Published in final edited form as:
Psychiatr Genet. 2012 August ; 22(4): 168–176. doi:10.1097/YPG.0b013e3283518586.

Involvement of *PTPN5*, the gene encoding the STriatal-Enriched protein tyrosine Phosphatase (STEP), in schizophrenia and cognition

Ilana Pelov[1,*,&], **Omri Teltsh**[1,*], **Lior Greenbaum**[1], **Amihai Rigbi**[1], **Kyra Kanyas-Sarner**[1], **Bernard Lerer**[1], **Paul Lombroso**[2], and **Yoav Kohn**[1,3,+]

[1]Biological Psychiatry Laboratory, Psychiatry Department, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

[2]Child Study Center, Yale University School of Medicine, New Haven, CT, USA

[3]Jerusalem Mental Health Center, Israel

Abstract

Objective—STriatal-Enriched protein tyrosine Phosphatase (STEP) is a brain-specific member of the PTP family that has been implicated in learning and memory. In this study, we examined the association of the *PTPN5* (protein-tyrosine-phosphatase non-receptor 5) gene, which encodes for STEP, with both schizophrenia and cognitive functioning in the Israeli Jewish population.

Methods—A 868 subjects schizophrenia (SZ) case-control study was performed (286 cases and 582 controls). Eleven STEP tagging SNPs were selected, and single markers and haplotypes association analyses were performed. A cognitive variability study included 437 healthy females who completed a computerized cognitive battery. We performed univariate associations between the SNPs and cognitive performance. The possible functional role of these variants was examined by studying their association with gene expression levels in the brain.

Results—In the SZ study, we found nominal association in the whole sample between rs4075664 and SZ. SZ males showed a more significant association for 3 SNPs (rs4075664, rs2278732, rs4757710). Haplotypes of the studied SNPs were associated with SZ both in the overall sample and within the male sub-sample. Expression analysis provided some support for the effects of the associated SNPs on *PTPN5* expression level. The cognitive variability study showed positive associations between *PTPN5* SNPs and different cognitive subtests. Principal component analysis demonstrated an “Attention Index” neurocognitive component that was associated with two SNP pairs (rs10832983*rs10766504 and rs7932938*rs4757718).

Conclusion—The results imply a model in which *PTPN5* may play a role in normal cognitive functioning and contributes to aspects of the neuropathology of schizophrenia.

[+]Correspondence: Dr. Yoav Kohn, Biological Psychiatry Laboratory, Department of Psychiatry, Hadassah – Hebrew University Medical Center, Ein Kerem, Jerusalem 91120 Israel, Tel: 972-2-5705128 Fax: 972-2-5340024, yoavk@ekmd.huji.ac.il.
[*]These authors contributed equally to this work.
[&]This study was conducted as part of the requirements for this author's MD degree at the Hadassah-Hebrew University School of Medicine.

Conflicts of Interest: Other authors report no biomedical financial interests or potential conflicts of interest.

Keywords

schizophrenia; *PTPN5*; psychiatric genetics; cognitive function; association study

1. Introduction

STriatal-Enriched protein tyrosine Phosphatase (STEP) is implicated in the regulation of synaptic plasticity. This occurs through the regulation of NMDAR (N-methyl-D-aspartate receptor) trafficking by STEP (Snyder et al., 2005; Xu et al., 2009; Zhang et al., 2010). Dephosphorylation of a regulatory tyrosine (Y^{1472}) leads to the internalization of NR1/NR2B receptor complexes. In addition, STEP dephosphorylation of the GluR2 subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPAR) leads to internalization of GluR1/GluR2 receptors (Zhang et al., 2008; Zhang et al., in press). STEP also dephosphorylates several kinases that include the mitogen-activated protein kinases (MAPKs) family members extracellular signal regulated kinase (ERK1/2) and p38 (Paul et al., 2003; Paul et al., 2000; Pulido et al., 1998; Valjent et al., 2005), and the tyrosine kinase Fyn (Nguyen et al., 2002). As these kinases and receptors are implicated in the consolidation of memories, a model has emerged that suggests that STEP normally opposes the development of synaptic strengthening (Braithwaite et al., 2006a). Based on these studies, we tested the association of STEP with neurocognitive function and its possible contribution to schizophrenia (SZ).

SZ is a serious mental disorder that affects up to 1% of the population worldwide. This multifactorial disorder has been the subject of numerous family, twin and adoption studies. These studies indicate that the risk of illness is increased among the relatives of affected individuals mostly due to genetic factors (Owen, 2005a; Owen et al., 2005b; Riley and Kendler, 2006). Genetic epidemiology studies indicate that the transmission of SZ is complex and compatible with a multi-locus model (Owen, 2005a). Supported by rapidly developing technology, genetic research in schizophrenia has focused recently on genome-wide association studies (GWASs), which can capture the majority of common variation in the human genome and putatively identify susceptibility genes with effect sizes expected for the disorder. Up to now, fourteen case-control and two family-based GWASs for schizophrenia and two meta-analyses have been published (Athanasiu et al., 2010; Chen et al., 2010; Curtis et al., 2010; Huang et al., 2010; Ikeda et al., 2010; Kirov et al., 2009b; Lencz et al., 2007; Ma et al., 2011; Mah et al., 2006; O'Donovan et al., 2008; Potkin et al., 2009; Purcell et al., 2009; Shi et al., 2009; Shifman et al., 2008; Stefansson et al., 2009; Sullivan et al., 2008; Wang et al., 2010; Yamada et al., 2011). Our group recently published the results of two GWASs in SZ in the Arab (Alkelai et al., 2011a) and Jewish (Alkelai et al., 2011b) populations from Israel.

Although these studies identified candidate genes with small effect sizes such as *PLXNA2* (Mah et al., 2006), *CSF2RA* and *IL3RA* (Lencz et al., 2007), *CCDC60* and *RBP1*(Kirov et al., 2009b), *RELN* (Shifman et al., 2008), *ZNF804A* (O'Donovan et al., 2008; Purcell et al., 2009), *MYO18B* (Purcell et al., 2009), MHC region (Purcell et al., 2009; Stefansson et al., 2009), *NRGN* and *TCF4* (Stefansson et al., 2009), some of the findings did not achieve genome-wide significance and there was no overlap between significant results. In addition, none of these GWASs demonstrated significant replication of leading, biologically plausible, schizophrenia candidate genes (Duan et al., 2010). Moreover, while some of the genes found have potential pathophysiological relevance to schizophrenia, unambiguous pathogenic variants have not been identified in the implicated genes (Owen et al., 2009). Recently published studies also provided support for an involvement of Copy Number Variations (CNVs) in schizophrenia (Ingason et al., 2011; International Schizophrenia

Consortium, 2008; Kirov et al., 2009a; McCarthy et al., 2009; Mulle et al., 2010; Stefansson et al., 2008; Walsh et al., 2008; Xu et al., 2008), but their relevance to the genetics of SZ in general is not clear yet (Bassett et al., 2010). Thus, despite developments in the genetic research of SZ, it is well accepted that few of the disease loci have been unequivocally identified by now (Gejman et al., 2010; Nothen et al., 2010) and many are yet to be discovered.

