Association of *DISC1/TRAX* Haplotypes With Schizophrenia, Reduced Prefrontal Gray Matter, and Impaired Short- and Long-term Memory

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Context: Chromosome 1q42 is among several genomic regions showing replicated evidence of linkage with schizophrenia, but the specific susceptibility mechanisms underlying this relationship remain to be identified.

Objective: To examine a series of haplotype blocks of single-nucleotide polymorphic markers from a segment of 1q42 spanning the disrupted-in-schizophrenia 1 (*DISC1*) and translin-associated factor X (*TRAX*) genes for association with schizophrenia and several endophenotypic traits thought to be involved in disease pathogenesis.

Design: Population-based twin cohort study.

Setting: Finland.

Participants: Two hundred thirty-six subjects, consisting of 7 twin pairs concordant for schizophrenia (6 monozygotic [MZ] and 1 dizygotic [DZ]), 52 pairs discordant for schizophrenia (20 MZ and 32 DZ), and 59 demographically balanced normal pairs (28 MZ and 31 DZ), were drawn from a twin cohort consisting of all of the same-sex twins born in Finland from 1940 through 1957.

Main Outcome Measures: Psychiatric diagnosis, performance on neurocognitive tests of short- and long-term memory, and gray matter volume measurements taken from high-resolution magnetic resonance images.

Results: A common haplotype incorporating 3 single-nucleotide polymorphic markers near the translocation break point of *DISC1* (odds ratio, 2.6 [$P = .02$]) and a rare haplotype incorporating 4 markers from the *DISC1* and *TRAX* genes (odds ratio, 13.0 [$P = .001$]) were significantly overrepresented among individuals with schizophrenia. These haplotypes were also associated with several quantitative endophenotypic traits previously observed to covary with schizophrenia and genetic liability to schizophrenia, including impairments in short- and long-term memory functioning and reduced gray matter density in the prefrontal cortex, as demonstrated using a population-based brain atlas method, with a trend toward association with reduced hippocampal volume.

Conclusions: Specific alleles of the *DISC1* and *TRAX* genes on 1q42 appear to contribute to genetic risk for schizophrenia through disruptive effects on the structure and function of the prefrontal cortex, medial temporal lobe, and other brain regions. These effects are consistent with their production of proteins that play roles in neuritic outgrowth, neuronal migration, synaptogenesis, and glutamatergic neurotransmission.

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SCHIZOPHRENIA IS A COMplexly inherited disorder involving multiple genes of small effect influencing numerous central nervous system trait deficits.[1] Two genes in the chromosome 1q42 region—disrupted-in-schizophrenia 1 (*DISC1*) and translin-associated factor X (*TRAX*)—represent particularly good candidate loci based on positional and functional considerations. Although the evidence for linkage of this region to schizophrenia has been negligible in some studies,[2] the translocation break point that cosegregates with schizophrenia in a Scottish pedigree[3,4] and the peak linkage signal in the 1q42 region within the Finnish population[5-7] are intragenic to *DISC1*, with several other linkage and association findings also pointing to this region.[8-15] The *DISC1* gene is expressed in neurons and glia and is translated to a protein that has an impact on neurodevelopmental and neurochemical processes thought to be involved in the pathophysiology of schizophrenia, including neuritic outgrowth, neuronal migration, synaptogenesis, and glutamatergic transmission.[16-19] Recently, 2 haplotypes incorporating different blocks of single-

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Table 1. Sociodemographic Characteristics of the Control, Patient, and Co-twin Samples*

Characteristic	Controls (n = 118)	Probands (n = 65)	Co-twins (n = 53)
Monozygotic	56 (47.5)	32 (49.2)	20 (37.7)
Female	58 (49.2)	33 (50.8)	29 (54.7)
Left-handed	8 (6.8)	5 (7.7)	5 (9.4)
Substance abuse	6 (5.1)	14 (21.5)	8 (15.1)
Age, mean (SD), y	48.6 (6.9)	47.6 (5.1)	47.7 (4.6)
Parental social class, mean (SD)†	6.5 (1.3)	6.5 (1.4)	6.4 (1.4)

*Unless otherwise indicated, data are expressed as number (percentage) of subjects.

