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Genetic predictors of response to treatment with citalopram in depression secondary to traumatic brain injury

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Abstract

Objectives—To determine which serotonergic system-related single nucleotide polymorphisms (SNPs) predicted variation in treatment response to citalopram in depression following a traumatic brain injury (TBI).

Methods—Ninety (50 M/40 F, aged 39.9, SD = 18.0 years) post-TBI patients with a major depressive episode (MDE) were recruited into a 6-week open-label study of citalopram (20 mg/day). Six functional SNPs in genes related to the serotonergic system were examined: serotonin transporter (5HTTLPR including rs25531), 5HT1A C-(1019)G and 5HT2A T-(102)C, methylene tetrahydrofolate reductase (MTHFR) C-(677)T, brain-derived neurotrophic factor (BDNF) val66met and tryptophan hydroxylase-2 (TPH2) G-(703)T. Regression analyses were performed using the six SNPs as independent variables: Model 1 with response (percentage Hamilton Depression (HAMD) change from baseline to endpoint) as the dependent variable and Model 2 with adverse event index as the dependent variable (Bonferroni corrected p-value <0.025).

Results—MTHFR and BDNF SNPs predicted greater treatment response (R^2= 0.098, F = 4.65, p = 0.013). The 5HTTLPR predicted greater occurrence of adverse events (R^2= 0.069, F = 5.72, p = 0.020).

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Conclusion—Results suggest that polymorphisms in genes related to the serotonergic system may help predict short-term response to citalopram and tolerability to the medication in patients with MDE following a TBI.

Keywords

Traumatic brain injury; serotonin receptors; serotonin transporter; brain derived neurotrophic factor (BDNF); methylenetetrahydrofolate reductase (MTHFR); tryptophan hydroxylase (TPH)

Introduction

It has been estimated that the incidence of a major depressive episode (MDE) following a traumatic brain injury (TBI) ranges from 25–44% [1, 2]. The risk of developing an MDE has been shown to remain increased from 1 year post-injury [3], until decades later [4]. An MDE following mild-to-moderate TBI is one of the most common neuropsychiatric disorders and presents a substantial hurdle to the recovery process, having been linked to cognitive impairment [5], increased post-concussive symptoms [6] and poor outcome [7]. If left untreated, these symptoms may worsen, leading to increased risk of suicide and cardiovascular disease [8, 9].

Increased mood symptoms following a TBI are believed to be caused by injuries to specific brain regions, particularly the anterior frontal lobe regions, which are areas that are heavily innervated by the serotoneric system [10–12]. Despite possible links with the serotonergic system, there is a paucity of data concerning efficacy and adverse effects for selective-serotonin reuptake inhibitor (SSRI) treatment in depressed TBI patients. Only two randomized controlled trials [13, 14], one single-blind trial [15] and four open-label trials [16–19] have examined SSRI treatment in this patient population and those studies reported a significant improvement in depressive symptoms. More recently, in an open-label citalopram treatment study (20–50 mg/day for 6–10 weeks) on 65 patients with TBI and MDE (54 with major depression due to TBI and 11 with depressive features), a 28% response rate was observed [20]. For tolerability, 54/65 (83%) completed at least 6 weeks of the study, with 10 dropouts due to adverse events.

As the serotonergic system is a main target for SSRIs, inherited variablility in genes within this system may contribute to a patient's response to SSRIs and influence treatment outcomes in a clinically important manner. There are several genes that change the function of the serotonergic system that are polymorphic in the population, meaning that they lead to a genetic variant that appears in at least 1% of a population. The impact of these common genetic variants in the serotonergic system may be particularly important following TBI, where both animal and human studies have demonstrated important serotonergic damage [21–24].