SZ also has a strong neurocognitive component. Deficits in SZ exist in relation to most neurocognitive tasks; e.g. global and selective verbal memory, nonverbal memory, bilateral and unilateral motor performance, visual and auditory attention, general intelligence, spatial ability, executive function, language, and interhemispheric tactile-transfer test performance (Heinrichs and Zakzanis, 1998; Rajji et al., 2009; Wong and Van Tol, 2003). Working memory deficits are present in schizophrenia independent of the specific modality of the task (Lee and Park, 2005). Impairments are broadly present by the first-episode of the illness and are greatest for the domain of immediate verbal memory (Mesholam-Gately et al., 2009). There is considerable evidence suggesting the involvement of ionotrophic glutamate receptors in SZ (Coyle, 2006; Javitt, 2007). Specifically, disruption of NMDAR trafficking has been found (Stephan et al., 2009) and is consistent with the glutamate hypothesis of SZ (Marek et al., 2010).

Part of the genetic etiology of schizophrenia is probably related to inherited neurocognitive deficits. We therefore tested the hypothesis that variants in *PTPN5,* the STEP encoding gene involved in glutamate receptor trafficking, is associated with both the diagnosis of SZ and with neurocognitive function in general. To the best of our knowledge no association study between *PTPN5* (or any PTP family genes) with SZ or neurocognitive functioning has been performed until now.

2. Methods

2.1. Sample recruitment

2.1.1. Schizophrenia case-control study—Our study sample included 868 Israeli Jewish participants, of whom 286 were patients with SZ and 582 were healthy controls. SZ patients were included with information regarding ethnicity (Ashkenazi vs. non-Ashkenazi origin). The diagnosis of SZ was established according to DSM-IV criteria by clinical interview and review of patient files by two board-certified psychiatrists. At recruitment, all patients were hospitalized in one of five Israeli psychiatric in-patient services: Beer-Yaacov, Hadassah Ein-Kerem, Herzog, Shaar-Menashe, Lev-Hasharon. As controls, we used 582 Jewish individuals who had available information regarding ethnicity (self reported), gender and age. All women in the control group were included in the “Why Do Young Women Smoke Project” (Greenbaum et al., 2006; Rigbi et al., 2008). This is a previous project on genetic and environmental factors in smoking and neurocognitive functioning in young women (see more details below). These women were screened for a history of psychiatric treatment. Approximately half of the control women were active or past smokers. Men were recruited after filling a screening form for mental illness in the immediate family. Written informed consent was obtained from all participants. The study was approved by the Helsinki Committee (Internal Review Board) of Hadassah-Hebrew University Medical Center, Jerusalem, Israel. As shown in Table 1, schizophrenia patients were older than controls ($p<0.001$). In addition, there was an over-representation of women in the control group. This stems from sampling bias and does not represent a gender ratio of the disease. There were no significant differences between the groups in terms of ethnic ancestry (Ashkenazi/Non-Ashkenazi).

2.1.2. Cognitive variability study—The analysis included 437 healthy female participants who were recruited in the framework of the 'Why Do Young Women Smoke' Project, and also served as part of the control group described above. The participants in the current study performed the CogScan battery (V4.0), a computerized cognitive test battery provided by AnimaScan Ltd, Ashdod, Israel, which includes 17 tests (16 computerized and one manually administrated) evaluating a wide range of cognitive domains including attention, memory, motor performance and planning. A brief description of the 17 tests encompassed in the battery is given in Supplementary Methods (Supplemental Digital Content 1). Detailed description of the tests and their psychometric properties can be found in the CogScan user manual (Kertzman and Sirota, 2003).

Cognitive testing took place in a room with maximal privacy and minimal distractions. Participants received a general explanation of the tests and help with any technical problems throughout the test period. During most of the tests, there was no research team member in the room to minimize distraction. The test session lasted ~70 minutes. Instructions were provided before each test on the computer screen. After completing the computerized tests, subjects continued to the manually administered digit span test.

2.1.3. Post-mortem brain sample for expression study—Microarray Expression levels of *PTPN5* in human post-mortem brain tissue were obtained from the publicly available database of the Stanley Medical Research Institute (SMRI) (www.stanleygenomics.org). Briefly, DNA production and purification was carried out at SMRI. The panel consisted of 104 subjects (69 males), 35 of whom were diagnosed with schizophrenia, 34 with bipolar disorder, and 35 were unaffected controls (27, 16 and 26 of each group were males). Diagnoses were made according to DSM-IV criteria. Four different microarray expression datasets were available for analysis. These datasets include expression levels in the frontal area BA46 as measured by different array platforms (hgu133p and codelink) and different probes. Further information about this expression data source is available (Higgs et al., 2006) and at the website. Genotyping STEP SNPs in these samples was performed in our lab as described below. The goal of the expression analysis was to provide initial mechanistic insight into the possible biological effect of associated SNP by studying their correlation with the STEP gene (*PTPN5)* expression. Therefore, and also in order to reduce the burden of multiple testing, only 3 SNPs that were found to be associated with SZ (see below) were genotyped in this sample.

2.2. SNPs selection and genotyping

We used the statistical program Haploview (version 4.1) (Barrett et al., 2005) to define Linkage Disequilibrium blocks on the full DNA sequence of *PTPN5* (11p15.1, 63.5 kilobases long) and additional regulatory sequences that were 3kb upstream and 10kb downstream of the gene. We used the international HapMap project (www.hapmap.org) database to select tagging SNPs and matched to every LD block its suitable tagging SNP (Table 2). SNP genotyping was performed using the TaqMan Assay-On-Demand purchased from Applied Biosystems (Foster City, CA, USA) as previously described (Greenbaum et al., 2009). The Haploview program was used for linkage disequilibrium (LD) determination between markers, Hardy-Weinberg equilibrium calculations and haplotypes block definitions (see Table 2).

2.3. Data analysis

2.3.1. Schizophrenia case-control study—Single markers and haplotypes association analyses were performed with the program Plink (version 1.06) (Purcell et al., 2007). In these analyses, we used a logistic regression model in order to correct for gender, age and ethnicity (Ashkenazi vs. Non-Ashkenazi ancestry). Even though there was no statistically

significant difference between cases and controls, we did correct for ethnicity as mixed ancestries in samples can lead to false positive results in case-control association studies, due to population stratification. Since the studied tagging SNPs are partially correlated with each other and the study of *PTPN5* as a candidate gene for schizophrenia is based on plausible neurobiological hypothesis, we decided that a Bonferroni correction for multiple testing was too conservative and used the less stringent False Discovery Rate (FDR) method. Following van den Oord and Sullivan recommendations for candidate genes studies, we used p=0.01 (two-sided) as a pragmatic level of significance accounting for multiple testing (van den Oord and Sullivan, 2003). This significance level controls the FDR at 10% (only 10% of results are false positive). FDR of 0.1 renders good balance between controlling false positives results and finding true effects, with a minimum cost of phenotyping and genotyping (van den Oord and Sullivan, 2003).