†Determined according to the Rauhala scale of socioeconomic status as implemented in the Finnish National Population Register.

nucleotide polymorphic (SNP) markers in the *DISC1* gene were found to be associated with schizophrenia (one undertransmitted and the other overtransmitted to affected cases) in a study of multiplex families from Finland.[6] How these genetic variations influence central nervous system trait components associated with schizophrenia remains to be determined, although it is notable that carriers of the (1;11)(q42;q14.3) translocation show deficits in the amplitude of the P300 electrophysiological response.[12] Another locus affected by the balanced translocation in the Scottish pedigree *DISC2* is not known to form a protein but is thought to act through its RNA as a regulator of *DISC1*.[3]

The *TRAX* gene is located immediately centromeric to and in the same orientation as *DISC1* and was identified as a potential candidate gene when intergenic splicing was found to form fusion proteins between *TRAX*, *DISC1*, and combinations of 4 intragenic exons located between these 2 genes.[20] Although this discovery was made in vitro, it highlights that such events could be possible in vivo, and that mutations affecting *TRAX* may also affect *DISC1*. It has also recently been shown that orthologs of *DISC1* are highly conserved in genomic structure and in their location close to the *TRAX* orthologs on the mouse[21] and fugu[22] genomes, implying some significance for the physical vicinity of the *TRAX* and *DISC1* genes. In addition, such potential interplay between the *DISC1* and *TRAX* genes in the etiology of schizophrenia was highlighted when association was observed by Hennah et al[6] to a haplotype located solely within the *TRAX* gene that was independent of the *DISC1*-associating haplotypes. The *TRAX* protein is known to form a brain-enriched complex with translin that can bind single-stranded DNA and RNA, through which it is involved in protein regulation[23] and, consequentially, development and function of the nervous system.

In the context of complex inheritance, endophenotypic traits reflecting processes intermediate between gene expression and clinical diagnosis are likely to be particularly useful in isolating DNA sequence variations associated with susceptibility to illness.[10,12,24-26] For example, such traits are sensitive to gradations in phenotypic liability in patients and their nonschizophrenic relatives, who are expected to manifest disease-promoting haplotypes to a degree intermediate between probands and the general population.[25] Deficits in short-term (or working) memory and long-term episodic memory are reliably observed in patients with schizophrenia and vary in a dose-dependent manner with genetic proximity to an individual with schizophrenia among their nonaffected relatives.[27] The same pattern is observed for reductions in gray matter volume in the frontal cortex and medial temporal lobe structures,[28,29] regions known to play critical roles in the mediation of working memory[30] and episodic memory,[31] respectively. These reductions in cortical gray matter volume appear to reflect deficits in dendritic arborization and synaptic contacts on cortical pyramidal neurons.[32] Such deficits in neuropil volume in the region of the prefrontal cortex would be expected to affect the distribution and functioning of the dopamine D_1 receptor, which is critically involved in the mediation of spatial working memory functioning through its modulation of glutamatergic neurotransmission in pyramidal neurons.[33,34]

Herein we sought to determine whether haplotypes of segregating blocks of SNP markers of the *DISC1* and *TRAX* genes influence liability for schizophrenia, regional cortical gray matter volume, and neurocognitive functioning in the domains of short- and long-term memory. We evaluated variations in these genes for linkage and association with schizophrenia and with quantitative neuroanatomical and neuropsychological traits in samples of twin pairs concordant and discordant for schizophrenia and in healthy control twins from Finland.

METHODS

SUBJECTS AND CLINICAL EVALUATION

The study protocol was reviewed and approved by the institutional review boards of the University of California–Los Angeles and the National Public Health Institute, Helsinki, Finland, and all subjects signed institutional review board–approved informed consent forms.

Two hundred thirty-six subjects, consisting of 7 twin pairs concordant for schizophrenia (6 monozygotic [MZ] and 1 dizygotic [DZ]), 52 pairs discordant for schizophrenia (20 MZ and 32 DZ), and 59 normal pairs (28 MZ and 31 DZ) were drawn from a twin cohort consisting of all of the same-sex twins born in Finland from 1940 through 1957 in which both members of each pair were alive and residing in Finland as of 1967.[35] As shown in **Table 1**, the patients, co-twins, and control twins were balanced on age, sex, handedness,[36] and parental social class. As previously indicated, probands and their co-twins had higher rates of substance use compared with control twins.[27] Each co-twin was interviewed using the Structured Clinical Interview for *DSM-III-R* Disorders, Patient or Nonpatient Edition,[37] by a different examiner who was blind to the zygosity and diagnostic status of their co-twin, and the twins were assigned diagnoses based on the *DSM-IV* definitions.[38] Personality disorder symptoms for co-twins and healthy subjects were rated (eg, cluster A) on the Structured Clinical Interview for *DSM-III-R* Personality Disorders.[39] Mean ± SE diagnostic reliability was excellent (ie, $\kappa = 0.94 \pm 0.02$)[40]; final diagnoses were made by consensus among 3 independent raters (including T.D.C. and M.H.) after review of written case reports that summarized the information collected in the interviews and any hospital records. The patients had a mean ± SD age at onset of 24 ± 5 years and had been treated with (primarily traditional) antipsychotic drugs for a mean ± SD of 14 ± 10 years. Average symptom severity at the time of evaluation was in the moderate range

