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Genetic Variation in the *MET* Proto-oncogene is Associated with Schizophrenia and General Cognitive Ability

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Abstract

Objective: Despite increased exposure to cancer risk factors, several studies have demonstrated a decreased incidence of cancer in schizophrenia patients. Reduced cancer rates in first-degree relatives of schizophrenia patients suggest that the inverse relationship between cancer and schizophrenia may be related to genetic factors; however, few studies of schizophrenia have focused on cancer-related genes. The MET proto-oncogene (*MET*) is primarily linked to tumor metastasis but *MET* is also involved in neurodevelopment and it influences risk for autism. Thus, *MET* may be of particular interest as a candidate gene for neuropsychiatric diseases with a developmental etiology, including schizophrenia.

Methods: We examined the relationship between 21 SNPs in *MET* and schizophrenia in 173 Caucasian patients and 137 controls. We subsequently genotyped a second independent sample (107 patients/112 controls) for replication. Finally, we tested for *MET*'s effects on general cognitive ability (*g*).

Results: In the initial cohort, we identified four haplotype blocks and found one block to be globally associated with schizophrenia. In Block 3, the most common haplotype was over-represented in controls (47%) versus schizophrenia patients (33%) ($p= 4.0 \times 10^{-4}$; OR=0.56). We replicated the Block 3 finding in the second sample with similar frequencies: controls (46%) vs. schizophrenia patients (36%) (p=0.03; OR=0.66). Moreover, the protective haplotype was associated with higher *g* in the combined healthy control sample.

Conclusions: These data suggest that *MET* variation influences schizophrenia risk and neurocognition, supporting a neurodevelopmental role across CNS-relevant phenotypes. These results add to the growing evidence suggesting an intriguing relationship between cancer-related genes and schizophrenia susceptibility.

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INTRODUCTION

There is an increasing interest in the relationship between schizophrenia and cancer, as several studies have demonstrated a significant reduction in cancer incidence in schizophrenia patients versus the general population. This association is seemingly counterintuitive, given the increased environmental health risks in the majority of schizophrenia patients, such as heavy smoking, poor dietary habits, obesity, and substance abuse (1).

Hippisley-Cox et al. (2007)conducted a study to determine the risk of six common cancers in schizophrenia patients. In a sample of 40,441 incident cases of cancer, odds ratios for cancer risk associated with schizophrenia and bipolar disorder were calculated with adjustments made for smoking, body mass index, socioeconomic status, comorbidities, and medication use. Analyses revealed a 47% decreased risk of respiratory cancer in schizophrenia patients as compared to patients without schizophrenia. In contrast, risk rates associated with bipolar illness in this cohort were comparable to those reported in non-psychiatric samples, suggesting a relatively specific effect in schizophrenia (2). These findings are consistent with a recent meta-analysis of cancer incidence in schizophrenia patients and their first-degree relatives, which reported decreased rates for a number of non-smoking related cancers in schizophrenia patients as well as a reduced risk of lung cancer after controlling for smoking prevalence (1). Taken together, these studies suggest that the discrepancy between cancer risk exposure and cancer incidence in schizophrenia is consistent with a protective effect; however, the nature of the proposed protective effect is unknown.

It has been hypothesized that decreased cancer susceptibility in schizophrenia is either related to medications used to treat the illness (3) or genetic, linked with tumor suppressor genes (4) or enhanced natural killer cell activity (5). To date, results are inconsistent with regard to the potentially protective effects of antipsychotic medication, with some studies reporting decreased cancer rates in antipsychotic-treated patients (6), while others have reported an *increased* incidence of certain cancers (i.e. colon) in patients treated with antipsychotics versus patients not treated with these agents (2). A genetic influence on the paradoxical cancer-schizophrenia relationship is supported by family studies, in which decreased rates of cancer have been reported in unaffected family members of schizophrenia patients never exposed to antipsychotic medications (1,7-9) as well as case-control studies describing associations between the tumor suppressor genes adenomatous polyposis coli (*APC*) (10) and p53 and schizophrenia (11,12). Tumor suppressor genes may act to increase risk for schizophrenia by disruption of cell growth, or through abnormal apoptosis during neurodevelopment while simultaneously acting to decrease risk for cancer due to the same, in this case advantageous, apoptotic mechanism (4).

