Progress in Neuro-Psychopharmacology & Biological Psychiatry 36 (2012) 155–160

Contents lists available at SciVerse ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Hopelessness, a potential endophenotpye for suicidal behavior, is influenced by TPH2 gene variants

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ARTICLE INFO

Article history:
Received 25 July 2011
Received in revised form 1 September 2011
Accepted 1 September 2011
Available online 14 September 2011

Keywords:
Beck's Hopelessness Scale
Tryptophan hydroxylase
Suicide
Haplotype analysis
Depression

ABSTRACT

Objectives: Hopelessness is one of the strongest risk factors for suicidal behavior but relevant genetic studies are poorly available. Tryptophan hydroxylase (TPH) is widely considered to be a good candidate for genetic association studies on depression and suicide, however, investigations on these complex, multifactorial phenotypes have resulted in conflicting data. We hypothesized that hopelessness could be a mediating phenotype between TPH2 gene, depression and suicidal behavior.
Methods: Depressive phenotype and suicidal risk were investigated of 760 individuals from general population by Zung Self Rating Depression Scale (ZDS), Beck's Hopelessness Scale (BHS) and a detailed background questionnaire. All participants' DNA samples were genotyped for 7 tag SNPs in TPH2 gene. Generalized linear models were performed for single marker association studies and *p*-values were corrected by Bonferroni criteria. In haplotype analyses score tests were used and permutated *p*-values were computed.
Results: Four SNPs of TPH2 gene showed association with hopelessness but only *rs6582078* had a significant effect on the BHS scores after Bonferroni's correction; GG individuals had significantly higher BHS scores, while GT and TT had intermediate and lower BHS scores respectively ($p = 0.0047$). Compared with other genotypes, homozygous GG individuals also had almost three times greater estimated suicidal risk, as did carriers of the AA genotype of *rs6582078* (OR = 2.87; $p = 0.005$) and also of *rs1352250* (OR = 2.86; $p = 0.006$). A risk and a protective haplotype of TPH2 gene were also identified in association with hopelessness. ZDS scores have not shown any association with TPH2 gene.
Conclusions: We found that hopelessness, with its allied increased suicidal risk was strongly associated with TPH2 gene variants in multiple tests. These findings suggest that TPH2 gene confers risk for suicidal behavior while hopelessness can be a potential endophenotype for suicidal vulnerability.

1. Introduction

It is widely discussed that hopelessness, a cognitive symptom of depression is strongly associated with suicidal behavior (Large et al., 2011; Milnes et al., 2002; Minkoff et al., 1973; Nekanda-Trepka et al., 1983; van Heeringen et al., 2003; Wetzel et al., 1980); according to some authors hopelessness accounts for the relationship between depression and suicidal intent (Salter and Platt, 1990); and a recently published study suggested that among sixteen significant risk factors for suicide, the hopelessness score was the strongest predictor in a multiple logistic regression analysis (OR = 7.68) (Zhang et al., 2011). The involvement of genetic factors in suicidal behavior is supported by family, twin and adoption studies (Roy et al., 1999), however, genetic studies concerning association between suicide and candidate genes have provided ambiguous results (Courtet et al., 2005; Mann et al., 2009).

Tryptophan hydroxylase (TPH) is the rate-limiting enzyme in the synthesis of serotonin and it has two isoforms. In the brain both TPH isoforms are expressed in different brain regions, with the highest expression of TPH2 messenger RNA being found in the raphe nuclei where the serotonergic neurons are the main neuronal components (Zill et al., 2007). The TPH2 gene located at chromosome 12q15, comprises eleven exons and covers a region of 93.5 kb. TPH2 has significant role in the emotion regulation as demonstrated by fMR studies with amygdale

Abbreviations: 5-HTTLPR, serotonin transporter-linked polymorphic region; BHS, Beck's Hopelessness Scale; BPD, bipolar depression; DNA, dezoxyribonucleic acid; fMRI, functional magnetic resonance imaging; LD, linkage disequilibrium; MAF, minimal allele frequency; MDD, major depressive disorder; OR, odds ratio; RNA, ribonucleic acid; SD, standard deviation; S.E.M., standard error of mean; SNP, single nucletoid polymorphism; TPH, tryptophan hydroxylase; UPD, unipolar depression; ZDS, Zung Self-Rating Depression Scale.

