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Research report

Tryptophan hydroxylase 1 gene (TPH1) moderates the influence of social support on depressive symptoms in adults

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Abstract

Background: Tryptophan hydroxylases (TPHs) are involved in the biosynthesis of serotonin and are therefore candidate genes for psychiatric disorders, including depression. We examined whether the common 218 A > C and 779 A > C polymorphisms in the tryptophan hydroxylase 1 gene (TPH1) moderated the association between perceived social support and sub-clinical depressive symptoms in adults.

Methods: The subjects were a randomly selected subsample (n=341) of individuals participating in the Cardiovascular Risk in Young Finns study, who had data on social support on one assessment time and depressive symptoms on two assessment times. Social support was assessed on the Perceived Social Support Scale Revised (PSSS-R) and depressive symptoms on a modified version of the Beck's Depression Inventory (BDI).

Results: We found that low social support predicted depressive symptoms more strongly in individuals carrying A alleles of the TPH1 than in others. The interaction effect was observed in a cross-sectional analysis and when predicting depressive symptoms over a four-year period.

Limitations: We did not have data on TPH2, which has recently been identified as the primary TPH isomorphism affecting serotonin synthesis in the brain.

Conclusions: TPH1 gene may be involved in the development of depressive symptoms by moderating the impact of depressogenic social influences.

Keywords: Tryptophan hydroxylase; TPH1; Social support; Depressive symptoms; Gene-environment interaction; Vulnerability

1. Introduction

Depression is an etiologically complex disorder affecting approximately 7–11% of individuals at some point in life (Ayuso-Matéos et al., 2001), and subclinical depressive symptoms may be even more prevalent (Henderson and Pollard, 1992, see Judd et al., 2002). Negative life experiences and other environmental

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influences increase the risk of depression onset, but genetic factors are also involved (Kendler et al., 2002). Evidence indicates that the serotonergic neurotransmitter system plays a significant role in its pathophysiology (Maes and Melzer, 1995). Consequently, genes related to serotonin functioning have attracted accumulating interest in molecular genetic studies of depression (Veenstra-VanderWele et al., 2000).

Tryptophan hydroxylase (TPH) is a rate-limiting enzyme in the biosynthesis of serotonin and therefore a crucial step in serotonin functioning (Young and Leyton, 2002). Due to their central role in serotonin synthesis, genes encoding for TPH are regarded as candidate genes in susceptibility to psychiatric disorders, including depression. Two TPH genes, TPH1 and TPH2, have been identified in humans. Most of the molecular genetic studies on TPH so far have examined one of the two polymorphisms of the TPH1, A218C and A779C, which have been found to be in complete or strong linkage disequilibrium in previous studies (Nielsen et al., 1997).

The majority of studies investigating the role of TPH1 in behavior have focused on suicidal behavior. Three meta-analyses have been conducted to investigate the reliability of this association. The first of them found no overall association of TPH1 with suicidal behavior (Lalovic and Turecki, 2002), whereas the other two (Rujescu et al., 2003; Bellivier et al., 2004) concluded that the A allele of the TPH1 has a small yet significant effect on the risk of suicidal behavior. The A allele of the TPH1 has also been associated with an increased susceptibility to bipolar disorder (Bellivier et al., 1998), but a number of subsequent studies have failed to found this association in either bipolar (Furlong et al., 1998; Kirov et al., 1999; McQuillin et al., 1999) or major depressive disorders (Furlong et al., 1998; Frisch et al., 1999; Serretti et al., 2001a).

In addition to the need for studies on the main effects of genes, researchers have also emphasized the need to study gene-environment interactions in the development of behavioral phenotypes (Cadoret et al., 1996; Caspi et al., 2003; Ozkaragoz and Noble, 2000). The effects of a given gene are likely to be expressed differently in individuals with different life circumstances and developmental histories. For instance, at least three studies (Caspi et al., 2003; Eley et al., 2004; Grabe et al., 2005) have found that the impact of stressful life events on mental and physical health are moderated by a polymorphism in the serotonin transporter 5-HTTLPR gene.

While stressful life experiences are risk factors for depression, research indicates that available social support is an important protective factor (Brown and Andrews, 1986; Cohen and Wills, 1985; House et al., 1988; Katainen et al., 1999). Social support refers to available interpersonal resources for coping with potentially harmful experiences, whether they are major life events or daily hassles (Thoits, 1995). Social support acts as a buffer against negative life events, but it has also been demonstrated to influence well-being directly, i.e., independently of major life events (Cohen and Wills, 1985). Studies have shown that higher social support decreases the risk of depression, increases the likelihood of remaining healthy when confronted with stressful life events (House et al., 1988; Sarason et al., 1994) and predicts shorter recovery time from depressive episodes (Johnson et al., 1999).