While previous studies have focused on tumor suppressor genes and their potential role in disorders such as schizophrenia, one widely studied cancer-related gene is the *MET* proto-oncogene, whose primary functions are related to the metastasis of several forms of cancer and peripheral organ development and repair (13-16). *MET* spans 125kb on chromosome 7q31, consists of 21 exons, and codes for the MET receptor tyrosine kinase. While activation of the MET signaling pathway can result in the abnormal growth and spread of cancerous tumors, *MET* also plays a critical role in cortical and cerebellar development (17-20), making it a candidate gene of interest for a broad range of neuropsychiatric disorders with a neurodevelopmental etiology, including autism. Campbell et al. (2006) reported that the C allele at a single nucleotide polymorphism (SNP rs1858830) in the promoter region of *MET*, was significantly over-transmitted to affected family members in two independent family cohorts ascertained for autism spectrum disorders (21) and have subsequently replicated this finding in a third independent sample (22).

Although DSM-IV-TR criteria exclude the presence of schizophrenia and autism in the same individual (23), both disorders may be related to abnormal neurodevelopment. There are clear distinctions between the two illnesses; however, there are also a number of clinical features that are common to both disorders. Autism spectrum disorders are characterized by social deficits, abnormal language development, restricted interests, and repetitive behaviors. In addition, approximately 30% of autism cases are significantly cognitively impaired, although the degree of impairment varies by disorder subtype (24). Similarly, schizophrenia patients also commonly display social deficits (asociality), reduced interests in pleasurable activities (anhedonia) (23), and significant neurocognitive impairment (25). Finally, data from family and molecular genetic studies suggest an overlap between these illnesses (26).

To date, there have been no studies examining the relationship between *MET* and susceptibility to schizophrenia, or other phenotypes common to autism and schizophrenia such as neurocognitive impairment. Thus, we initially conducted a case control study comprised of 173 Caucasian schizophrenia patients and 137 Caucasian healthy controls. We genotyped 21 SNPs within *MET* and tested for an association with schizophrenia. We next carried out a replication study of the same SNPs in a second sample of 107 patients with schizophrenia and 112 healthy controls. Finally, we explored the effect of *MET* variation on neurocognition in a combined sample of 191 schizophrenia patients and 188 healthy controls.

METHODS

Subjects

The initial study group included 173 Caucasian schizophrenia patients [63 female/110 male; mean age=37.7 ± 10.7 years; age of onset=21.4 ± 5.9 years; global assessment of function (GAF)=39.4 ± 17; and estimated IQ (based on the Wide Range Achievement Test-3rd version-Reading-WRAT-3)=96.5 ± 12.4]. The second sample was comprised of 107 schizophrenia patients [37 female/70 male; mean age=37.4 +/− 11.6 years age of onset=24.4 +/− 8.4 years; GAF score=42.1 +/− 16.6; and an estimated IQ=96.6 +/− 12.8]. All subjects provided written informed consent to an Institutional Review Board-approved protocol. Patients for both the initial and replication samples were recruited from the Zucker Hillside Hospital in Glen Oaks, NY.

Caucasian healthy control subjects were recruited from the general population and were excluded if they had a DSM-IV Axis I diagnosis or a first degree relative with a known or suspected Axis I disorder. Controls in the initial sample (n=137) were 61 female/ 76 male, had a mean age of 42.9 ± 13.0 years and an estimated IQ of 104.2 ± 9.4. Controls in the replication sample (n=112) were 69 female/ 43 male, had a mean age of 54.8 ± 21.9 years and an estimated IQ of 105.9 ± 7.2.

Race was self-identified as Caucasian and population structure was assessed using a principal components analysis approach applied to the full dataset (n=365,721 SNPs passing quality control filters (27), implemented in SVS7 software (GoldenHelix, Inc., Bozeman, MT), using default settings derived from EIGENSTRAT (28). The first two principal components had eigenvalues > 1 (2.04 and 1.95); and the remaining eight ranged from 0.83-0.63. Cases and controls did not differ on the first principal component (p=0.99); however, case-control differences were noted on both the second and third principal components ($p \leq .001$). These two variables were included as covariates in association analyses described below. There were no significant differences between cases and controls on any of the remaining principal components.