Several genes related to the serotonergic system have been identified as being particularly important to SSRI response. The serotonin-transporter-linked promoter region (5HTTLPR) is adjacent to the *SLC6A4* gene—a gene which codes for the soluble serotonin transporter protein (5HTT) [25]. As a promoter, 5HTTLPR regulates the transcriptional activity of SLC6A4 and thus the eventual downstream production of 5HTT. 5HTTLPR is characterized

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by a 44 base pair segment that is present in those with the 'long' (*L*) allele (alternative form of the gene) and absent in those with the 'short' allele (*S*). The *S* allele of 5HTTLPR has been associated with decreased transcriptional activity of the *SLC6A4* gene and, as a result, lowered 5HTT expression [26] and poorer outcome following treatment with SSRIs [27–30]. In addition to longer and shorter alleles of 5HTTLPR, individuals may also have single-nucleotide polymorphisms (SNPs) within the 5HTTLPR region that further affect the promoter's activity and the downstream production of 5HTT. The presence of the rs25531 G SNP in the long allele (L_G) has been demonstrated to result in reduced 5HTT expression levels compared to *L* allele without the G SNP. The levels of 5HTT in individuals with L_G are comparable to 5HTT expression in those with the *S* allele [31]. The rs25531 G SNP can also occur in the 5HTTLPR *S* allele [32].

In addition to polymorphisms of the 5HTTLPR promoter, changes may occur in serotonin receptor genes, which can also effect the response to citalopram. SNPs in genes coding for serotonergic receptors, such as 5HT1A C-(1019)G (a SNP in a 5HT1A receptor gene) and 5HT2A T-(102)C (a SNP in the 5HT2A receptor gene), have been linked to SSRI response [27, 33]. The *G* SNP in the 5HT1A C-(1019)G polymorphism is thought to increase gene expression [34], while some studies have suggested that the *C* SNP T-(102)C polymorphism in the 5HT2A alters the expression levels of the receptor due to differential DNA methylation (an epigenetic change that effects gene expression) [35]. A recent genomewide association study of citalopram response suggested that 5HT2A is indeed a genetic target worthy of further consideration [36].

Another gene of importance within the serotonergic system is tryptophan hydroxylase (TPH2), a brain-specific enzyme responsible for the conversion of tryptophan to serotonin that has been previously linked to major depression [37]. Finally, two more polymorphisms in genes of interest associated with the serotonergic system involve brain-derived neurotrophic factor (BDNF) and the methylenetetrahydrofolate reductase (MTHFR) enzyme. BDNF is stimulated by serotonin and vice versa. BDNF affects function of the serotonin transporter [38] and antidepressants influence neuronal plasticity via BDNF [39, 40]. Some individuals have a polymorphism in the BDNF gene known as the val66met polymorphism, which is responsible for an amino acid substitution in the BDNF protein. The val66met polymorphism in the BDNF gene has been shown to lead to an increased risk of depression in some, but not all, studies [41–44] and has been associated with treatment resistant depression in conjunction with the 5HT1A C-(1019)G SNP mentioned previously [45]. MTHFR may also influence serotonin levels. MTHFR is responsible for homocysteine metabolism to methionine. Homocysteine metabolism provides the methyl group necessary for the production of serotonin through the 1-carbon metabolism pathway [46]. Thus, improper metabolism of homocysteine through reduced MTHFR enzyme activity, as demonstrated with the MTHFR C-(677)T SNP [47], could possibly deplete levels of serotonin in the brain. Data linking polymorphisms in the MTHFR gene with depression have been contradictory [48, 49] and have yet to be investigated as a predictor of treatment response. As these genetic variants are related to the serotonergic system, they may play a role in individual response to SSRI treatment, particularly within the depressed TBI patient population.

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This study hypothesized that one or more of these variants would act as genetic predictors of treatment response to a 6-week open-label trial of citalopram in post-TBI patients who had been diagnosed with a MDE.