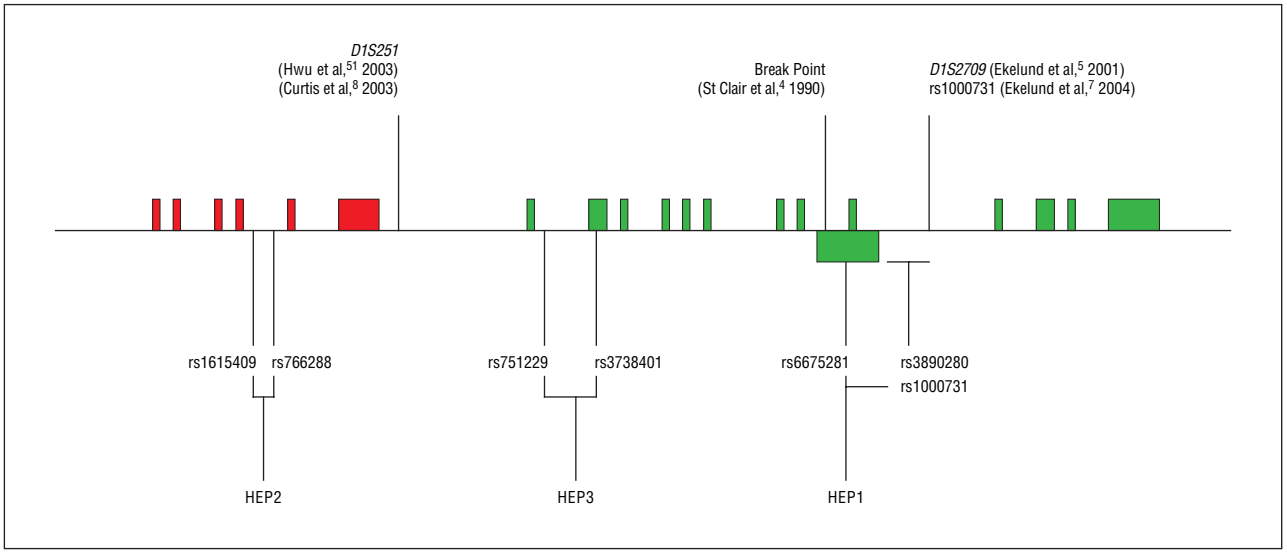

Figure 1. Schematic of the single-nucleotide polymorphic markers genotyped in the translin-associated factor X (red) and disrupted-in-schizophrenia 1 (green) genes on chromosome 1q42. Haplotype HEP1, HEP2, and HEP3 associations with schizophrenia were identified by Hennah et al.[6]

in terms of negative symptoms (mean±SD scores of 2.0±1.0 on global items on the Scale for the Assessment of Negative Symptoms[41]) and in the moderate to severe range in terms of positive symptoms (mean±SD scores of 2.3±0.8 on global items on the Scale for the Assessment of Positive Symptoms[42]).

A comprehensive neuropsychological test battery was administered to each co-twin by a different examiner (A.T.-H. or T.P.) who was blind to zygosity and to the diagnostic status of the other co-twin. Variables selected for quantitative trait locus analysis consisted of 8 test indexes that discriminated affected from unaffected co-twins, degree of genetic loading for schizophrenia, or both, as previously described[27]: spatial working memory,[43] divided attention,[44] choice reaction time,[45] verbal learning and memory,[46] intrusions during verbal memory retrieval,[46] semantic clustering during verbal memory retrieval,[46] visuospatial learning and memory,[43] and motor speed.[47] All groups were within 1 SD of normal in terms of a composite average of the age-scaled standard scores on the vocabulary, similarities, block design, and digit symbol subtests of the Wechsler Adult Intelligence Test–Revised.[48] Patient performance on this measure was signficantly worse (mean±SD score, 8.2±2.5) than that of co-twins (mean±SD score, 9.9±2.6) and control twins (mean±SD score, 11.1±1.7), and the performance of co-twins was significantly worse than that of control twins.