Diagnostic Measures

Patient diagnosis was established via the Structured Clinical Interview for DSM-IV (SCID-IV) (29) and confirmed by diagnostic consensus conference, which utilizes expert clinical opinion alongside SCID-IV and corroborating medical record information. Healthy controls for the project were assessed using the SCID-IV-Non-Patient edition to rule out Axis I diagnoses. In addition, subjects with history of CNS trauma, neurological disorder, or previously diagnosed learning disability were excluded.

Cognitive Measures

Subjects were clinically stable and were administered measures to asses estimated intellectual functioning (WRAT-3), auditory attention and verbal working memory (WAIS-R-Digit Span), visual attention [Continuous Performance Test –Identical Pairs], rapid visual search (Trails A), verbal learning [California Verbal Learning Test], and executive functioning (letter/category fluency), set-shifting (Trails B) (30). A measure of "general cognitive ability", or (*g*), was calculated with an unrotated principal components analysis as in our prior work (31). A single factor model resulted including extracted variables with eigenvalues of > 1.0. This single factor explained 49.5% of the variance and represented *g*. Cognitive analysis focused on *g* since global cognitive impairment is characteristic to both autism and schizophrenia, making this a phenotype of particular interest with regard to *MET*.

DNA Procedures

We genotyped 21 SNPs in *MET* on 7q31 (B36 positions 116057424-116253319) using the Affymetrix 500K chip (SA1). The Tagger program (r^2=1.0) (http://www.broad.mit.edu/mpg/tagger/) was utilized to reduce the redundancy of the included SNPs prior to analyses; 16 SNPs were retained with frequencies >0.05. Using pairwise tagging ($r^2 > 0.80$) and downloaded data from the HapMap project CEU sample, we calculated that these 16 SNPs were able to capture 71% (70/98 alleles) of the common allelic variation in the *MET* region. Linkage disequilibrium structure was examined using Haploview 3.32 (32) with solid spine D' > 0.80 (Figure 1). In the replication sample, identical genotyping methods were used (SA1). Phase and diplotype assignments were estimated using PHASE 2.1.1 (33), for each of the *MET* haplotype blocks individually and in each sample separately.

Statistical Analyses

MET disease association—Haploview was utilized to test for significance of each haplotype (with frequency ≥ 10%) within the defined blocks, and global χ^2 were calculated using the VassarStats website (http://faculty.vassar.edu/lowry/VassarStats.html). Phased individual haplotypes were tested in SPSS Version 11.5 to determine the best model for significant associations and neurocognitive analyses utilized the best-fit genetic model. Correction for multiple testing was carried out using permutation testing in Haploview, including 10,000 permutations. Odds ratios (OR) were calculated as a measure of effect size for all association analyses with 95% confidence intervals.

MET association with cognition—To optimize power, we tested for *MET*'s effect on cognition using a univariate analysis of covariance (ANCOVA) first in the combined healthy control sample (n=188). Secondary analyses in the schizophrenia cohort included 191 patients with complete neurocognitive data. *MET* diplotype status was entered as a fixed factor and age was used as a covariate. Eta^2 was calculated as an estimate of effect size.

RESULTS

First, we tested for association between *MET* variation and schizophrenia in the initial sample. Four haplotype blocks were identified, each consisting of 3 major haplotypes. The strongest association was noted in Block 3, with the most common haplotype (GCAATACA) being over-represented in healthy controls (47% frequency) vs. schizophrenia (33% frequency) (Table 1). Post hoc analyses indicated that the best fit model was a dominant model of inheritance, with subjects carrying at least one copy of GCAATACA being significantly less likely to develop schizophrenia as compared with subjects carrying no copies ($\chi^2 = 13.4$; $p = 2.5 \times 10^{-4}$; OR=0.40; CI=0.24-0.65). Results remained significant after correction with permutation (corrected permutation p=0.0019). Individual SNP associations for the initial sample are presented in Table 2. Three of the SNPs survived correction, all residing in Block 3; rs2237717 is located in intron 11, rs41735 is located in intron 19, and rs42336 is just downstream from the *MET* coding region. At each of these individual SNPs the associated 'protective' allele is the ancestral allele.