2.3.2. Expression analysis—We studied the possible association of the level of STEP expression with three *PTPN5* SNPs (rs4075664, rs2278732 and rs4757710) that we found were associated with SZ (see below). This was tested in a model of allele of interest carriership versus non-carriership by a series of t-tests or Mann-Whitney non-parametric test, as required. Normality was assessed by Kolmogorov-Smirnov test, while homoscedacity was assessed by Leven's test for equality of variance. These statistical calculations were done using SPSS software (version 15.0).

2.3.3. Cognitive variability study—Statistical analyses were performed using SPSS 15 (SPSS Inc., Chicago IL, 1989-2003). Univariate associations between the SNPs and cognitive performance measures were computed using ANOVA or non-parametric Kruskal-Wallis test depending on the distribution of the dependent cognitive measure. Normality of the measures distribution was assessed by Kolmogorov-Smirnov test. For the purpose of data reduction, all test measures that had a nominal significant association ($p<0.05$) with a certain genetic variant were submitted to principal component analysis (PCA) using an oblique rotation method (direct oblimin). Factor loading was determined by absolute factor loadings of 0.40 and above (Kline, 1993). Factor scores were determined using regression factor scoring method and a Cronbach α coefficient was used for reliability estimation. Associations between the components and their relevant genetic variants were computed using univariate general linear model (GLM).

3. Results

3.1. Single SNPs and haplotypes analysis

Three of the eleven genotyped *PTPN5* SNPs (rs4237729, rs873670, rs6483524) were excluded from further analysis as they showed deviation from Hardy-Weinberg Equilibrium. The remaining 8 SNPs (rs2278732, rs4757710, rs10832983, rs4075664, rs4073915, rs10766504, rs4757718, rs7932938) had minor allele frequencies (MAF) greater than 0.05 (Table 2).

We used logistic regression (additive model) to study association of the 8 tagging SNPs with SZ, controlling for age, gender and ethnic origin (Ashkenazi/non-Ashkenazi). The rs4075664 SNP was nominally associated with SZ (p=0.01) (Table 2). Two additional SNPs, rs2278732 and rs4757710, showed a trend for association with disease (p=0.07).

To study a possible gender specific effect of the *PTPN5* gene on SZ, we analyzed the association of the 8 SNPs in males and females separately. The three SNPs that were found to be associated with SZ in the general sample (at nominal or trend level) were more significantly associated with disease in the male subsample: rs2278732 (p=0.006,

withstanding our FDR based criteria for significance), rs4757710 (p=0.05) and rs4075664 (p=0.045). In contrast, no significant association was found within the female subsample.

We next investigated the association of haplotypes in consecutive windows of 2-3 SNPs and of haplotypes composed of the SNPs that were found to be associated with the disease in the male subsample. We did not include haplotype analysis of all 8 SNPs due to the low frequencies of these haplotypes, ranging around 0.01-0.03, and the lack of more significant results than for 2-3 SNPs per consecutive haplotypes (data not shown). There were no statistically significant associations of haplotypes in consecutive windows, but we did find significant associations between disease and haplotypes of SNPs that were found to be associated with the disease in the male subsample. Using the Gabriel method (Gabriel et al., 2002), two linkage disequilibrium blocks were detected: the first LD block includes rs2278732 and rs4757710 (D'=0.97), and the second LD block is composed of rs4075664 and rs4073915 (D'=0.96) (see Table 2 and Figure 1, Supplemental Digital Content 3 and 4). We implemented haplotype-based analysis methods to study association with SZ of two-SNPs haplotype composed of one SNP from each of the two identified LD blocks. Using logistic regression model, controlling for age, gender and ethnicity, we found significant association of the “CT” haplotype, composed of rs4757710-C allele and rs4075664-T allele, with SZ in the whole sample (p=0.002) and in the male subsample (p=0.0015), both withstanding our FDR based criteria for significance (Table 3). An additional significant association was found for the “GC” haplotype, composed of rs2278732-G allele and rs4075664-C allele, with SZ (p=0.006) in the whole-sample and in the male subsample (p=0.001) (Table 3), again withstanding our FDR based criteria for significance.

3.2. SNP Association with *PTPN5* expression

When studying the association of the expression level of *PTPN5* in the whole SMRI sample with the three SZ associated SNPs (rs4075664, rs2278732, rs4757710), no association was demonstrable. However, since the association of these SNPs with schizophrenia was most prominent in male gender, we also performed the analysis in males only. Among the male unaffected controls (no diagnosis of schizophrenia or bipolar disorder, and no life-time exposure to antipsychotics), the rs4075664 SNP was nominally associated with *PTPN5* level of expression: carriers of the “C” allele (CC+CT genotypes, n=14) had higher levels of expression than non-carriers of this allele (GG homozygous, n=6) (p=0.027).

3.3. SNP association with cognitive performance

Test measures that had a nominally significant association with the studied SNPs ($p<0.05$) are presented in Table 4. In order to explain the variety of the single test measures results and to try and identify groups of theory-based inter-related variables (and thus also to reduce chance finding due to multiple testing), an exploratory PCA of all measures associated with SNPs produced six components (see Table 1, Supplemental Digital Content 2); however, only the first component could be explained by an adequate theoretical basis. This component was mostly loaded by the three Continuous Performance Test (CPT) measures: Reaction time-Boring phase, Reaction time-Loading phase and Standard deviation of reaction time (SD of RT)-Boring phase with factor loadings of 0.92, 0.86 and 0.75, respectively. Together with Digit running-Reaction time-Grand mean test measure, this component accounted for 18.30% of the variance. Cronbach α reliability coefficient of the four simple measures was 0.77. The Digit running-Reaction time measure was also loaded on another component (Component 5); however, its factor loading was smaller (0.32) compared to its loading on Component 1 (0.53), suggesting a weaker link to Component 5 compared to Component 1. Thus, the first component was termed “Attention Index” (AI) and the composite score of this index was computed by regression scoring method. The AI

variable distributed normally (K-S: z=1.34, p=0.053) ranging between -1.95 to 3.00 (the lower the score, the better the performance).

In order to explore the association between the AI score and its relevant SNPs, a 4-way ANOVA was performed. The SNPs that were found in the univariate analysis to be associated with the single CPT test measures (rs10832983, rs4757718, rs7932938, rs10766504) served as independent variables and the AI served as the dependent variable. The analysis showed that although no SNP was associated individually with AI, two interactions were nominally significant: rs10832983 × rs10766504 (F=3.29; df=(3,197); p=0.02) and rs7932938 × rs4757718 (F=2.94; df=(3,197); p=0.03). Importantly, the SNPs included in each interaction pair are not in LD and are poorly correlated with each other (rs10832983, rs10766504, D′=0.12, r^2=0; rs7932938, rs4757718, D′=0.64, r^2=0.18) (see Table 2, Supplemental Digital Content 3).