Method

Participants

The Research Ethics Board of Sunnybrook Health Sciences Centre approved this study and all participants provided written informed consent. Subjects were recruited from a larger cohort of consecutive referrals attending the Traumatic Brain Injury Clinic at the Sunnybrook Health Sciences Centre from October 2003 to May 2007. Ninety mild-to-moderate TBI subjects diagnosed with MDE in the context of mood disorder secondary to TBI, based on the depression module of the structured clinical interview for DSM-IV depression (SCID) [50] as administered by the study psychiatrist, were included as previously described [20]. That previous study reported on 65 patients who completed a 6–10 week variable dose study. This study now reports on 90 subjects who completed the 6-week fixed dose phase. Clinical characteristics and demographics information were recorded regarding the TBI including mechanism of accident, CT head scan results (classified as normal, atrophy or focal injury) and any other injuries sustained during the accident. The severity of the TBI (mild, moderate or severe) was determined by the study physician, based on guidelines put forth by The American Congress of Rehabilitation Medicine [51]. Baseline demographics were also recorded. Patients were excluded from this study if they had a prior traumatic brain injury, a significant acute medical illness, current antidepressant usage, presence of a pre-morbid psychiatric diagnosis of schizophrenia, dementia or bipolar disorder or any contraindications to receiving treatment with citalopram.

Measures

Percentage change on the Hamilton Depression Rating Scale (HAMD) [52, 53] was the primary outcome measure in this study. The HAMD (17-item scale) was administered by trained research co-ordinators with supervision and direct review by staff physicians. For descriptive analysis, a ‘response’ to medication was defined as ≥50% decrease in HAMD scores from baseline and ‘remission’ was defined as a drop in HAMD total to ≤8 at endpoint.

Study design

Once eligibility was established, subjects began a 6-week treatment phase, receiving 20 mg/day p.o. of citalopram. Citalopram was given open-label to mimic clinical practice. At the end of the 6-week treatment phase, subjects were reassessed. The study physician and the study co-ordinator were blinded to the genotype results during the study and genotype analyses were performed blinded to any clinical information.

Adverse events

Information regarding the occurrence of any adverse events (AEs) was recorded at scheduled visits and telephone conversations. Adverse events assessed as being possibly or probably related to study medication were rated in terms of severity (0–3) and duration (in days) and

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summed over adverse events to calculate an adverse event index for each patient, as previously described [28]. Adverse event indices ranged from 0–56 within our study population.

DNA analysis

Once eligible, patients provided written consent regarding participation in this study and peripheral venous blood samples (~1–5 ml) were collected. Blood samples ($n = 28$) were later replaced with buccal swabs ($n = 62$), due to their less invasive nature. Blood samples and buccal swabs were extracted using Qiagen (DNA midi and QIAamp DNA mini) kits, respectively (Maryland). Stock DNA samples were diluted to 20 ng/μl concentration for direct use in genotyping. All DNA extractions and analyses were performed by the laboratory of Dr James L. Kennedy from the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada under the direction of Dr John Strauss. The following markers were genotyped using primers, probes and polymerase chain reaction (PCR) conditions supplied by Applied Biosciences: 5HT1A C-(1019)G (rs6295), 5HT2A T-(102)C (rs6313), BDNF (rs6265), TPH2 (rs4570625) and MTHFR (rs180113). The amplification and detection of the PCR products were performed using an ABI Prism 7500 Sequence Detection System (Applied Biosystems Inc., Foster City, CA) and using default settings, as recommended by the manufacturer. The detection of PCR products corresponded to an increase in reporter dye fluorescence during the PCR extension phase when the probes were cleaved by the 5′ exonuclease activity of the Taq DNA polymerase. Genotypes were resolved based on the distribution of fluorescence on an X–Y scatter plot using the post-read allelic discrimination option (SDS software for allelic discrimination v1.2.3, Applied Biosystems Inc.). 5HTTLPR and 5HTT rs25531 were genotyped by PCR followed by digestion and resolved on an agarose gel using the conditions described by Heils et al. [25] with the addition of digestion of the amplified product overnight at 37°C by 10 U of Msp1 (New England Biolabs, Ipswich, MA). Genotypes were determined manually against a 100 bp ladder.