For replication, we repeated the Block 3 haplotype association analyses in a second independent sample and tested the effect of *MET* GCAATACA on disease susceptibility. The results were highly consistent with the initial analyses, both at the haplotype and SNP level. The most common haplotype in Block 3 (GCAATACA) was over-represented in healthy controls (46% frequency) vs. schizophrenia patients (36% frequency) (Table 1). The dominant model was also significant with subjects carrying at least one copy of GCAATACA being significantly less likely to develop schizophrenia versus subjects carrying no copies ($\chi^2 = 4.0$; $p = 0.05$; OR=0.55; CI=0.30-0.99). SNP associations for the replication sample are consistent with results from the initial sample (Table 2). To address the possible influence of population stratification, we carried out a backward stepwise logistic regression with subject type as the dependent variable and included GCAATACA haplotype status, as well as the second and third principal component from the population structure analysis as independent factors. We found that although both principal components remained in the model ($p \leq 0.001$), GCAATACA haplotype remained significant (p=0.001) (SA1).

MET Association with Cognition

We next tested for an effect of *MET* on neurocognition. To maximize power, we merged the initial and replication datasets for all subjects with complete neurocognitive data (191 schizophrenia patients/188 healthy controls) and tested for effects in each diagnostic group separately.

The sample characteristics by *MET* GCAATACA haplotype group are presented in Table 3. The haplotype groups did not significantly differ on age in the healthy controls (t=1.5; df=186; p=0.14) or in the schizophrenia sample (t=1.7; df=176; p=0.09) nor did they differ on estimated premorbid IQ (healthy: t=0.30; df= 176; p=0.77; schizophrenia: t=0.73; p=0.47). There were significant differences noted for sex distribution within the schizophrenia sample ($\chi^2 = 6.8$; df=1, p=0.01) but not in the healthy controls ($\chi^2 = 0.001$; df=1; p=0.99). In addition, in the patient group, illness characteristics including GAF score (t=0.15; df=169; p=0.88), age at onset (t=0.37; df=169; p=0.71), and duration of illness (t=0.18; df=169; p=0.86) did not differ by genotype.

Univariate analyses of covariance (ANCOVA) in the combined healthy control sample revealed a significant effect of *MET* GCAATACA (F=3.99; df=1,187; p=0.05), and age (F=16.99; df=1,187; p<0.001) on general cognitive ability (*g*) (Figure 2). *MET* GCAATACA carriers had significantly better cognitive performance than non-carriers, with *MET* haplotype explaining approximately 2.1% of the variance in *g*. In the schizophrenia sample a similar pattern of performance was revealed with carriers outperforming non-carriers (Figure 2);

however, the results did not achieve statistical significance [*MET* GCAATACA (F=1.48; df=1,190; p=0.23); eta^2= 0.01].

DISCUSSION

We report a significant influence of genetic variation within the *MET* proto-oncogene and susceptibility to schizophrenia in two independent cohorts. The strongest association was with a haplotype spanning the majority of the coding region of *MET*, as subjects carrying one or more copies of the most common haplotype (GCAATACA) were significantly less likely to develop schizophrenia than subjects carrying no copies (OR=0.40; 95% CI= 0.3-0.8). These data represent the first report of an association between *MET* and schizophrenia and the second association of *MET* with susceptibility to neuropsychiatric illness. Previously, Campbell et al. (21) reported an association between a SNP within the promoter region of *MET* (rs1858830) and autism, subsequently replicating this finding and expanding the association to include several other genes within the *MET* pathway (22).

We also report that *MET* GCAATACA genotype had a significant impact on neurocognition; such that healthy control *MET* GCAATACA carriers performed significantly better than non-carriers on an empirically derived factor of general cognitive ability (*g*). This preliminary evidence of a role for *MET* in neurocognitive function may shed light on the mechanism through which variation in *MET* might influence risk for both autism and schizophrenia, as the phenotype of neurocognitive impairment is common to both diseases. These data could be interpreted to indicate that the influence of *MET* on disease susceptibility might not be specific to risk for schizophrenia or autism. Rather, these findings may be reflective of the effects that *MET* may have on brain function in general. This potential explanation warrants follow up in other clinical disorders characterized by brain morphological abnormalities, neurodevelopmental pathology, and/or cognitive impairment.