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doi:10.1016/j.pnpbp.2011.09.001

and hippocampus (Brown et al., 2005; Fudalej et al., 2011) and it is investigated as a potential candidate gene for both major depression disorder (MDD) and suicide. Zill et al. reported a significant association between suicide and a polymorphism (*rs1386494*) and also haplotypes of the TPH2 gene previously described as being associated with MDD (Zill et al., 2004b). In a large-scale study of 670 families of patients with unipolar depression (UPD), bipolar depression (BPD) or schizoaffective disorder, Lopez de Lara et al. compared those depressed patients who had attempted suicide (n = 114) to those who had not made any suicide attempts (n = 145) with respect to TPH2 gene variants (Lopez de Lara et al., 2007). Four SNPs from fourteen investigated polymorphisms showed significant association with suicidal behavior, however, the polymorphism *rs1386494* investigated by Zill et al. was not observed as being significantly associated with suicide. Haplotype analyses showed significant association with both BPD and suicide attempts and this was confirmed by Ke et al. (2006). Zhou et al. investigated the effect of fifteen TPH2 gene polymorphisms in African American, Finnish white, US white and southwestern American population including suicide attempters and major depressed patients; increased frequency of a haplotype was observed among Finnish and African American suicide attempters (Zhou et al., 2005). However, other results from case–control studies did not confirm the significant effect of TPH2 gene on suicide (Mouri et al., 2009; Must et al., 2009). The prevalence of TT genotype was significantly higher in suicide victims than in controls particularly in subjects with multiple suicide attempts (Fudalej et al., 2011). Studies investigated MDD samples without suicidal history resulted in also conflicting data (Garriock et al., 2005; Roy et al., 1997; Van Den Bogaert et al., 2006; Zhang et al., 2005; Zill et al., 2004a).

These results suggest that the TPH2 gene has a significant role in the basis of depression and suicidal behavior but being polygenic, multifactorial conditions, but neither of them is appropriate phenotype to detect the effect of one single gene. A potential candidate endophenotype can be hopelessness because it is a depressive symptom strongly associated with suicidal behavior (Large et al., 2011); it can be measured by a valid, reliable instrument; hopelessness score of the Hamilton Depression Scale was significantly associated with the exonic polymorphism of TPH2 gene (*rs7305115*) in a suicide positive group and in the same study hopelessness has been proven as the strongest predicting factor for suicidal behavior among the major risk factors in the recently demonstrated study of Zhang et al. (2011).

Therefore, the aim of our study was to investigate the association between TPH2 gene variants, general depressive symptoms and hopelessness in a large-scale Hungarian general population sample. Our results show that while the TPH2 gene does not appear to be associated with general depressive symptoms, a functional variant of TPH2 is indeed associated with hopelessness.

2. Methods

2.1. Sample

A total of 760 unrelated volunteers, 620 women and 140 men, were included in the study. Participants were recruited from the practices of general practitioners, adult students participating in a long-distance learning program and a community-based population. The inclusion of subjects was independent of any positive psychiatric anamnesis. All subjects were Hungarian and of Caucasian origin and gave written informed consent before entering the study. It is important to emphasize that Hungary is a country with very high suicide rate (despite of the improving trends in the last 20 years, the prevalence of suicides is the fifth highest in the world (Szanto et al., 2007)) and a large-scale, specific study demonstrated that hopelessness is associated with suicidal risk in the Hungarian population (Perczel et al., 2007). Descriptive data of the study population are shown in Table 1. The study was approved by the Central Ethics Committee.

Table 1
Phenotypic characteristics of the study population.