The purpose of the present study was to examine whether the influence of social support on depressive symptomatology was moderated by the common genetic variability in the TPH1 gene. Since concurrent associations between social support and health may be causally ambiguous, the most appropriate study design for investigating the influence of the former on the latter is a longitudinal one, in which changes in health over time are examined as a function of social support (Cohen and Wills, 1985). Accordingly, a two-wave prospective longitudinal design was used in the present study. We hypothesized that individuals carrying the putative risk allele (A218/A779) would be more vulnerable to deficits in social support than individuals without an A allele.

2. Materials and methods

2.1. Subjects

The subjects were 341 men and women participating in the on-going population-based 'Cardiovascular Risk in Young Finns' study (CRYF, Åkerblom et al., 1991), in which a randomly selected sample of 3596 Finnish healthy children and adolescents from six birth cohorts (age 3 to 18 years at the baseline) have been followed since 1980. Complete details of the CRYF are given elsewhere (Åkerblom et al., 1991). In the present study, a randomly selected subsample of 400 participants was derived from the original sample ($n=3596$). Data on psychological measures were on 341 of these participants, and of them 267–323 had data for measures used in the present analyses. All the subjects gave their written informed consent and gave blood samples in accordance with the Helsinki Declaration.

2.2. Design

The data used in the present study were collected during the 5th and 6th follow-up phases of the CRYF.

Table 1
Descriptive statistics (n=341)

	n (%)	Mean (SD)
Age at Year 0		27.4 (5.0)
Gender		
Men	155 (45.5)	
Women	186 (54.5)	
TPH1 haplotype		
A/A	68 (19.9)	
A/C	170 (49.9)	
C/C	103 (30.2)	
Year-0 depressive symptoms		43.7 (13.7)
Year-4 depressive symptoms		41.6 (13.7)
Year-0 social support (transformed)		2.8 (0.7)

Assessments of depressive symptoms and social support were made in 1997 (referred to as Year 0), the subjects being 20 to 35 years of age. Genotyping and the assessment of depressive symptoms were conducted in 2001 (referred to as Year 4), the subjects then being 24 to 39 years old.

2.3. Genotyping

DNA was extracted from peripheral blood leukocytes using a commercially available kit (Qiagen Inc., Hilden, Germany). TPH1 A218C and A779C genotypes were determined with the use of fluorogenic allele-specific oligonucleotide probes with a conjugated minor groove binder (MGB) group. The nucleotide sequences of the primers and probes used in the PCR were deduced from published sequences deposited in the GenBank and Celera databases, and were chosen and synthesized in conjugation with Applied Biosystems (Foster City, CA, USA). DNA samples were genotyped by employing the 5′ nuclease assay for allelic discrimination using the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA). PCR reaction containing genomic DNA, 1×Universal PCR Master Mix, 900 nM of each primer and 200 nM of each probe was performed in 96-well plated using the standard protocol for TaqMan MGB probes in a total volume of 25 μl. After the cycling, end-point fluorescence was measured and genotype calling was carried out by the allelic discrimination analysis module.

Table 3
Depressive symptoms regressed on Year-0 social support by TPH1 haplotype groups

	b	SE	β	p
1. Year-0 depressive symptoms regressed on social support				
A/A (n=56)	−13.08	2.26	−.66	<.001
A/C (n=139)	−9.27	1.44	−.50	<.001
C/C (n=90)	−6.78	1.63	−.40	<.001
2. Year-4 depressive symptoms regressed on social support				
A/A (n=53)	−14.19	2.70	−.66	<.001
A/C (n=132)	−6.01	1.49	−.35	<.001
C/C (n=82)	−3.13	1.78	−.19	.083
3. Year-4 depressive symptoms regressed on social support, controlling for Year-0 depressive symptoms				
A/A (n=53)	−9.72	3.29	−.45	.005
A/C (n=132)	.19	1.25	.01	.878
C/C (n=82)	.35	1.58	.02	.823

2.4. Psychological assessment

Social support was assessed using the Perceived Social Support Scale Revised (PSSS-R) devised by Blumenthal et al. (1987). The 12 items of the PSSS-R dealing with perceived support from family, friends and significant other(s) were rated on a five-point scale ranging from totally disagree (1) to totally agree (5). The scale was negatively skewed and was corrected by a cubic root transformation (i.e. by reversing the scale, applying a cubic square root transformation on the reversed scale, and finally reversing the transformed scale back). The scores for the transformed scale ranged from 1.0 to 4.0. The transformed regressor was used in the analysis, but the results were similar also with the nontransformed variable.