The role of MET in cancer has been definitively established. There are several mechanisms by which MET influences cancer development and progression: 1) overexpression of MET-the most common alteration of MET in human tumors; 2) autocrine/paracrine activation in which MET is activated by its ligand, hepatocyte growth factor, which may be abnormally produced by cancer cells; 3) hepatocyte growth factor-independent activation via transactivation by other membrane receptors; and 4) *MET* structural alterations, such as missense mutations, which result in hereditary forms of cancer. Regardless of the mechanism by which MET activity is altered, increased MET activation is associated with abnormal tissue growth related to tumor development and metastasis. In contrast, MET activation plays a beneficial role during normal physiological states and is critical to normal cortical and cerebellar development (17-20). Disrupted MET signaling in the cerebral cortex results in a decreased number of interneurons and abnormal interneuron migration from the ganglionic eminence (17,18). In the cerebellum, reduced MET signaling decreases proliferation of granule cells, resulting in cerebellar volume reductions especially in the vermis (19). Abnormalities that result from perturbation of this system are consistent with known changes in the brains of schizophrenia patients, including dysfunction and reduced number of inhibitory interneurons in the prefrontal cortex (34) and volumetric reductions in the vermis, both of which correlate with cognitive dysfunction common to the illness (35).

Taken together, these data suggest that *MET* may influence risk for disorders such as autism and schizophrenia via a *decreased* level of pathway activity during critical periods of neurodevelopment. This hypothesis is supported by data from Campbell et al. (2006), in which an autism risk allele (C) at rs1858830 was associated with a reduction in MET transcription. A subsequent study by the same group demonstrated that MET mRNA expression was decreased in the postmortem brain tissue of autism subjects, and that the level of MET

expression was associated with rs1858830 in healthy controls (36). In the present study, minor alleles of multiple intragenic SNPs (such as rs42336) were associated with increased risk of schizophrenia; these alleles, or perfect proxies of them, have similarly been associated with reduced gene expression in prior studies (37,38).

These data implicating the *MET* gene in schizophrenia, coupled with the autism data, are consistent with a recent study that utilized computational probabilistic modeling to investigate the relationship among multiple common disorders that might be likely to share genetic susceptibility including cancer, autism, and schizophrenia. Rzhetsky et al. (2007) proposed a disease network hypothesis based on the analysis of more than 1.5 million patient records from a clinical database and tested whether a genetic variant that predisposes an individual to a given disease may increase, or alternatively decrease, the risk for multiple other diseases (39). The tested hypothesis was, like many Mendelian disorders, that complex phenotypes are likely explained by genetic variation that is shared, in either a competitive or cooperative manner, by multiple disease phenotypes. Among 161 disorders studied, a highly connected network of pair-wise correlations emerged, including a strong positive correlation between autism and schizophrenia (p-value= 5.78×10^{-11}), suggesting significant genetic overlap, such that approximately 20-75% of autism-predisposing variants were estimated to also predispose an individual to schizophrenia. Of particular note, a strong *inverse* relationship between schizophrenia and breast cancer was also observed in these analyses (p-value= 1.22×10^{-10}) (49), providing support for the hypothesis that genetic variation at a single locus, such as *MET*, may have both shared and divergent effects across different phenotypes.

A specific example of the potential pleiotropic effects of *MET* is provided by a recent study (52) which investigated the effect of the *MET* promoter SNP rs1858830 on susceptibility to autism in 214 autism families who were characterized for gastrointestinal comorbid conditions. *MET* rs1858830 was associated with increased risk for autism *and* increased susceptibility to gastrointestinal disease in 118 families with at least one child with co-occurring autism and a gastrointestinal condition; however there was no association to autism noted in families with children who did not have a comorbid gastrointestinal disease. These data provide preliminary evidence that decreased activity in the *MET* pathway may have both central and peripheral effects, contributing to abnormal brain development (autism) as well as dysfunctional organ repair (40).

There are a number of limitations to this study. First, medications may confound analyses in chronic schizophrenia populations; however, we would not expect that medication type or dosage would differ significantly by genotype, as the severity of the illness was comparable between groups in our sample. We did not have sufficient data on medication dosage to conduct a formal test of this question. Second, the genotyped markers were selected using an Affymetrix 500K chip based on genomic spacing; we were only able to capture 71% of the common allelic variation within the MET region using the 16 SNPs analyzed. The use of genome-wide association methods raises the issue as to which analyses are considered appropriate in the context of statistically non-significant genome-wide results. In the strictest statistical sense, analytic follow-up of results that do not meet the genome-wide threshold after correction may not be considered valid. However, we suggest that genes, such as *MET*, with prior data suggestive of biological plausibility related to pathophysiology also warrant follow up, especially given the previous association with autism, and the consistency of our results in two independent samples. Finally, we acknowledge that the magnitude of the effect of *MET* on both disease susceptibility and neurocognitive function is relatively small which is consistent with the complexity of the genetic architecture of schizophrenia and its related phenotypes.