	Females	Males	Total
n (%)	620 (81.6)	140 (18.4)	760 (100)
Age (Mean ± S.D.)	29.64 ± 10.37	33.32 ± 11.32	30.3 ± 10.60
Test scores			
BHS>9 (n, %)	49 (7.9)	16 (11.4)	65 (8.6)
BHS>15 (n, %)	10 (1.6)	4 (2.9)	14 (1.8)
ZDS>48 (n, %)	27 (4.4)	7 (5.0)	34 (4.5)
BHS (Mean ± S.D.)	5.21 ± 2.86	5.27 ± 3.41	5.22 ± 2.96
ZDS (Mean ± S.D.)	39.15 ± 5.47*	37.83 ± 5.44*	38.91 ± 5.48
Lifetime prevalences			
MDD	126 (20.3)	25 (17.9)	151 (19.9)
Bipolar disorder	6 (1.0)	4 (2.9)	10 (1.3)
Anxiety disorder	125 (20.2)	27 (19.3)	152 (20.0)
Suicidal attempt	26 (4.2)	6 (4.3)	32 (4.2)
Family history			
MDD	36 (5.8)	14 (10.0)	106 (13.9)
Bipolar disorder	14 (2.3)	2 (1.4)	16 (2.1)
Anxiety disorder	48 (7.7)	10 (7.1)	58 (7.6)
Suicidal attempt	36 (5.8)	7 (5.0)	43 (5.7)
Marital status			
Single	315 (50.8)	62 (44.4)	377 (49.6)
Married	185 (29.8)	56 (40.0)	241 (31.7)
Couple	63 (10.2)	14 (10.0)	77 (10.1)
Divorced/separated	16 (2.6)	6 (4.2)	32 (4.2)
Education			
No qualification	3 (0.5)	1 (0.7)	4 (0.5)
Technical school	36 (5.8)	25 (17.9)	61 (8.0)
High school	485 (78.2)**	91 (65.0)**	576 (75.8)
Degree	156 (25.2)***	44 (31.4)***	200 (26.3)

BHS, Beck's Hopelessness Scale; ZDS, Zung Depression Scale; S.D., standard deviation.
* Significant ($p = 0.010$) difference between females and males in ZDS mean point according to *t*-test.
** Significantly ($p < 0.0001$) higher frequency of technical school among females compared to males according to chi square test.
*** Significantly ($p < 0.0001$) higher frequency of degree among males than in females according to chi square test.

2.2. Phenotype measures

Participants completed three questionnaires: a detailed background questionnaire, the Zung Self-Rating Depression Scale (ZDS) and the Beck Hopelessness Scale (BHS). The background questionnaire was adapted from the version developed by the Epidemiology Unit of the University of Manchester. This well-structured self-rating questionnaire consists of 22 items and collects detailed information about medical history including psychiatric history and medications, family psychiatric history and socio-economic background.

The Zung Self-Rating Depression Scale (ZDS) is a valid, reliable instrument used in several studies in order to measure depressive symptoms. It contains 20 items relating to general symptoms of depression. ZDS can be characterized by four factors: depressive; cognitive; anxiety and somatic factors (Romera et al., 2008). In ZDS hope is questioned by one item ("I feel hopeful about the future") and another item is indirectly associated with suicide ("I feel that others would be better off if I were dead"). Higher scores correspond to more frequent symptoms, thus this qualitative scale provided the dependent variable representing the depressive phenotype in the total sample (Agrell and Dehlin, 1989; Biggs et al., 1978; Gabrys and Peters, 1985). The number of individuals above the threshold (48 point) reflects clinically depressed persons which is equivalent with point prevalence of depression in Hungarian population (Szadoczky et al., 1998).

Hopelessness was measured by Beck's Hopelessness Scale (BHS) developed by Aaron Beck et al. (1974). This questionnaire is an

internationally accepted and well-used instrument and is considered by suicide experts to be the most reliable predictor (Sidley et al., 1999); the association between elevated BHS scores and suicidal behavior has been confirmed by several studies (Beck et al., 1985, 1999; Milnes et al., 2002; Samuelsson et al., 2006; van Heeringen et al., 2003). BHS contains 20 items, and 3 factors can be identified: feelings in association with future (affective aspect); loss of motivation (motivation aspect) and expectations of futures (cognitive aspect) (Beck et al., 1974). The total score can range from 0 to 20. International studies suggest that more than 9 points means an increased risk of suicide, while above 15 points indicates a serious danger of suicide (Beck et al., 1993). BHS has been validated previously in the Hungarian population (Perczel-Forintos et al., 2007).