These interactions are presented in Figure 1a and 1b. Figure 1a shows that the difference in the AI score among the genotype groups of rs10832983 depends on the number of the T alleles in rs10766504 genotypes. Carrying no T alleles of rs10766504 is not associated with a difference in AI score among the different genotypes on rs10832983. Carrying one T allele of rs10766504 is associated with a greater difference in AI score mainly between homozygous (AA, GG) genotypes of rs10832983. Within the rs10766504 TT carriers, there is a large difference between the rs10832983 heterozygous group (GA) and the rs10832983 AA groups. Carrying two T alleles in rs10766504 and two G alleles in rs10832983 is not shown in Figure 1a since there is only one participant with such a combination. Figure 1b shows that the difference in the AI score among the genotype groups of rs7932938 depends on the genotype difference in rs4757718 genotypes. Within the AA carriers in rs4757718, those who are also TT carriers in rs7932938 show lower (better) AI score. Within the AG carriers in rs4757718, those who are also TG carriers in rs7932938 show lower (better) AI score. Within the GG carriers in rs4757718 there are hardly any differences in AI score between the different rs7932938 genotype groups.

4. Discussion

Previous data regarding neurocognitive impairments in SZ motivated us to study the association of the *PTPN5* gene with both SZ and cognitive functioning. STEP, encoded by this gene, is involved in learning and memory processes through the regulation of ionotrophic glutamate receptor trafficking, rendering *PTPN5* a biological relevant candidate gene for SZ.

We performed a case-control association study of 8 tagging SNPs within this gene and the 5′ and 3′ regions and showed nominal association of the intronic SNP, rs4075664, with SZ in an Israeli Jewish sample. We found a gender effect in which 2 SNPs (rs4075664, rs4757710) were nominally and one significantly (rs2278732, at the level of p=0.01) associated with the phenotype among males. Haplotypes made up of SNPs located in the gene were significantly associated (at the level of p=0.01) with schizophrenia both in the overall sample and within the male sub-sample. Expression level analysis provided some support for association of rs4757710 with differences in *PTPN5* expression among unaffected males. The effect is most probably caused by a functional SNP (exonic or in a regulatory region) that is in LD with rs4075664.

We further studied the influence of these SNPs on neurocognitive functioning. We observed many positive, nominally significant associations between *PTPN5* SNPs and different cognitive sub-tests. In order to reduce the data, we performed a PCA and found interactions between two SNP pairs (rs10832983 × rs10766504 and rs7932938 × rs4757718) that were associated with the “Attention Index” neurocognitive components.

This is the first study to examine the association of *PTPN5* with SZ or cognition in humans. The case-control study supports previous findings that suggest that glutamate receptor internalization contributes to the pathogenesis of SZ (Gaspar et al., 2009). We propose that a mechanism to explain this process may be through STEP. The association between *PTPN5* expression and cognitive functioning has been suggested by previous studies. STEP protein levels are elevated in human Alzheimer's prefrontal cortex and in the cortex of several mouse models of Alzheimer's disease (Kurup et al., 2010a). The elevated levels of STEP were found to be due to a decrease in its normal degradation by a beta amyloid-inhibition of the proteasome (Kurup et al., 2010b). Genetic lowering of STEP levels by crossing an Alzheimer mouse model with STEP KO mice led to a significant attenuation of cognitive deficits (Zhang et al., 2008). These findings suggest that disruption of STEP expression contributes to the pathophysiology of Alzheimer's disease and led to the present study investigating its possible role in another disorder with impaired cognition, such as schizophrenia. However, the molecular involvement of STEP in specific attention processes (as shown in our association analysis) was not studied to date, and it may be interesting to test in animal models. In SZ, however, several meta-analyses reported deficits in different aspects of attention among patients compared to controls (Heinrichs and Zakzanis, 1998; Rajji et al., 2009).

Numerous sex differences have been described in SZ and can be related to our findings of association with SNPs mainly in men. Compared to females, an earlier onset of SZ, poorer medication response and premorbid functioning were found in men. Men have more negative symptoms and cognitive deficits, and greater structural brain and neurophysiological abnormalities than females (Aleman et al., 2003; Leung and Chue, 2000; Salem and Kring, 1998). While the sex differences are well known, there is little information on the molecular basis that might explain these differences. For example, Shifman et. al. (2008) performed a genome-wide association study (GWAS) among Ashkenazi Jews, and found gender specific (females) association of the *reelin* gene with schizophrenia. A genetic variant in the *COMT* gene was also reported to increase risk of schizophrenia only in women (Shifman et al., 2002). Thomson et al. showed that variation in *DISCI* may affect normal cognitive aging in women (Thomson et al., 2005). Thus, differences in genetic etiology of SZ between men and women may explain some of its clinical sexual dimorphism.

There are several limitations to the present study. Important among these are the possibility of spurious results as a consequence of multiple testing and the lack of a replication sample. It is important to note that the studied SNPs and different cognitive tests that associate with them are possibly co-dependent and as such, a Bonferroni correction might be too conservative. However, it is encouraging that the association of rs2278732 with schizophrenia among males withstands accepted FDR based criteria for significance in such studies. In addition, the FDR withstanding diplotypes (rs4757710-C and rs4075664-T; rs2278732-G and rs4075664-C) were associated with SZ more significantly than the single markers composing them. Haplotype based analysis tends to be more powerful than single SNP analysis when there are real effects (van den Oord and Sullivan, 2003). Therefore, the consistency of the findings and improvement of significance level by haplotype analysis may be interpreted as a confirmation that the single SNP significant associations are not false positive.

Another limitation is the gender difference between the two groups in the case-control study, but this limitation was taken into account and a correction through regression analysis was performed. Also it should be noted that the *PTPN5* gene is located on an autosomal chromosome (chromosome 11) and not on chromosomes X or Y, reducing the potential bias. In addition, the most significant associations in our study were demonstrated among the

male sub-sample. In this subsample, the absolute number of cases (n=184) is similar to that of controls (n=145), and the nominal association is prominent, suggesting that this association is real. An additional limitation is the lack of neurocognitive data on SZ patients and correlation of their cognitive functioning with *PTPN5* SNPs. In spite of these potential limitations, the results suggest that like other genes involving mental diseases, *PTPN5* gene may play a role in normal cognitive functioning and in SZ.

To conclude, we provide here for the first time preliminary evidences for the possible genetic contribution of *PTPN5* to schizophrenia, particularly among males, and to attention index of cognitive features. The findings are mostly at the nominal level, and further replication trials in other populations are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Y. Kohn was funded by the National Alliance for Research in Schizophrenia and Affective Disorders (NARSAD), US-Israel Binational Science Foundation (BSF), Israel Ministry of Health Chief Scientist and Milton Rosenbaum Foundation of the Hebrew University. Prof. B. Lerer was funded by the Israel Science Foundation (ISF). Prof. P. Lombroso was funded by the National Institute of Health (MH052711, MH091037).