Depressive symptoms were assessed using a modified version of Beck's Depression Inventory (Beck and Steer, 1987, see Katainen et al., 1999). In the original version of the BDI, subjects are asked to choose one of the four alternative response statements, representing ascending levels of symptom severity, in each of the 21 items. In the modified version used here, the items of the scale were the second mildest statements of the original BDI items (e.g. 'I often feel sad'). The subjects were asked to rate each of the 21 items on a five-point scale

Table 2
Depressive symptoms and social support scores (mean; SD) by TPH1 haplotype group

	A/A	A/C	C/C	p (ANOVA)
Year-0 depressive symptoms (n=285)	44.29 (13.75)	42.93 (14.63)	44.40 (12.24)	.836
Year-4 depressive symptoms (n=323)	43.07 (15.00)	40.97 (13.68)	41.52 (12.87)	.584
Year-0 social support (n=285)	2.79 (.70)	2.82 (.79)	2.94 (.72)	.611

ranging from totally disagree (1) to totally agree (5). The second mildest statements of the original BDI items were selected for the modified scale because they were expected to most accurately measure individual differences in depressive symptoms in a normal population (see Katainen et al., 1999).

The Cronbach's alpha reliabilities for social support and Year-0 and Year-4 depressive symptoms in the total CRYF sample were 0.93, 0.91 and 0.92, respectively, and the correlation between Year-0 and Year-4 depressive symptoms was $r=.65$ ($p<.001$).

2.5. Statistical analysis

The effect of the interaction between TPH1 (coded as a continuous regressor representing the number of C alleles: A/A=0, A/C=1, C/C=2) and perceived social support on depressive symptoms was assessed with linear regression analysis, controlling for age and gender. Three separate regression models were tested with the dependent variables being (1) Depressive symptoms at Year 0, (2) Depressive symptoms at Year 4, and (3) Depressive symptoms at Year 4 controlling for depressive symptoms at Year 0 (i.e. depressive symptoms at Year 0 entered as a covariate into the model).

3. Results

The TPH1 intron 7 A779C and A218C polymorphisms were found to be in 100% linkage disequilibrium (i.e., $r^2=1$) and forming three haplotypes A/A, A/C, and C/C. These haplotypes were used in the statistical analyses.

Descriptive statistics for the sample are presented in Table 1. TPH1 was not associated with depressive symptoms or social support (Table 2). Social support was associated with depressive symptoms at Year 0 ($b=-9.17$, SE=.96, $\beta=-.50$, $p<.001$) and at Year 4 ($b=-6.36$, SE=1.04, $\beta=-.36$, $p<.001$). Social support at Year 0 did not predict depressive symptoms at Year 4 when depressive symptoms at Year 0 were controlled for ($b=-.90$, SE=.96, $\beta=-.05$, $p=.348$).

The interaction between TPH1 and social support at Year 0 was statistically significant when predicting depressive symptoms at Year 0 ($b=3.00$, SE=1.42, $\beta=.50$, $p=.038$) and at Year 4 ($b=4.61$, SE=1.55, $\beta=.79$, $p=.003$), showing that while social support was associated with depressive symptoms in each of the haplotype groups, the association was stronger the more A alleles individuals were carrying (i.e., $\beta_{A/A}>\beta_{A/C}>\beta_{C/C}$; Table 3). The interaction effect was illustrated by plotting the model-predicted depressive symptoms at Year 4 against social support by TPH1 haplotype groups (Fig. 1).

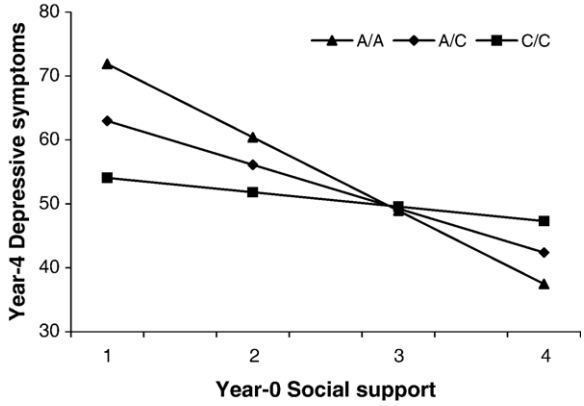

Fig. 1. Predicted Year-4 depressive symptoms plotted against Year-0 social support by TPH1 haplotype groups.