2.3. Genotyping

Buccal mucosa samples were collected from each subject and genomic DNA was extracted according to a protocol published by Freeman et al. (2003). DNA quality and quantity was determined with NanoDrop B-100 spectrophotometer, and all samples were diluted to a DNA concentration of 20 ng/μl. Seven intronic tagging SNPs (*rs1843809*, *rs1386493*, *rs6582078*, *rs10506645*, *rs1352250*, *rs1386485*, *rs1487275*) across the TPH2 gene were selected for genotyping using data from The International Hapmap Project (2003). SNPs were genotyped at Centre for Integrated Genomic Medical Research at The University of Manchester using the Sequenom® MassARRAY technology (Sequenom Inc., San Diego, CA, USA). The iPLEX™ assay, based on post-PCR single base primer extension, was performed according to manufacturer's instructions. Forward, reverse and extension primers (see Supplementary, Table S1) were designed using the Assay Design 3.0 software of Sequenom®. The iPLEX™ reaction products were dispensed onto a 384-well SpectroChip (Sequenom Inc.), processed and analyzed in a Compact Mass Spectrometer by MassARRAY Workstation 3.3 software (Sequenom Inc., San Diego, CA, USA). All laboratory work was performed under the ISO 9001:2000 quality management requirements and was blinded with regard to phenotype.

2.4. Statistical analysis

Descriptive statistics, including Hardy–Weinberg equilibrium, minimal allele frequency and pair-wise linkage disequilibrium (LD) between genotyped polymorphisms, were computed using Haploview 4.0 software (Barrett et al., 2005). Basic statistics of phenotypic parameters were computed with chi square tests and Pearsons correlation tests using SPSS 13.0 for Windows. Associations between ZDS and BHS and independent variables were computed performing multivariate linear regression analyses using SPSS 13.0 for Windows software, where polymorphisms were coded as 0, 1 or 2 depending on the carrier status of the minor allele. Single marker association analyses were performed under additive model.

We tested the effect of the haplotype constructed by the seven tagging TPH2 SNPs using the 'Hapstat' R-package software (Gonzalez et al., 2007). The effect of haplotypes was analyzed with score tests performing the 'Hapscore' of R package. The program computes the global effect of the model (p_{global}) and individual effect of haplotypes by comparison of each haplotype related score to the other's mean. Rare haplotypes less frequent than 1% were excluded from the analyses. To assess the reliability of the results, permutation procedures with 1000 random permutations were performed to generate empirical *p*-values in case of individual haplotype effect (p_{perm}).

All analyses were adjusted to age and gender. We applied Bonferroni corrections for multiple tests, thus *p*-values less than 0.007 (0.05/7) were considered nominally significant.

3. Results

3.1. Descriptive statistics

In our study of 760 individuals, the mean of the BHS score was 5.22 ± 2.97 points and 65 subjects (8.6%) scored more than 9 points which indicates suicide risk; 19 of these people scored more than 48 points on the ZDS (which is the threshold value indicating the presence of clinical depression). Almost 2% of the study population had above 15 points on the BHS which indicates serious hopelessness. The mean on ZDS scale was 38.91 ± 5.48 points and 4.5% of the participants exceeded the threshold value of 48 points for clinical depression. This result is in accordance with previous Hungarian epidemiologic data on depression. In terms of gender differences, women scored significantly higher on ZDS than men ($p = 0.010$). Pearsons' correlation test showed that ZDS and BHS are significantly correlated with each other at a moderate level ($r = 0.501$; $p < 0.001$). Phenotypic characteristics are shown in Table 1. All genotyped polymorphisms were in Hardy–Weinberg equilibrium and minimal allele frequency was more than 5% in each case (Table S1). Linkage disequilibrium tests showed that two haploblocks were constructed by the investigated polymorphisms according to the criteria of Gabriel et al. (2002) (Fig. 1).

