable since gender differences are evident both in depression and in temperament traits—for example, harm avoidance. Furthermore, it is beneficial that the sample is a 1-year birth cohort, as it is well established that some psychiatric traits, such as harm avoidance of temperament, are age-dependent. We can therefore isolate genetic effects from the effects of ageing.

Our results support a modest role of COMT and DRD2, two genes of monoamine neurotransmission, in the aetiology of depression conditional on environmental risk, particularly in males, though not direct effects of monoaminergic genes in this unselected population. These findings imply that the nature of the role of monoaminergic genes in depression should be examined further in future studies, and pending replication in other, independent population samples.

Author affiliations
1Public Health Genomics Unit, Institute for Molecular Medicine Finland FIMM, University of Helsinki and National Institute for Health and Welfare, Helsinki, Finland
2National Institute for Health and Welfare, Helsinki, Finland
3Department of Medical Genetics, University of Helsinki, Helsinki, Finland
4Department of Psychiatry, Helsinki University Central Hospital, Helsinki, Finland
5Department of Psychiatry, University of Oulu and Oulu University Hospital, Oulu, Finland
6Academy of Finland, Helsinki, Finland
7Tampere School of Public Health, University of Tampere, Tampere, Finland
8Department of Psychiatry, Tampere University Hospital, Tampere, Finland
9Institute of Health Sciences, University of Oulu, Oulu, Finland
10Department of Epidemiology and Public Health, Imperial College, London, UK
11Department of Child and Adolescent Health, National Public Health Institute, Helsinki, Finland
12Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, California, USA
13Program in Medical and Population Genetics, The Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA
14Wellcome Trust Sanger Institute, Cambridge, UK

Funding This study was funded by the Academy of Finland’s CoE in Complex Disease Genetics; the Biocentrum Helsinki Foundation; the Academy of Finland’s grant to the NFBC Studies to TP, Post-doctoral Fellowship to AL and Academy Researcher Fellowship to JM; the University of Helsinki Research Foundation grant for young researchers to ESN; and the Signe and Ane Gyllenberg Foundation grant to PM.

Competing interests None.

Patient consent Obtained.

Ethics approval Ethics approval was provided by the Ethical Committee of Oulu University Faculty of Medicine.
Early environment, gender and genes in depression

Contributors TP, ESN, SS, JM, M-RJ, JV, NF, PM and M-RJ designed the study and wrote the protocol. ESN and, to some extent, TP also managed the literature searches. SS and ESN undertook the statistical analyses. ESN and TP wrote the first draft of the manuscript, and all authors contributed to its later versions. All authors contributed to and have approved the final manuscript.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Additional data on this study available from the corresponding author at tiana.paulio@uth.edu.

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Interaction of early environment, gender and genes of monoamine neurotransmission in the aetiology of depression in a large population-based Finnish birth cohort


BMJ Open 2011 1: originally published online August 27, 2011
doi: 10.1136/bmjopen-2011-000087

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