Source of Funding: Dr. Y. Kohn reports research funding from NARSAD, US-Israel Binational Science Foundation (BSF), Israel Ministry of Health Chief Scientist and Milton Rosenbaum Foundation of the Hebrew University. Prof. B. Lerer reports research funding from the Israel Science Foundation (ISF). Prof. P. Lombroso reports research funding from the National Institute of Health (MH052711, MH091037).

References

Aleman A, Kahn RS, Selten JP. Sex differences in the risk of schizophrenia: evidence from meta-analysis. Arch Gen Psychiatry. 2003; 60:565–571. [PubMed: 12796219]

Alkelai A, Lupoli S, Greenbaum L, Giegling I, Kohn Y, Sarner-Kanyas K, et al. Identification of new schizophrenia susceptibility loci in an ethnically homogeneous, family-based, Arab-Israeli sample. FASEB J. 2011a in press.

Alkelai A, Lupoli S, Greenbaum L, Kohn Y, Kanyas-Sarner K, Ben-Asher E, et al. DOCK4 and CEACAM21 as novel schizophrenia candidate genes in the Jewish population. Int J Neuropsychopharmacol. 2011b:1–11.

Athanasiu L, Mattingsdal M, Kahler AK, Brown A, Gustafsson O, Agartz I, et al. Gene variants associated with schizophrenia in a Norwegian genome-wide study are replicated in a large European cohort. Journal of Psychiatric Research. 2010; 44:748–753. [PubMed: 20185149]

Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics. 2005; 21:263–265. [PubMed: 15297300]

Bassett AS, Scherer SW, Brzustowicz LM. Copy number variations in schizophrenia: critical review and new perspectives on concepts of genetics and disease. Am J Psychiatry. 2010; 167:899–914. [PubMed: 20439386]

Braithwaite SP, Paul S, Nairn AC, Lombroso PJ. Synaptic plasticity: one STEP at a time. Trends Neurosci. 2006a; 29:452–458. [PubMed: 16806510]

Chen X, Lee G, Maher BS, Fanous AH, Chen J, Zhao Z, et al. GWA study data mining and independent replication identify cardiomyopathy-associated 5 (CMYA5) as a risk gene for schizophrenia. Molecular Psychiatry. 2010 Sep 14.2010 Epub ahead of print.

Coyle JT. Glutamate and schizophrenia: beyond the dopamine hypothesis. Cell Mol Neurobiol. 2006; 26:365–384. [PubMed: 16773445]

Curtis D, Vine AE, McQuillin A, Bass NJ, Pereira A, Kandaswamy R, et al. Case-case genome-wide association analysis shows markers differentially associated with schizophrenia and bipolar

disorder and implicates calcium channel genes. Psychiatric Genetics. 2010; 21:1–4. [PubMed: 21057379]

Duan J, Sanders AR, Gejman PV. Genome-wide approaches to schizophrenia. Brain Res Bull. 2010; 83:93–102. [PubMed: 20433910]

Gabriel SB, Schaffner SF, Nguyen H, Moore JM, Roy J, Blumenstiel B, et al. The structure of haplotype blocks in the human genome. Science. 2002; 296:2225–2229. [PubMed: 12029063]

Gaspar PA, Bustamante ML, Silva H, Aboitiz F. Molecular mechanisms underlying glutamatergic dysfunction in schizophrenia: therapeutic implications. J Neurochem. 2009; 111:891–900. [PubMed: 19686383]

Gejman PV, Sanders AR, Duan J. The role of genetics in the etiology of schizophrenia. Psychiatr Clin North Am. 2010; 33:35–66. [PubMed: 20159339]

Greenbaum L, Kanyas K, Karni O, Merbl Y, Olender T, Horowitz A, et al. Why do young women smoke? I. Direct and interactive effects of environment, psychological characteristics and nicotinic cholinergic receptor genes. Mol Psychiatry. 2006; 11:312–322. [PubMed: 16314871]

Greenbaum L, Smith RC, Rigbi A, Strous R, Teltsh O, Kanyas K, et al. Further evidence for association of the RGS2 gene with antipsychotic-induced parkinsonism: protective role of a functional polymorphism in the 3′-untranslated region. Pharmacogenomics J. 2009; 9:103–110. [PubMed: 18347610]

Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology. 1998; 12:426–445. [PubMed: 9673998]

Higgs BW, Elashoff M, Richman S, Barci B. An online database for brain disease research. BMC Genomics. 2006; 7:70. [PubMed: 16594998]

Huang J, Perlis RH, Lee PH, Rush AJ, Fava M, Sachs GS, et al. Cross-disorder genomewide analysis of schizophrenia, bipolar disorder, and depression. American Journal of Psychiatry. 2010; 167:1254–1263. [PubMed: 20713499]

Ikeda M, Aleksic B, Kinoshita Y, Okochi T, Kawashima K, Kushima I, et al. Genome-wide association study of schizophrenia in a Japanese population. Biological Psychiatry. 2010; 69:472–478. [PubMed: 20832056]

Ingason A, Rujescu D, Cichon S, Sigurdsson E, Sigmundsson T, Pietilainen OP, et al. Copy number variations of chromosome 16p13.1 region associated with schizophrenia. Molecular Psychiatry. 2011; 16:17–25. [PubMed: 19786961]

International Schizophrenia Consortium. Rare chromosomal deletions and duplications increase risk of schizophrenia. Nature. 2008; 455:237–241. [PubMed: 18668038]

Javitt DC. Glutamate and schizophrenia: phencyclidine, N-methyl-D-aspartate receptors, and dopamine-glutamate interactions. Int Rev Neurobiol. 2007; 78:69–108. [PubMed: 17349858]

Kertzman, SBNZ.; Sirota, A. CogScan V4.0 – Cognitive Scanning System System description. Ashdod: AnimaScan Ltd; 2003.

Kirov G, Grozeva D, Norton N, Ivanov D, Mantripragada KK, Holmans P, et al. Support for the involvement of large copy number variants in the pathogenesis of schizophrenia. Human Molecular Genetics. 2009a; 18:1497–1503. [PubMed: 19181681]

Kirov G, Zaharieva I, Georgieva L, Moskvina V, Nikolov I, Cichon S, et al. A genome-wide association study in 574 schizophrenia trios using DNA pooling. Molecular Psychiatry. 2009b; 14:796–803. [PubMed: 18332876]

Kline, P. An easy guide to factor analysis. New-York NY: Routledge; 1993.

Kurup P, Zhang Y, Venkitaramani DV, Xu J, Lombroso PJ. The role of STEP in Alzheimer's disease. Channels (Austin). 2010a; 4:347–350. [PubMed: 20699650]

Kurup P, Zhang Y, Xu J, Venkitaramani DV, Haroutunian V, Greengard P, et al. Abeta-mediated NMDA receptor endocytosis in Alzheimer's disease involves ubiquitination of the tyrosine phosphatase STEP61. J Neurosci. 2010b; 30:5948–5957. [PubMed: 20427654]

Lee J, Park S. Working memory impairments in schizophrenia: a meta-analysis. J Abnorm Psychol. 2005; 114:599–611. [PubMed: 16351383]

Lencz T, Lambert C, DeRosse P, Burdick KE, Morgan TV, Kane JM, et al. Runs of homozygosity reveal highly penetrant recessive loci in schizophrenia. Proceedings of the National Academy of Sciences of the United States of America. 2007; 104:19942–19947. [PubMed: 18077426]

Leung A, Chue P. Sex differences in schizophrenia, a review of the literature. Acta Psychiatr Scand Suppl. 2000; 401:3–38. [PubMed: 10887978]

Ma X, Deng W, Liu X, Li M, Chen Z, He Z, et al. A genome-wide association study for quantitative traits in schizophrenia in China. Genes Brain Behav. 2011 Jun 16.2011 Epub ahead of print.