3.2. Single marker associations between TPH2 gene polymorphisms and ZDS and BHS scores

Four SNPs (*rs1843809*, *rs1386493*, *rs1352250*, *rs6582078*) showed association with BHS scores in our sample (Table 2). The association of *rs6582078* and BHS score remained significant after Bonferroni

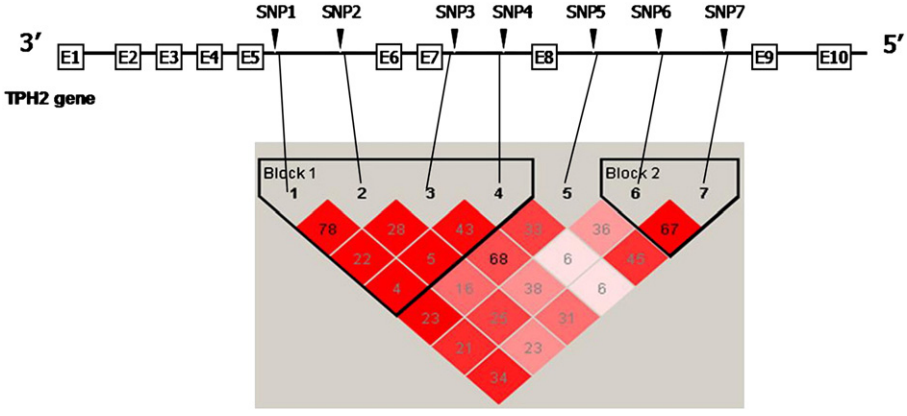

Fig. 1. Location and linkage disequilibrium map of the investigated polymorphisms of TPH2 gene E, exon; SNP1, *rs1843809* (G/T); SNP2, *rs1386493* (C/T); SNP3, *rs6582078* (G/T); SNP4, *rs10506645* (C/T); SNP5, *rs1352250* (A/G); SNP6, *rs1487275* (G/T); SNP7, *rs1386485* (A/C).

Table 2
Single marker associations between TPH2 gene polymorphisms and BHS score.

SNP	Genotypes	N	B	Mean ± S.E.M.	t	95% C.I.	*p*-value
rs6582078	TT	274		4.85 ± 0.164			
	TG	341	0.47	5.35 ± 0.168	1.91	−0.12–0.91	
	GG	132	0.87	5.72 ± 0.308	2.69	0.24–1.51	0.005[a]
rs1843809	TT	559		5.05 ± 0.121			
	TG	175	0.69	5.73 ± 0.271	2.64	0.18–1.21	
	GG	15	0.33	5.35 ± 0.607	0.41	−1.22–1.89	0.017
rs1386493	CC	525		5.04 ± 0.124			
	CA	210	0.67	5.70 ± 0.248	0.01	0.18–1.16	
	AA	23	0.25	5.31 ± 0.484	0.69	−1.01–1.52	0.021
rs1352250	AA	281		4.87 ± 0.156			
	AG	338	0.45	5.34 ± 0.176	1.83	−0.32–0.92	
	GG	135	0.69	5.57 ± 0.278	2.18	0.07–1.31	0.018

Results of single marker associations from generalized linear models are presented (data not shown if $p>0.05$). SNP, single nucleotide polymorphism; S.E.M, standard error of mean.
[a] Association between *rs6582078* SNP and BHS scores remains significant after correction of *p*-value.

correction ($BHS_{GG}=5.72\pm0.308$ vs. $BHS_{TG}=5.35\pm0.168$ vs. $BHS_{TT}=4.85\pm0.164$; $p=0.005$; Fig. 2, Table 2), although the association between the three other SNPs (rs1843809 rs1386493 and rs1352250) and BHS score did not survive Bonferroni correction ($p_{rs1843809}=0.017$; $p_{rs1386493}=0.021$; $p_{rs1352250}=0.018$). The three remaining SNPs (*rs10506645*, *rs1487275*, *rs1386485*) of TPH2 gene were not associated significantly with BHS score ($p_{rs10506645}=0.764$; $p_{rs1386485}=0.562$; $p_{rs1487275}=0.072$). None of the investigated TPH2 gene polymorphisms showed any significant effect on ZDS score ($p_{rs1843809}=0.346$; $p_{rs1386493}=0.440$; $p_{rs6582078}=0.907$; $p_{rs10506645}=0.663$; $p_{rs1352250}=0.857$; $p_{rs1386485}=0.628$; $p_{rs1487275}=0.844$).