Statistical analysis

Descriptive statistics were calculated for all variables of interest. Continuous measures such as age were summarized using means and standard deviations, whereas categorical measures were summarized using counts and percentages.

An Intent-to-Treat (ITT) analysis was implemented, where a last observation carried forward (LOCF) was used for endpoint data. In genotype analysis, the long variant of the 5HTTLPR with the *G* substitution (L_G) was treated as equivalent to the short allele (*S*) variant [31]. ITT analysis was used rather than an observed cases analysis to place results within the context of the total number of participants who were treated. The primary outcome, percentage HAMD change, was assessed using a backward stepwise linear regression model and independent variables were polymorphisms 5HT2A (C/C vs T/C vs T/T), 5HT1A (C/C vs G/C vs G/G), BDNF (G/G vs A/G vs A/A), MTHFR (C/C vs T/C vs T/T), TPH2 (G/G vs T/G vs T/T) and 5HTTLPR (S/S vs S/L vs L/L). Backward stepwise elimination was chosen because, as all polymorphisms were related to the serotonergic system, the aim was to assess joint predictive capability. Unlike forward selection procedures, this will detect if the subsets

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of polymorphisms have significant predictive capability, even if individually they do not. The direction of results was determined by a one-way ANOVA. Similarly, for adverse events, a backward linear regression was performed to determine the association between the polymorphisms mentioned previously and the dependent variable adverse event index. Adverse event was converted to a logarithimic scale to correct for the skewedness of the variable, before being entered into the linear regression. A removal value of 0.05 was used in both regressions. To account for the fact that there were two primary analyses, a p-value of 0.025 (0.05/2) was considered to indicate statistical significance of the regression models. In addition, the impacts of TBI severity, education, gender, age and marital status were explored by entering them individually into both regression models. Statistical analysis was performed using the program SPSS version 15.0.

Results

Demographics and response to treatment

Of roughly 560 eligible patients, 122 were depressed and 90 were treated with citalopram and observed in this study. Subjects were enrolled, on average, 3.3 (SD = 3.2) months following their injury. Demographic, clinical and polymorphism distribution data are presented in Table I. Caucasians made up the largest ethnicity in the study group and the majority of patients met criteria for mild TBI to moderate TBI. Additionally, 46.7% of the population had focal injuries while 2.2% had atrophy on CT scan results. Within the total study group, 15.6% of subjects dropped out prior to the 6-week endpoint ($n = 14$) due to either adverse events ($n = 11$, 12.2%), loss to follow-up ($n = 2$, 2.2%) or diagnosis of an acute unrelated illness ($n = 1$, 1.1%). Changes in HAMD following citalopram are shown in Table II.

Polymorphisms and treatment response

All polymorphisms examined were in Hardy-Weinburg equilibrium (there are no disturbing influences in the distribution of polymorphisms examined in this study in this population). In the final overall model of the backward linear regression using percentage HAMD change as the dependent variable, polymorphisms in the MTHFR ($\beta = 0.30$, $p = 0.016$) and BDNF ($\beta = 0.28$, $p = 0.021$) genes were found to nominally predict the level of response to citalopram, together accounting for 9.8% of the variance ($R^2 = 0.098$, $F_{2,68} = 4.65$, $p = 0.013$). Specifically, the C/C group of the MTHFR polymorphism and the G/G homozygotes (Val/Val) of the BDNF polymorphism were associated with a greater percentage change on the HAMD. All other variables were removed from the model.

Polymorphisms and adverse events

Seventy-three patients (81.1%) reported one or more adverse events that most commonly included dry mouth (25.4%), nausea (19.2%), somnolence (10.7%) and sexual side-effects (8.5%). Adverse events were rated as mild (46.8%), moderate (34.3%) or severe (18.8%). In linear regression analysis (Table II), only the 5HTTLPR polymorphism (S/S vs S/L vs L/L, $\beta = 0.29$, $p = 0.02$) significantly predicted an adverse drug event index, accounting for 6.9% of the variance ($R^2 = 0.069$, $F_{1,64} = 5.72$, $p = 0.02$). All other variables were excluded from the final model. One way ANOVA analysis showed a significant effect of 5HTTLPR

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haplotype on adverse event index ($F_{2,75} = 4.11$, $p = 0.02$). Specifically, post-hoc Tukey tests showed that the S/L ($p = 0.016$) haplotype of 5HTTLPR had a higher adverse event index value compared to the S/S group.