Mah S, Nelson MR, Delisi LE, Reneland RH, Markward N, James MR, et al. Identification of the semaphorin receptor PLXNA2 as a candidate for susceptibility to schizophrenia. Molecular Psychiatry. 2006; 11:471–478. [PubMed: 16402134]

Marek GJ, Behl B, Bespalov AY, Gross G, Lee Y, Schoemaker H. Glutamatergic (N-methyl-D-aspartate receptor) hypofrontality in schizophrenia: too little juice or a miswired brain? Mol Pharmacol. 2010; 77:317–326. [PubMed: 19933774]

McCarthy SE, Makarov V, Kirov G, Addington AM, McClellan J, Yoon S, et al. Microduplications of 16p11.2 are associated with schizophrenia. Nature Genetics. 2009; 41:1223–1227. [PubMed: 19855392]

Mesholam-Gately RI, Giuliano AJ, Goff KP, Faraone SV, Seidman LJ. Neurocognition in first-episode schizophrenia: a meta-analytic review. Neuropsychology. 2009; 23:315–336. [PubMed: 19413446]

Mulle JG, Dodd AF, McGrath JA, Wolyniec PS, Mitchell AA, Shetty AC, et al. Microdeletions of 3q29 confer high risk for schizophrenia. American Journal of Human Genetics. 2010; 87:229–236. [PubMed: 20691406]

Nguyen TH, Liu J, Lombroso PJ. Striatal enriched phosphatase 61 dephosphorylates Fyn at phosphotyrosine 420. J Biol Chem. 2002; 277:24274–24279. [PubMed: 11983687]

Nothen MM, Nieratschker V, Cichon S, Rietschel M. New findings in the genetics of major psychoses. Dialogues Clin Neurosci. 2010; 12:85–93. [PubMed: 20373670]

O'Donovan MC, Craddock N, Norton N, Williams H, Peirce T, Moskvina V, et al. Identification of loci associated with schizophrenia by genome-wide association and follow-up. Nature Genetics. 2008; 40:1053–1055. [PubMed: 18677311]

Owen MJ. Genomic approaches to schizophrenia. Clin Ther. 2005a; 27(A):S2–7. [PubMed: 16198198]

Owen MJ, Craddock N, O'Donovan MC. Schizophrenia: genes at last? Trends Genet. 2005b; 21:518–525. [PubMed: 16009449]

Owen MJ, Williams HJ, O'Donovan MC. Schizophrenia genetics: advancing on two fronts. Current Opinion in Genetics and Development. 2009; 19:266–270. [PubMed: 19345090]

Paul S, Snyder GL, Yokakura H, Picciotto MR, Nairn AC, Lombroso PJ. The Dopamine/D1 receptor mediates the phosphorylation and inactivation of the protein tyrosine phosphatase STEP via a PKA-dependent pathway. J Neurosci. 2000; 20:5630–5638. [PubMed: 10908600]

Paul S, Nairn AC, Wang P, Lombroso PJ. NMDA-mediated activation of the tyrosine phosphatase STEP regulates the duration of ERK signaling. Nat Neurosci. 2003; 6:34–42. [PubMed: 12483215]

Potkin SG, Turner JA, Guffanti G, Lakatos A, Fallon JH, Nguyen DD, et al. A genome-wide association study of schizophrenia using brain activation as a quantitative phenotype. Schizophrenia Bulletin. 2009; 35:96–108. [PubMed: 19023125]

Pulido R, Zuniga A, Ullrich A. PTP-SL and STEP protein tyrosine phosphatases regulate the activation of the extracellular signal-regulated kinases ERK1 and ERK2 by association through a kinase interaction motif. Embo J. 1998; 17:7337–7350. [PubMed: 9857190]

Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007; 81:559–575. [PubMed: 17701901]

Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 2009; 460:748–752. [PubMed: 19571811]

Rajji TK, Ismail Z, Mulsant BH. Age at onset and cognition in schizophrenia: meta-analysis. Br J Psychiatry. 2009; 195:286–293. [PubMed: 19794194]

Rigbi A, Kanyas K, Yakir A, Greenbaum L, Pollak Y, Ben-Asher E, et al. Why do young women smoke? V. Role of direct and interactive effects of nicotinic cholinergic receptor gene variation on neurocognitive function. Genes Brain Behav. 2008; 7:164–172. [PubMed: 17559419]

Riley B, Kendler KS. Molecular genetic studies of schizophrenia. Eur J Hum Genet. 2006; 14:669–680. [PubMed: 16721403]

Salem JE, Kring AM. The role of gender differences in the reduction of etiologic heterogeneity in schizophrenia. Clin Psychol Rev. 1998; 18:795–819. [PubMed: 9827322]

Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I, et al. Common variants on chromosome 6p22.1 are associated with schizophrenia. Nature. 2009; 460:753–757. [PubMed: 19571809]

Shifman S, Bronstein M, Sternfeld M, Pisante-Shalom A, Lev-Lehman E, Weizman A, et al. A highly significant association between a COMT haplotype and schizophrenia. Am J Hum Genet. 2002; 71:1296–1302. [PubMed: 12402217]

Shifman S, Johannesson M, Bronstein M, Chen SX, Collier DA, Craddock NJ, et al. Genome-wide association identifies a common variant in the reelin gene that increases the risk of schizophrenia only in women. PLoS Genetics. 2008; 4:e28. [PubMed: 18282107]

Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, et al. Regulation of NMDA receptor trafficking by amyloid-beta. Nat Neurosci. 2005; 8:1051–1058. [PubMed: 16025111]

Stefansson H, Rujescu D, Cichon S, Pietilainen OP, Ingason A, Steinberg S, et al. Large recurrent microdeletions associated with schizophrenia. Nature. 2008; 455:232–236. [PubMed: 18668039]

Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D, et al. Common variants conferring risk of schizophrenia. Nature. 2009; 460:744–747. [PubMed: 19571808]

Stephan KE, Friston KJ, Frith CD. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophr Bull. 2009; 35:509–527. [PubMed: 19155345]

Sullivan PF, Lin D, Tzeng JY, van den Oord E, Perkins D, Stroup TS, et al. Genomewide association for schizophrenia in the CATIE study: results of stage 1. Molecular Psychiatry. 2008; 13:570–584. [PubMed: 18347602]