In summary, we present evidence that variation within *MET* influences the risk for schizophrenia and affects general cognitive ability (*g*). These data highlight the importance of

assessing molecular networks that may be implicated in the pathophysiology of multiple CNS disorders with overlapping phenotypes. Further, these results provide evidence for at least one potential genetic locus that may explain both a cooperative polymorphism model (increasing risk for both schizophrenia and autism) and a competitive polymorphism model (increasing risk for schizophrenia and protecting against cancer) via a specific hypothesized biological mechanism.

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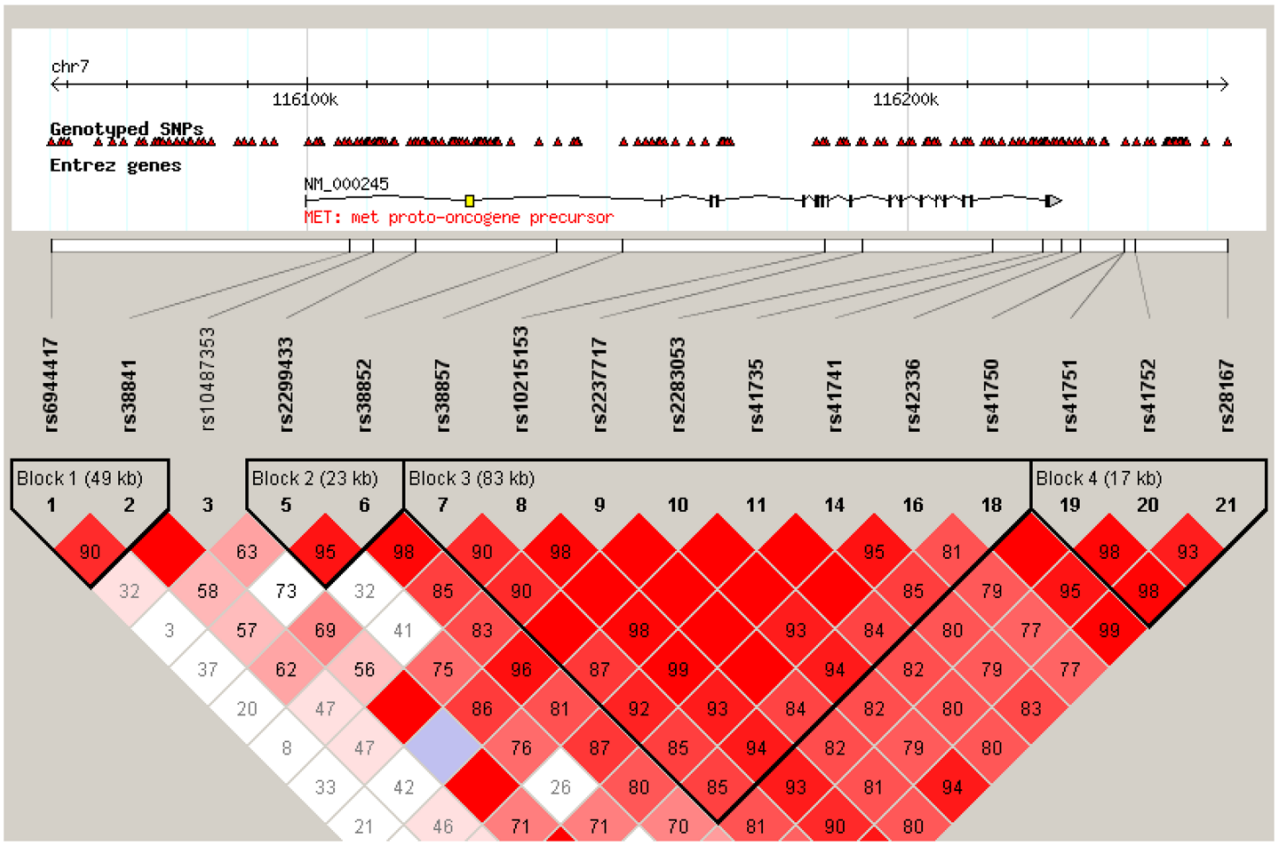

Figure 1. Linkage Disequilibrium Structure of *MET* Haplotype Blocks in the Initial Sample
Linkage disequilibrium (D′) for the region typed using Haploview 3.32 (24).