The impact of ethnicity and other demographics on treatment response and adverse events

Comparing genotype distributions between only the Caucasian and Asian sub-groups, 5HTTLPR, BDNF val66met and TPH2 were significantly different (Table III). A sub-analysis evaluating the possible impact of ethnicity on the regression model where treatment response was the dependent variable showed that dividing the population between Caucasians, Asians and other ethnicities did not significantly predict treatment response, as this variable was removed from the model ($p = 0.09$). A similar sub-analysis was performed looking at the impact of ethnicity on adverse events. In the previously described regression model, where the adverse event index was the dependent variable and ethnicity (Caucasian, Asian and other ethnicities) in addition to the polymorphisms were the independent variables, ethnicity was removed from the final model ($p = 0.72$).

This study also explored the impact other demographic variables including age, gender, marital status, education and TBI severity had on MDE by entering those variables in the final regression models. Only female gender had a significant association, showing statistical significance ($p = 0.039$) in the backward linear regression model with treatment response as the dependent variable.

Discussion

The response to treatment in the study group could be considered low, with a mean percentage change on the HAM-D of −26.2 ± 32.9, 21/90 responders (23%) to medication and 15/90 (17%) remitting. The HAM-D was selected as the primary outcome due to the fact that it is considered the ‘gold standard’ of antidepressant treatment trials and is considered superior by many over self-reported scales [54]. This overall poor response to treatment may be due to the fact that some participants, who were on doses of 20 mg/day for 6 weeks, were treated sub-optimally. A 10-week variable dose study in the clinic, on the same patient population, found a response rate of only 28% at 6-weeks, while patients treated for 10 weeks with adjustable doses of citalopram had a much higher rate of response (46%), indicating that dose and duration may account for some of the non-response in this study [20].

It was found that a combination of polymorphisms in BDNF (val/val) and MTHFR significantly predicted better treatment response. BDNF and its expression in depression and antidepressant treatment response has been rigorously studied. Hippocampal and serum levels of BDNF have been shown to increase with the administration of antidepressants in both animal models [55] and human subjects [56, 57]. Polymorphisms of BDNF and other genes may occur on one or both copies of the gene. Previous studies on BDNF have demonstrated the importance of zygosity in this polymorphism or whether the polymorphism occurs on one (heterozygous–Val/Met), both (homozygous mutant–Met/Met) or neither (homozygous wild-type–Val/Val) copy of the gene. Specifically, studies with the

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BDNF val66met polymorphism have linked the heterozygous G/A (Val/Met) group with the greatest response to milnacipran and fluvoxamine [58] and fluoxetine [59], while no significant association was found with mirtazapine [60]. A recent study looking at the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in treatment resistant patients with depression in the absence of TBI (n = 36) found that G/G homozygote (Val/Val) patients had the greatest response to treatment [61]. Another study using citalopram demonstrated similar results, where G/A (Val/Met) and A/A (Met/Met) individuals had a greater change in percentage HAMD compared to G/G (Val/Val) individuals [62]. Our results agree with the findings from the rTMS study, but differed from the previous citalopram study as we observed the greatest improvement on HAMD scores was associated with the G/G (Val/Val) genotype. A possible reason for the contradictory results may be that BDNF was assessed with MTHFR and other serotonergic polymorphisms rather than as a single predictor. In addition, this study sample differed in that they had all experienced a recent TBI and because of their widely variable ethnic make-up.