Thomson PA, Harris SE, Starr JM, Whalley LJ, Porteous DJ, Deary IJ. Association between genotype at an exonic SNP in DISC1 and normal cognitive aging. Neurosci Lett. 2005; 389:41–45. [PubMed: 16054297]

Valjent E, Pascoli V, Svenningsson P, Paul S, Enslen H, Corvol JC, et al. Regulation of a protein phosphatase cascade allows convergent dopamine and glutamate signals to activate ERK in the striatum. Proc Natl Acad Sci U S A. 2005; 102:491–496. [PubMed: 15608059]

van den Oord EJ, Sullivan PF. False discoveries and models for gene discovery. Trends Genet. 2003; 19:537–542. [PubMed: 14550627]

Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM, et al. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science. 2008; 320:539–543. [PubMed: 18369103]

Wang KS, Liu XF, Aragam N. A genome-wide meta-analysis identifies novel loci associated with schizophrenia and bipolar disorder. Schizophrenia Research. 2010; 124:192–199. [PubMed: 20889312]

Wong AH, Van Tol HH. Schizophrenia: from phenomenology to neurobiology. Neurosci Biobehav Rev. 2003; 27:269–306. [PubMed: 12788337]

Xu B, Roos JL, Levy S, van Rensburg EJ, Gogos JA, Karayiorgou M. Strong association of de novo copy number mutations with sporadic schizophrenia. Nature Genetics. 2008; 40:880–885. [PubMed: 18511947]

Xu J, Kurup P, Zhang Y, Goebel-Goody SM, Wu PH, Hawasli AH, et al. Extrasynaptic NMDA receptors couple preferentially to excitotoxicity via calpain-mediated cleavage of STEP. J Neurosci. 2009; 29:9330–9343. [PubMed: 19625523]

Yamada K, Iwayama Y, Hattori E, Iwamoto K, Toyota T, Ohnishi T, et al. Genome-wide association study of schizophrenia in Japanese population. PLoS One. 2011; 6:e20468. [PubMed: 21674006]

Zhang Y, Venkitaramani DV, Gladding CM, Kurup P, Molnar E, Collingridge GL, et al. The tyrosine phosphatase STEP mediates AMPA receptor endocytosis after metabotropic glutamate receptor stimulation. J Neurosci. 2008; 28:10561–10566. [PubMed: 18923032]

Zhang YF, Kurup P, Xu J, Carty N, Fernandez S, Nygaard HB, et al. Genetic reduction of the tyrosine phosphatase STEP reverses cognitive and cellular deficits in a mouse model of Alzheimer's disease. PNAS. 2010; 107:19014–19019. [PubMed: 20956308]

Zhang YF, Kurup P, Xu J, Anderson G, Greengard P, Nairn AC, et al. Reduced levels of the tyrosine phosphatase STEP block beta amyloid-mediated GluA1/GluA2 receptor internalization. J Neurochemistry. in press.

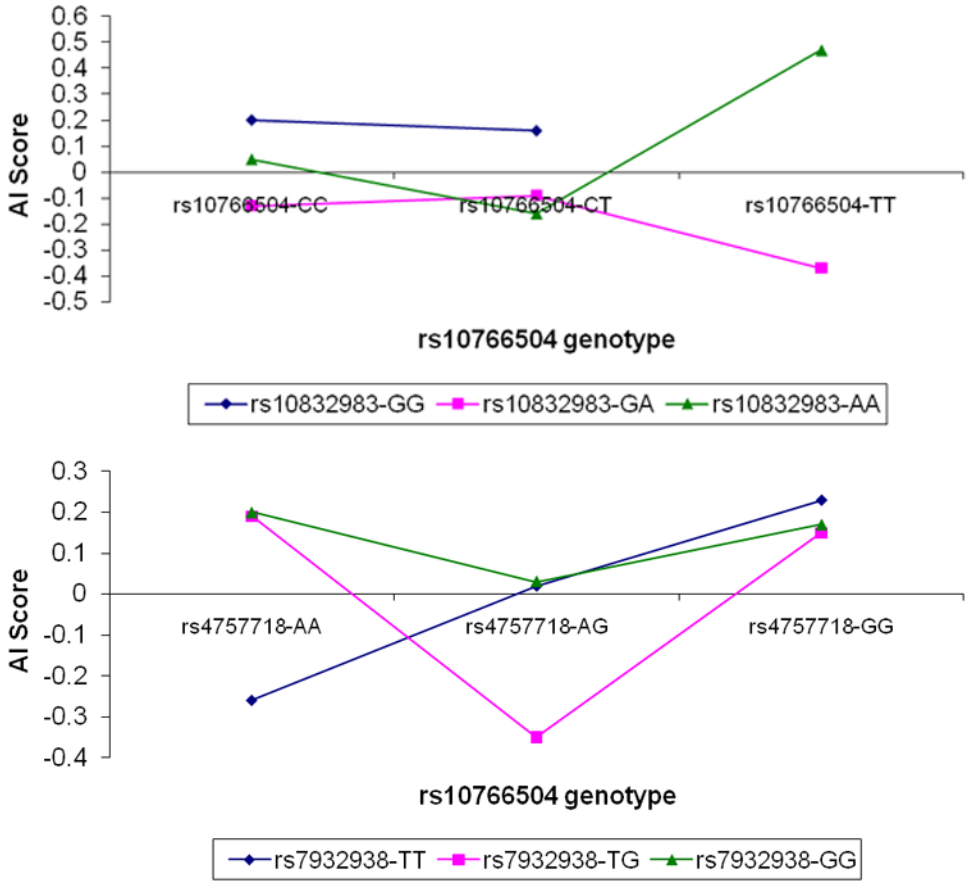

Figure 1.
SNP-SNP interaction with cognitive performance.
Figure 1A: Interaction effect between rs10832983 and rs10766504 on Attention Index (AI) score. Scores and number of individuals are given per cell.

	rs10766504-CC	rs10766504-CT	rs10766504-TT
rs10832983-GG	0.2, (40)	0.16, (38)	(1)
rs10832983-GA	-0.13, (70)	-0.09, (43)	-0.37, (10)
rs10832983-AA	0.05, (25)	-0.16, (13)	0.47, (8)

AI SCORE= the lower the score, the better the performance
Figure 1B: Interaction effect between rs7932938 and rs4757718 on Attention Index (AI) score. Scores and number of individuals are given per cell.

	rs4757718-AA	rs4757718-AG	rs4757718-GG
rs7932938-TT	-0.26, (18)	0.02, (44)	0.23, (36)
rs7932938-TG	0.19, (41)	-0.35, (61)	0.15, (12)
rs7932938-GG	0.2, (31)	0.03, (8)	0.17, (39)

AI SCORE= the lower the score, the better the performance

Table 1
Demographic features of participants in the case-control association study

Variable	Overall	Schizophrenia	Control	P value
Number	868	286	582	
Age (Mean±SD)	35.39 ± 11.73	40.85 ± 13.37	32.86 ± 9.92	p<0.001
Males	329 (37.9%)	184 (64.3%)	145 (24.9%)	p<0.001
Ashkenazi origin	444 (51.2%)	138 (48.3%)	306 (52.6%)	NS

Abbreviations: SD-Standard Deviation.