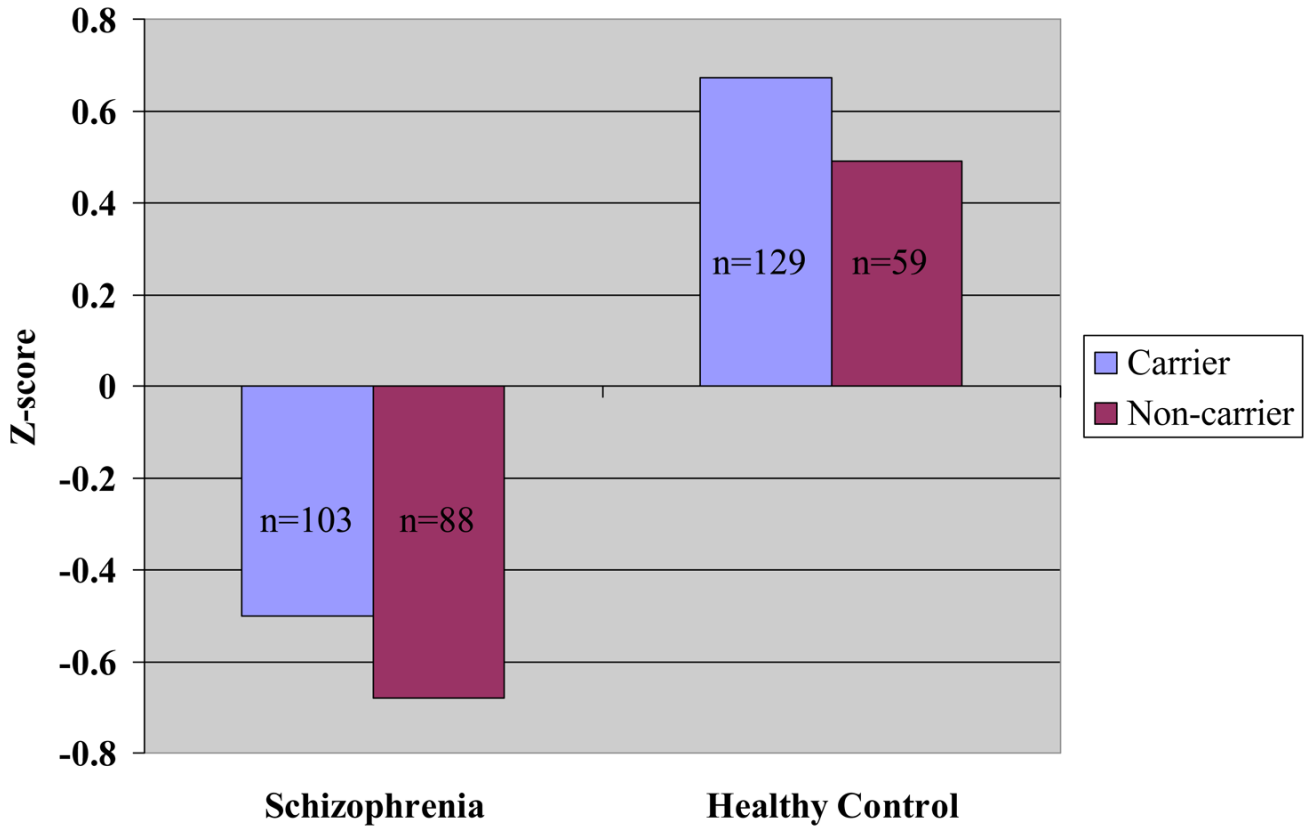

Figure 2. Effects of *MET* on General Cognitive Ability in the Combined Sample

The X-axis labels the subject groups by *MET* genotype. The Y-axis represents the composite g using a z-score scale with a mean of 0 and SD of 1. The effect of *MET* GCAATACA on neurocognition is significant in the healthy control sample (p=0.05) but not in the schizophrenia sample (p=0.23).