Odds ratios for the risk of suicide were also investigated for association with the TPH2 gene polymorphisms. Individuals with a BHS score above 9 points (n = 65) were regarded as having a suicide risk based on literature (Beck et al., 1993). Comparing subgroups with score below 9 points (n = 580), we found that subjects with homozygous GG genotype for *rs6582078* and for *rs1352250* polymorphisms had almost threefold higher risk for suicide compared to TT and AA homozygous carriers, respectively (Table 3), with an intermediate increased risk for the heterozygotes. Based on sample size, the power of the study was 87.25% to detect a significant effect of *rs6582078* on BHS score using the additive model (MAF = 0.402, $B_G=0.498$).

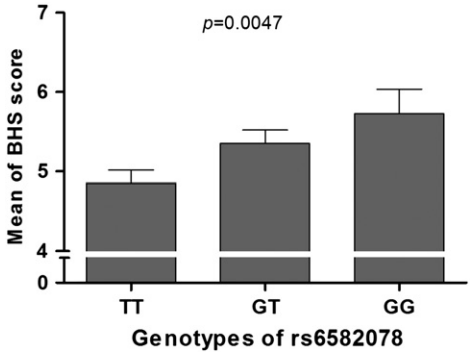

Fig. 2. Individual effect of TPH2 polymorphism (*rs6582078*) on the BHS score. Means and standard error of means of BHS scores are shown. The BHS score is associated with the G allele carrier status in a dose-dependent manner ($p=0.0047$).

Table 4
Individual effect of TPH2 gene haplotypes on BHS score ($p_{global}=0.006$).

Haplotypes	Frequencies	Estimated BHS score	P_{perm}
GCGCGCC	47.18%	−1.02	0.319
GCGCGGC	3.22%	+2.54	*0.016*
GCTTATA	10.41%	+1.09	0.287
GCTTAGC	7.67%	+0.44	0.650
TTTCATA	12.15%	−2.08	*0.040*
GCGCATA	2.35%	−0.85	0.420
GCTTAGA	1.49%	+0.57	0.562
GCGCGTA	1.27%	−1.58	0.109
GCGCAGC	1.25%	−0.01	0.994

Significant permutated *p*-values are presented by italicized numbers. BHS, Beck's Hopelessness Scale; p_{perm}, permutated *p*-value of individual haplotype effect.

3.3. Haplotype analyses of the TPH2 gene

We analyzed BHS and ZDS scores against the haplotypes constructed from seven polymorphisms of the TPH2 gene. There were nine haplotypes with a frequency greater than 1% (Table 4) and the global model was significant on BHS score ($p_{global}=0.006$). We identified a risk haplotype (*GCGCGGC*) which was associated with a significantly higher estimated BHS score compared to the mean score of the other haplotypes (BHS = +2.54; $p_{perm}=0.016$; freq = 3.22%) (Table 3), and a protective haplotype (*TTTCATA*) which was associated with a significantly lower score (freq = 12.5%; BHS = −2.08; $p_{perm}=0.040$). Associations between ZDS score and haplotypes were not significant (data not shown).

4. Discussion

This is the first genetic study on hopelessness – which is a significant depressive symptom strongly associated with suicidal behavior – in association with TPH2 gene. We found that the gene (TPH2), coding for the rate-limiting enzyme in the synthesis of serotonin, significantly associated with BHS score in a large-scale general population sample; four SNPs (*rs6582078* and *rs1352250*, plus two polymorphisms in linkage with *rs6582078*) were associated with increased BHS scores, while *rs6582078* survived Bonferroni correction, the other three did not. In addition, an almost threefold greater risk of suicide (as estimated by BHS scores) was observed in carriers of GG genotype for *rs6582078*

Table 3
Odds ratios for suicide risk based on BHS points and TPH2 gene polymorphism genotype.

SNP Genotypes	BHS< 9 (n)	BHS> 9 (n)	OR (BHS>9)	95% C.I.	B	S.E.	Beta	t	*p*-value
rs6582078									
TT	246	13	1						
GT	291	45	1.97	1.01–3.86					
GG	108	16	2.87	1.33–6.18	−0.038	0.014	−0.98	−2.687	0.005
rs1352250									
AA	250	12	1						
GA	283	32	2.36	1.09–4.69					
GG	111	15	2.86	1.29–6.31	−0.034	0.014	−0.089	−2.451	0.006

SNP, single nucleotide polymorphism; OR, odds ratio; C.I., confidence interval; BHS, Beck's Hopelessness Scale.

and for *rs1352250*. Haplotypes of the whole TPH2 gene were significantly related to the BHS score and one of them was significantly associated with an increased BHS score while another one has been proven protective against hopelessness. Furthermore, hopelessness measured by BHS was differentiated from other depressive symptoms of ZDS by TPH2 gene polymorphisms.