Table 2

Association of 8 tagging SNPs with schizophrenia, as a function of genotype (additive model), age, gender and self reported ethnicity (Ashkenazi vs. non Ashkenazi) in an Israeli Jewish sample

					Whole sample				Men gender			
SNP	**Position**	**SNP type**	**Allele (Major, Minor)**	**MAF (In whole sample)**	**Risk Allele**	**Cases/Controls**	**P value**	**Odds ratio**	**Risk allele**	**Cases/Controls**	**P value**	**Odds ratio**
rs2278732	18720689	Intron 6	G,A	0.422	G	0.606, 0.564	0.07	1.25	G	0.609, 0.517	**0.006** *	1.64
rs4757710	18732258	Intron 3	C,A	0.181	A	0.195, 0.174	0.07	1.3	A	0.190, 0.134	**0.05**	1.54
rs10832983	18744702	Intron 2	G,A	0.427	G	0.593, 0.564	0.15	1.19	G	0.595, 0.562	0.95	1.01
rs4075664	18749936	Intron 2	T,C	0.407	C	0.435, 0.393	**0.01**	**1.36**	C	0.435, 0.355	**0.045**	1.41
rs4073915	18753056	Intron 1	G,A	0.302	A	0.305, 0.300	0.55	1.09	G	0.693, 0.669	0.58	1.11
rs10766504	18758916	Intron 1	C,T	0.269	C	0.753, 0.721	0.19	1.2	C	0.750, 0.731	0.51	1.14
rs4757718	18761510	Intron 1	A,G	0.398	G	0.398, 0.398	0.35	1.11	G	0.385, 0.372	0.79	1.04
rs7932938	18771871	5′	T,G	0.393	T	0.614, 0.604	0.45	1.1	G	0.397, 0.376	0.44	1.14

In Bold – Nominally significant association (p=0.05).

* - significant at the level of p=0.01.

Abbreviations: MAF- Minor Allele Frequency

Table 3

Case-control haplotype association analysis of two SNPs composed haplotypes. Association is a function of haplotype, gender, age and self reported ethnicity (Ashkenazi vs. Non Ashkenazi).

	Whole sample			Male gender		
Haplotype	**Frequency**	**Cases, controls**	**P value**	**Frequency**	**Cases, controls**	**P value**
rs2278732-rs4075664						
GT	0.31	0.310,0.312	0.66	0.31	0.311,0.312	0.9
AT	0.28	0.255,0.296	**0.01**	0.29	0.255,0.333	**0.01**
GC	0.27	0.296,0.252	**0.006***	0.26	0.298,0.205	**0.001***
AC	0.14	0.139,0.141	0.625	0.14	0.137,0.15	0.26
rs4757710-4075664						
CC	0.32	0.337,0.312	0.08	0.32	0.338,0.292	0.28
CT	0.49	0.468,0.513	**0.002***	0.52	0.472,0.573	**0.001***
AT	0.1	0.097,0.094	0.37	0.08	0.093,0.071	0.27
AC	0.09	0.098,0.08	**0.04**	0.08	0.097,0.063	**0.04**

In Bold – Nominally significant association (p=0.05).

* - significant at the level of p=0.01.

Table 4

Significant associations between cognitive test measures and SNPs

Test and test measure	SNP	Major Homozygous Performance (n, M±SD)	Heterozygous Performance (n, M ±SD)	Minor Homozygous Performance (n, M±SD)	p-value
Simple reaction time-*omissions*	rs4073915	GG (216, 0.13±0.39)	GA (179, 0.06±0.29)	AA (35, 0.17±0.38)	0.03
Delayed picture recognition- *reaction time (msec)*	rs10832983	GG (127, 1136±364.77)	GA (198, 1050.29±278.6)	AA (78, 1012.6±257.41)	0.03
Delayed face recognition- hits	rs4757710	CC (279, 95.84±11.24)	CA (134, 97.76±8.37)	*	0.02
	rs4757718	AA (151, 95.62±10.55)	AG (198, 97.67±9.27)	GG (72, 95±12.44)	0.02
Immediate face recognition- *correct rejections*	rs10766504	CC (220, 97.72±6.36)	CT (173, 96.87±8.99)	TT (34, 92.94±9.7)	0.001
Immediate face recognition- *accuracy index*	rs10766504	CC (218, 98.49±3.52)	CT (168, 98.32±3.68)	TT (34, 96.22±4.86)	0.004
Delayed face recognition- *accuracy index*	rs10832983	GG (132, 97.21±5.12)	GA (202, 620.77±58.81)	AA (80, 96.61±5.55)	0.04
Digit running-*reaction time, grand mean*	rs10832983	GG (137, 636.54±63.97)	GA (199, 95.44±6.37)	AA (84, 638.75±70.54)	0.025
Stroop-*commissions, neutral*	rs4757718	AA (150, 0.37±0.67)	AG (201, 0.27±0.78)	GG (73, 0.5±1.02)	0.01
Stroop-*commissions, incongruent*	rs4757718	AA (149, 3.46±2.57)	AG (201, 3.6±2.41)	GG (73, 4.79±3.28)	0.006
Digit symbol- commissions, grand mean	rs10832983	GG (136, 0.65±0.46)	GA (202, 0.59±0.45)	AA (85, 0.73±0.5)	0.04
CPT- *RT, boring*	rs10832983	GG (135, 417.19±52.79)	GA (202, 400.7±53.74)	AA (85, 408.73±54.36)	0.022
	rs4757718	AA (152, 416.83±57.84)	AG (200, 398.52±49.19)	GG (72, 411.85±55.02)	0.005
	rs7932938	TT (157, 410.48±50.98)	TG (201, 399.59±54.11)	GG (71, 423.11±55.98)	0.01
CPT- *SD of RT, boring*	rs10832983	GG (136, 68.86±18.73)	GA (202, 64.74±19.93)	AA (85, 69.62±20.98)	0.01
	rs4757718	AA (152, 69.01±19.61)	AG (200, 64.28±18.58)	GG (73, 70.09±22.82)	0.03
CPT-*RT, loading*	rs4757718	AA (152, 362.73±58.98)	AG (198, 343.92±47.87)	GG (73, 355.92±54.14)	0.004
	rs7932938	TT (156,351.84±49.66)	TG (201, 348.06±54.33)	GG (71, 368.97±57.55)	0.017
CPT- *omissions, loading*	rs10766504	CC (218, 0.54±0.94)	CT (170,0.44±0.73)	TT (34, 0.972±1.32)	0.04
Matching familiar figures - 1st reaction time	rs2278732	GG (104, 12.68±6.68)	AG (137, 11.91±6.52)	AA (52, 14.69±7.49)	0.043

*all subsequent analyses excluded the homozygous subjects for the minor allele because the frequency was <5%.

Abbreviations: CPT - Continuous Performance Test, RT – Reaction time, SD-Standard Deviation.