Contradictory results have been previously reported in different ethnic populations with regard to the val66met SNP. One such example is the observation that the allele conferring a valine in the BDNF protein was associated with risk factors linked to depression in Caucasian populations [63, 64], whereas this association was not observed in Asian populations [59, 65]. Two similar case-control studies looking at Mexican Americans (n = 272 and 284) compared to healthy controls found an association, indicating that individuals homozygous for the G SNP were at greater risk of developing depression [66, 67]. On the other hand, two studies, one in a Spanish Caucasian population (n = 374) [68] and the other in a Taiwanese population (n = 110) [59] found no significant association. At the biological level, a recent animal study found that BDNF protein with a methionine was secreted improperly from neuronal cells and resulted in decreased response to fluoxetine compared to the wild-type strain [69]. These results confirm this finding, as individuals who were carriers for the polymorphism had less of a response to SSRI treatment, compared to the G/G group.

With respect to the MTHFR C-(677)T SNP, individuals with one or two *T* SNPs had less of a response to treatment compared to C/C individuals in the present study. Although the polymorphism in the MTHFR has not been previously linked to antidepressant treatment response, low folate levels have been shown to decrease response to fluoxetine [70]. Folate, like MTHFR, is necessary for homocysteine metabolism and subsequent production of serotonin. These results suggest that another member of the 1-carbon metabolism pathway, the MTHFR, may also influence response to SSRIs.

Polymorphisms that were found not to predict treatment outcome included the 5HT1A C-(1019)G, 5HT2A T-(102)C, 5HTTLPR and TPH2 G-(703)T. An association between the 5HTTLPR polymorphism and SSRI treatment response has been previously demonstrated in mood disorder patients [30]. While a meta-analysis suggests that the S/S genotype is linked to poorer outcome in treatment with SSRIs in Caucasian populations with mood disorders [30], a recent study demonstrated that OCD patients with an S/L haplotype had a better response to venlafaxine compared to the S/S and L/L haplotype groups [71]. In contrast to the finding in Caucasians, Asian populations have shown a link between better treatment outcome and the *S* allele [58,72], indicating that ethnicity in addition to polymorphism may

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influence treatment outcome. The Caucasian subgroup within this study population were predominantly carriers or homozygous for the *L* allele, whereas 82% of individuals who identified themselves as Asians were homozygous for the *S* allele (Fisher's Exact, $p < 0.01$). A recent meta-analysis investigating 5HTTLPR revealed that polymorphisms in the gene alone are not associated with greater risk of depression [73]. That meta-analysis did not investigate the effects of 5HTTLPR polymorphisms on citalopram response. The distribution of the BDNF and TPH2 genotypes were also significantly different between Caucasians and Asians within this study population. A majority of Caucasians (78%) had the G/G (Val/Val) haplotype of the BDNF gene, whereas Asians (66.7%) were heterozygous (Val/Met) for this polymorphism. With regard to the TPH2 G-(703)T, Caucasians were predominantly G/G (72.5%), whereas Asians were more equally distributed between the three haplotypes (G/G, G/T, T/T). In order to further explore the possibility of an effect on treatment response, ethnicity (Caucasian, Asian and other ethnicity) was entered into a regression model along with the six polymorphisms as independent variables and HAMD percentage change as the dependent variable. Ethnicity was eventually removed from the final model, indicating that it did not independently predict treatment outcome in the post-TBI group. The demographic variables age, marital status, education and TBI severity were not significant in the final regression model, although female gender predicted better treatment response. This gender effect has been previously demonstrated in the literature [74, 75].

In order to determine if ethnicity could predict tolerability to medication, this was added into a regression model with the six polymorphisms as independent variables and the adverse event index as the dependent variable. Ethnicity was eventually removed from the final regression model, indicating that, similar to treatment response, it did not predict the occurence of an adverse event. Similarly, age, gender, marital status, education and TBI severity were not significant in the final regression model predicting adverse events.