Table 1

MET Association with Schizophrenia

Haplotype	Schizophrenia (%)	Control (%)	X^2	*P*-value (OR; 95% CI)[t]
INITIAL SAMPLE				
BLOCK 1	---	---	**2.8**	**0.25**
CA	56.2	49.5	2.8	0.10
CG	31.7	37.4	2.2	0.14
AA	11.9	12.4	0.04	0.83
BLOCK 2	---	---	**7.3**	**0.02** (0.66; 0.48-0.91)
CT	38.8	49.0	6.4	0.01* (0.68; 0.49-0.94)
CA	33.5	25.3	4.9	0.02* (1.49; 1.04-2.11)
TA	27.2	25.1	0.35	0.56
BLOCK 3	---	---	**11.2**	**0.004***
GCAATACA	33.2	47.4	12.9	0.0003** (0.56; 0.45-0.77)
ATGACCTG	29.9	25.6	1.4	0.24
GCGGCATA	20.6	14.5	3.9	0.05
BLOCK 4	---	---	**6.7**	**0.03**
GCC	39.0	48.4	5.6	0.02* (0.68; 0.49-0.94)
ATT	36.5	31.3	1.8	0.17
ATC	23.5	17.9	2.9	0.09
REPLICATION SAMPLE				
BLOCK 3				
GCAATACA	***36.3***	***46.3***	***4.6***	***0.03* (0.66; 0.45-0.97)***
ATGACCTG	23.1	21.5	0.3	0.60
GCGGCATA	20.9	15.7	2.0	0.16

Table 2

Individual SNP Association with Schizophrenia: Initial Sample

rs number	Position (B36)	Associated Allele	Minor Allele Frequency Case, Control	X^2	p-value
Block 1	---	---	---	---	---
rs6944417	116057424	C	0.121, 0.131	0.2	0.69
rs38841	116107162	A	0.321, 0.385	2.7	0.10
Block 2	---	---	---	---	---
rs2299433	116118114	T	0.276, 0.261	0.2	0.68
rs38852	116141761	A	0.392, 0.496	6.6	0.01
Block 3	---	---	---	---	---
rs38857	116152649	A	0.338, 0.285	2.0	0.15
rs10215153	116186367	T	0.349, 0.293	2.2	0.14
rs2237717	116192623	G	0.374, 0.496	9.4	0.002**
rs2283053	116214255	G	0.209, 0.162	2.3	0.13
rs41735	116222652	C	0.379, 0.496	8.6	0.003**
rs41741	116225747	C	0.391, 0.310	4.3	0.04
rs42336	116228825	T	0.623, 0.488	10.5	0.001**
rs41750	116236236	G	0.361, 0.315	1.4	0.23
Block 4	---	---	---	---	---
rs41751	116236286	A	0.391, 0.496	6.6	0.01
rs41752	116238091	T	0.602, 0.488	7.6	0.006
rs28167	116253319	T	0.369, 0.328	1.1	0.29
Individual SNP Association with Schizophrenia: Replication Sample					
rs number	**Position (B36)**	**Associated Allele**	**Minor Allele Frequency Case, Control**	X^2	p-value
Block 3	---	---	---	---	---
rs38857	116152649	A	0.269, 0.246	0.3	0.58
rs10215153	116186367	T	0.276, 0.252	0.3	0.57
rs2237717	116192623	G	0.565, 0.469	4.1	0.04*

Am J Psychiatry. Author manuscript; available in PMC 2010 April 3.

rs number	Position (B36)	Associated Allele	Minor Allele Frequency Case, Control	X^2	p-value
rs2283053	116214255	G	0.229, 0.171	2.3	0.13
rs41735	116222652	C	0.565, 0.473	3.7	0.05
rs41741	116225747	C	0.337, 0.280	1.6	0.21
rs42336	116228825	T	0.569, 0.472	3.9	0.05
rs41750	116236236	G	0.314, 0.304	0.1	0.82

Table 3

Subject Characteristics by *MET* GCAATACA Haplotype in the Combined Sample for Cognitive Analyses

Characteristic	Carrier Mean	SD	Non-Carrier Mean	SD
Schizophrenia	N=103	---	N=88	---
Age	38.18	10.9	38.22	10.8
Sex	60male/43female	---	67male/21female	
Estimated IQ	98.40	10.1	97.32	10.4
Age at Onset	21.58	5.9	21.25	5.8
GAF Score	39.05	15.0	38.70	14.7
Healthy Controls	N=129		N=59	
Age	41.14	12.4	38.20	13.2
Sex	57male/72female	---	26male/33female	---
Estimated IQ	103.78	8.9	103.34	9.1