The intronic polymorphism *rs6582078* investigated here is in strong linkage ($D' = 1$, $R^2 = 0.928$) with an exonic functional polymorphism *rs7305115*, which SNP was associated significantly with hopelessness score of the Hamilton Depression Scale in suicide positive MDD group compared to suicide negative MDD group (Zhang et al., 2011). However, a molecular study is also available on allelic expression imbalance of *rs7305115* calling attention for potential explanation of biological function of *rs6582078*. The authors reported that five closely linked SNPs, including the intronic *rs6582078*, showed statistically significant correlation with TPH2 gene expression. In addition, the authors demonstrated the crucial role of these intronic SNPs in human gene function (Lim et al., 2007). As different TPH2 gene expression can result in altered serotonin synthesis, these polymorphisms can influence serotonergic system function from early cognitive development. Thus, genetic alteration of serotonergic system can be the basis of learned dysfunctional cognitive reactions (such as hopelessness) for certain environmental factors, e.g. negative life events. Several evidences demonstrated the role of serotonergic dysfunction in hopelessness. van Heeringen et al. (2003) showed that lower binding potential of frontal 5-HT2A receptors was associated with higher level of hopelessness, and in this sample BHS score was correlated positively with score of harm avoidance and negatively with scores of cooperativeness and self-transcendence (van Heeringen et al., 2003). Moreover, learned helplessness, which can be a match for the human hopelessness and one of the most applied models of depression in animals, can be prevented and reversed by administration of serotonergic agents (i.e. selective serotonin reuptake inhibitors) (Malkesman et al., 2009). Changes in serotonergic transmission are also described as a consequence of a learned helplessness paradigm (Hellhammer et al., 1984; Petty et al., 1992). A functional polymorphism in the serotonin transporter promoter region (5-HTTLPR) is also associated with hopelessness in human studies (Gonda et al., 2009; Kangelaris et al., 2010; Russ et al., 2000). These data in line with our results suggest that TPH2 gene variants can be one of multiple molecular components that contribute to serotonergic disbalance increasing risk of cognitive phenotypes, such as hopelessness being a part of suicidal behavior. According to this theory, TPH2 gene variants are not directly but rather through hopelessness can be linked to suicidal behavior and this hypothesis can explain previously reported contradictory results in studies investigating associations of TPH2 and suicide.

In our study, TPH2 gene polymorphisms were significantly associated with hopelessness (as measured by BHS), but not with general symptoms of depression (measured by ZDS). In line with our results, increased frequency of the G allele of TPH2 -703 G/T SNP was associated with elevated suicidal behavior itself, rather than with the diagnosis of major depression in a recently published study (Yoon and Kim, 2009).These data can suggest that hopelessness is associated more specifically with TPH2 gene function, while other phenotypes of depression may depend mainly on other genes, and also on environmental factors (e.g. threatening life events) as has been demonstrated in our previous study (Lazary et al., 2008).

In the present paper we demonstrated for the first time a significant association between hopelessness and TPH2 gene variants which have previously shown functional consequences in gene expression studies. Our results confirm the potential role of TPH2 in suicidal behavior and suggest hopelessness as an endophenotype differentiated from other depressive symptoms. Furthermore, the association between hopelessness and cardiovascular morbidity may also be dependent on TPH2 gene function. These data suggest that TPH2 gene variants may have a crucial role in increased mortality in depression.

Supplementary materials related to this article can be found online at doi:10.1016/j.pnpbp.2011.09.001.

Conflict of interest

None to declare.

Acknowledgments

These studies were supported by the Sixth Framework Programme of the EU, LSHM-CT-2004-503474, HRF T03298/2000, Hungarian Ministry of Health RG 318-041-2009 and TAMOP-4.2.1.B-09/1/KMR-2010-0001. Special thanks to Hazel Platt and Krisztina Mekli for contribution in genotyping procedures.

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