Unlike previous studies, this study has taken into consideration rs25531 in the subject population. One study suggested that the *G* SNP was linked to a reduced response to citalopram [76]; however, in a study using a larger sample ($n = 1914$), no association was found between this polymorphism and treatment response, although it was not a study of depression post-TBI [77]. The use of the rs25531 SNP augments the existing knowledge of the 5HTTLPR in comparison with previous reports that have not examined it. An individual who was initially categorized as an L/L individual may have expression levels similar to an S/L heterozygote or even S/S for rs25531 *G* SNP homozygotes. Within this study population, only 21.3% had a 'true' L/L phenotype (two copies of the L allele in 5HTTLPR, both lacking the rs25531 G SNP) and, of those, 82.3% were Caucasians. Nevertheless, this study suggests that this polymorphism did not significantly predict response to citalopram treatment in this depressed TBI population.

Polymorphisms in the serotonin transporter gene predicted the occurrence of adverse events. The most common adverse events reported were dry mouth, nausea, somnolence and sexual side-effects. Individuals with two S alleles experienced fewer adverse events while on citalopram than individuals with one *L* allele. This contradicts previous reports that linked the *S* allele to greater adverse events with SSRI treatment [28, 78]. The data suggest that S/L individuals will experience more adverse events while on citalopram. A correlation looking

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at the level of adverse events and percentage HAMD change from baseline was performed. No statistically significant association was found ($p = 0.88$), thus indicating that the number of adverse events did not influence treatment response.

A limitation to this study was the variability in ethnicity within this population. While ethnicity did not significantly predict treatment response, the ability to detect such effects was limited by no single ethnicity having a sufficient sample size. Furthermore, as polymorphisms in the 5HTT, BDNF and TPH2 genes were significantly different between Caucasians and Asians, ethnicity may have been a confounder in this study. From a demographic perspective, the few clinical trials that have been conducted vary somewhat, not only in ethnicity, but also in age, gender and education of the study population. Subjects in this study are older and have predominantly mild-to-moderate TBI compared to subjects in other TBI studies. These results might not be generalizable to younger subjects and those with more severe injuries. It may, thus, be difficult to generalize conclusions regarding efficacy in the TBI population [13, 14, 18]. Another limitation to this study would be the modest sample size. Although it remains in the allowable limits of the ratio of sample size to number of predictors per dependent variable, a larger study sample will be required to confirm these findings. Additionally, since all participants were treated clinically with citalopram, ‘response’ following the initiation of medication includes both drug and placebo responses. Thus, clinical effectiveness rather than efficacy was measured. Finally, an ITT analysis rather than an observed cases analysis may be considered a limitation of this study, since ITT analysis assumes that data is missing at random (which may not be the case in this analysis of adverse event index, where many drop-outs were due to adverse events). This distinction is much more important, however, in a randomized placebo controlled trial, where excluding cases presents a bias between the two arms of the study—this is less of a limitation in an open-label study such as this.

Ultimately, the goal of such research is to determine if certain genotypes in the depressed TBI populations would be associated with a favourable response to citalopram treatment over a 6-week period. In many cases, patients suffering from depression may have to undergo up to four different trials of antidepressants before they remit [79]. Access to the genetic likelihoods of response or remission for a certain treatment intervention may decrease the time TBI patients remain depressed.

In conclusion, this study demonstrated that polymorphisms in BDNF and MTHFR may predict outcome to short-term naturalistic treatment with citalopram in a TBI population with MDE. Additionally, a polymorphism in the 5HTTLPR appeared to predict tolerability to the medication. The clinical implications of these findings are speculative, but they identify a sub-set of serotonergic genes that independently predict citalopram response and tolerability, suggesting that further investigation is required. However, contrary to the expectations in a group defined by mild-to-moderate TBI who may be expected to have suffered insults to the serotonergic system, serotonergic polymorphisms accounted for a relatively small amount of the variance in both response and tolerability. These results should be considered preliminary and warrant further testing in a larger sample population in order to confirm these associations. The identification of these genetic predictors may shed

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light on the mechanisms involved in treatment non-response and lack of tolerance to citalopram in TBI patients.