Next we examined whether the interaction between TPH1 and social support predicted a change in depressive symptoms over time. This was studied by using TPH1, social support, and their interaction effect to predict depressive symptoms at Year 4, with depressive symptoms at Year 0 entered as a covariate into the model. The interaction effect between TPH1 and social support was significant ($b=2.54$, SE=1.27, $\beta=.44$, $p=.047$) and indicated that low social support predicted an increase in depressive symptoms over time only among subjects carrying the A/A haplotype (Table 3). The difference in regression coefficients between the A/A haplotype group and others was considerably larger when predicting the change in depressive symptoms than in the other two regression analyses, suggesting the possibility of a statistical artifact. However, we did not detect any outliers (as identified by extreme z-scores, Mahalanobis distance and Cook's distance) in any of the haplotype groups that would have had considerable influence on the regression coefficients.

4. Discussion

We found that the TPH1 haplotype had no main effect on depressive symptoms or social support, but that it moderated the association between social support and depressive symptoms in a cross-sectional analysis and when predicting depressive symptoms over a four-year period. Low social support was related to depressive symptoms in all haplotype groups. However, the association was stronger in individuals carrying A alleles of the TPH1 haplotype than in others. In addition, low social support predicted an increase in

depressive symptoms over time only in individuals carrying the A/A haplotype of the TPH1. The results suggest that individuals carrying A alleles of the TPH1 may be more vulnerable to the lack of social support than those not carrying A alleles.

Low serotonergic functioning has been implicated in depression (Maes and Melzer, 1995), and social support has been shown to influence serotonin functioning (Iny et al., 1993, see also Oehler et al., 1987). The A allele of the TPH1 has been associated with low serotonin levels (Jönsson et al., 1997) and with a poorer response to the psychopharmacological treatment of depression (Serretti et al., 2001b; Peters et al., 2004). In line with these findings, the A allele was found to be the high-risk allele in the present study. Our finding therefore suggests that the A allele of the TPH1 gene might increase the sensitivity of the serotonergic system to social influences.

Given that the A218C and A779C polymorphisms are located in an intron of the TPH1, it has been suggested that their phenotypic associations might be due to linkage disequilibrium (LD) with a functional polymorphism (Nielsen et al., 1997). Indeed, a strong LD between the A218C polymorphism and a functional polymorphism in the promoter region of the TPH1 has been recently reported (Sun et al., 2005), suggesting that the intronic A218C and A779C polymorphisms may serve as markers for this functional promoter polymorphism.

The present study examined the direct influence of social support independently of major life events, but future research should extend investigations to include three-way interactions of TPH1 gene, life events, and social support. For example, Kaufman et al. (2004) found that the 5-HTTLPR polymorphism moderated the influence of maltreatment on depression in children, and that this interaction effect was further moderated by the availability of social supports. Maltreated children with the s/s genotype and no social supports had higher depression scores than maltreated children with the s/s genotype who had adequate social supports.

HERE, social support was treated as an environmental variable. However, it should be noted that it is partially heritable in itself (Kessler et al., 1992), and may be related to personality. This means that social support is not only an environmental provision, but also reflects relatively stable individual differences (Sarason et al., 1986). Therefore, it is possible that the causal relation between social support and depression is bidirectional, i.e. depression may lead to reduced support, too (Stice et al., 2004). In the present case, TPH1 had no significant main effects on depressive symptoms or social support, but it moderated the association of social support with depressive symptomatology over time.

Studies on rodents (Patel et al., 2004; Walther et al., 2003; Zhang et al., 2004) suggest that a second TPH isomorphism, TPH2, may be the primary isomorphism involved in the synthesis of serotonin in the central nervous system, while TPH1 is primarily expressed peripherally and only in small amounts in the brain. On the other hand, a human postmortem study (Zill et al., 2007) found both the TPH1 and TPH2 to be expressed in several areas of the brain. While TPH2 mRNA was more abundant in the raphe nuclei, TPH1 mRNA was more abundant in the hypothalamus and amygdala. In addition, Nakamura et al. (2006) found in rodents that TPH1 was associated with brain serotonin levels during late development, but not in adults. Thus, TPH1 may be involved in the development of serotonergic neurons, which is likely to influence adult behavior (Nakamura et al., 2006). We did not have data on the TPH2 polymorphism for the present analysis. However, it will be of interest to evaluate the gene-environment interaction demonstrated here also with the second TPH isomorphism.

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