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Table I

Background information on study population.

Variable	*n* (%) (total *n* = 90)
Demographics	
Age	39.9 (SD = 18.0)
Male sex (%)	50 (55.6)
Marital status	
Married	51 (56.7)
Single	32 (35.6)
Other	7 (7.8)
Race	
Caucasian/European	47 (52.2)
Asian	12 (13.3)
Other	31 (34.4)
Years of education (%)	
Grade school	14 (15.7)
High school	35 (39.3)
Higher education	39 (43.8)
No formal education	1 (1.1)
Illness	
TBI severity (%)	
Mild	44 (48.9)
Moderate	45 (50.0)
Severe	1 (1.1)
Distribution of polymorphisms, *n* (%)	
5HTTLPR (including the A→G SNP)	
S/S	36 (45.6)
S/L	26 (32.9)
L/L	17 (21.5)
5HT2A T-(102)C	
C/C	17 (17.8)
T/C	45 (51.7)
T/T	26 (29.9)
5HT1A C-(1019)G	
C/C	19 (23.1)
C/G	34 (37.8)
G/G	26 (28.9)
TPH2 G-(703)T	
G/G	51 (66.2)
T/G	24 (31.2)
T/T	2 (2.6)
BDNF val66met	

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Variable	*n* (%) (total *n* = 90)
G/G	53 (66.3)
A/G	23 (28.8)
A/A	4 (5.0)
MTHFR C-(677)T	
C/C	29 (35.4)
T/C	45 (54.9)
T/T	8 (9.8)

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Table II

Results.

Outcomes	*n*	*F*	df	R^2	*p*	*β*
Baseline HAMD	23.6 (SD = 6.5)					
Mean change HAMD	6.2 (SD = 7.6)					
% change HAMD	−26.2 (SD = 32.9)					
Responders (≥50% change in HAMD)	21 (23.3%)					
Remitters (≤8 on HAMD)	15 (16.7%)					
Adverse Event Index	11.4 (SD = 13.8)					
Regression analyses★						
Dependent variable: % HAMD change						
Backward Stepwise Linear Regression						
Overall Model		4.65	2,67	0.098	0.013	
BDNF val66met					0.015	0.30
MTHFR C-(677)T					0.023	0.28
Dependent variable: Adverse Event Index						
Backward Stepwise Linear Regression						
Overall Model		5.72	1,64	0.069	0.020	
5HTTLPR					0.020	0.29

★Bonferroni Correction $p < 0.025$.

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Table III

Distribution of polymorphisms in Caucasian vs Asians.

	Caucasian, *n* (%)	Asian, *n* (%)	*p*
5HTTLPR (including the A→G SNP)			
S/S	12 (28.6)	9 (81.8)	<0.01★
S/L	16 (38.1)	2 (18.2)	
L/L	14 (33.3)	0 (0)	
5HT2A T-(102)C			
C/C	8 (18.2)	5 (38.5)	0.11
T/C	21 (47.7)	7 (53.8)	
T/T	15 (34.1)	1 (7.7)	
5HT1A C-(1019)G			
C/C	11 (26.2)	3 (27.3)	0.39
C/G	20 (47.6)	3 (27.3)	
G/G	11 (26.2)	5 (45.5)	
TPH2 G-(703)T			
G/G	29 (72.5)	5 (41.7)	0.013★
T/G	11 (27.5)	5 (41.7)	
T/T	0 (0)	2 (16.7)	
BDNF val66met			
G/G	32 (78.0)	2 (16.7)	<0.01★
A/G	9 (22.0)	8 (66.7)	
A/A	0 (0)	2 (16.7)	
MTHFR C-(677)T			
C/C	10 (24.4)	6 (46.2)	0.21
T/C	27 (65.9)	5 (38.5)	
T/T	4 (9.8)	2 (15.4)	

★Pearson Chi-Square, $p < 0.05$.