Discordant pairs in which the proband had a diagnosis of schizoaffective disorder, affective type, or in which the co-twin had a psychotic disorder diagnosis, currently or on a lifetime basis, were excluded. Control pairs were excluded if there was a history of psychosis-related treatment in their first-degree relatives or if either co-twin was judged to have a psychotic disorder. Studied probands were comparable to the remainder of the discordant twin proband population in terms of year of birth, sex, age at first hospital admission, number of hospital admissions, and eligibility for disability pension.[27] Studied MZ probands were equivalent to studied DZ probands in terms of age at evaluation, age at onset, positive symptom severity, and negative symptom severity.[27] There were no differences in demographics, illness history, or symptom severity between probands from discordant and concordant pairs.[27] We have previously found that the heritability of schizophrenia is 0.83 in the twin population in Finland.[35] This estimate is comparable to those from the United Kingdom.[49] The genetic variation in Finland is expected to be the same as in other populations for common diseases such as schizophrenia.[50]

DNA METHODS

Genomic DNA was extracted from a 20-mL venous blood sample from each subject. We used as pregenotyping quality control samples a high proportion of sample duplicates and negative water controls to ensure a low genotyping error rate. A set of 7 SNPs spanning 315 kilobases from intron 4 of the *TRAX* gene to intron 9 of the *DISC1* gene were genotyped (**Figure 1**).[4,5,7,8,51] These SNPs represent the most informative subset of a larger panel of SNPs used in a prior study of Finnish families multiply affected with schizophrenia and expose the allelic diversity in this population.[6] In that study, Hennah et al[6] observed 3 major regional SNP haplotypes, 1 overtransmitted (HEP1) and 2 undertransmitted (HEP2 and HEP3) to affected individuals (Figure 1). The SNPs were originally identified from public databases, contig alignments, and expressed sequence tag alignments, and by sequencing. Potential SNPs that were not located by sequencing were verified in 16 Finnish controls. The SNPs were genotyped in the entire sample using the MassArray system (Sequenom, Inc, San Diego, Calif).[52]

For all pairs, zygosity was determined by DNA analysis using the following markers: *D1S80* (20 alleles), *D17S30* (13 alleles), apolipoprotein B (20 alleles), *COL2A1* (10 alleles), *vWA* (9 alleles), and *HUMTH01* (6 alleles). Assuming an average heterozygosity rate of 70% per marker, we estimate that this procedure will falsely classify a DZ pair as MZ in approximately 1 of 482 cases.

IMAGE ACQUISITION AND ANALYSIS

The T1-weighted MPRAGE magnetic resonance imaging volumes were acquired on a 1.0-T scanner (Siemens Medical Systems, Malvern, Pa) in the Department of Radiology, Helsinki University Central Hospital, Helsinki (128 contiguous 1.2-mm slices in the sagittal plane; repetition time, 11.4 milliseconds; echo time, 4.4 milliseconds; 256×256 matrix). Trained operators outlined the brain parenchyma on each section, eliminating pixels corresponding to the skull and meninges. A radiofrequency bias field correction algorithm eliminated intensity drifts due to scanner field inhomogeneity. Images were histogram matched, and a supervised, nearest-neighbor tissue classifier generated detailed maps of gray matter, white matter, and cerebrospinal fluid. Briefly, 120 samples of each tissue class were

interactively tagged to compute the parameters of a Gaussian mixture distribution that reflects statistical variability in the intensity of each tissue type.[53]

3-DIMENSIONAL CORTICAL MAPS

A high-resolution surface model of the cortex was automatically extracted from the segmented image for each subject.[54] Medial regions visible from the exterior cortical surface were included, but other regions (including inferior medial prefrontal, cingulate, and medial temporal lobe) were excluded from the analysis, as models of these regions were not obtainable using the surface extraction procedure. A single rater blinded to zygosity, diagnosis, and all demographic information drew 38 gyral and sulcal boundaries, representing the primary gyral pattern, as 3-dimensional (3D) curves on each of the digitized models, using a detailed anatomical protocol (available at: http://www.loni.ucla.edu/~esowell/new_sulcvar.html). This protocol was compiled by neuroanatomists with reference to a sulcal atlas,[55] as described previously.[56,57] Raters are trained on a set of 6 brains until they can trace landmarks with interrater and intrarater 3D root-mean-square errors of no greater than 2 mm everywhere and less than 1 mm on average.

Three-dimensional location information was retained through color coding as each cortical image was flattened and projected onto a sphere. Cortical models were used to compute a 3D vector deformation field, which was then used to reconfigure each subject's anatomy to the average configuration of the normal twins, matching landmark points, surfaces, and curved anatomical interfaces.[57] A local measurement termed *gray matter density* was made in each subject,[58,59] representing the proportion of gray matter measured in a small sphere of fixed radius (15 mm) around each cortical point. This metric thus reflects the ratio of voxels segmenting as gray matter in the sphere relative to the total, which may also include voxels segmenting as white matter, cerebrospinal fluid, or background. Maps representing the variability in gray matter density across cortex can then be generated for any within-group or between-subject contrast.

STATISTICAL METHODS

Haplotypes were resolved using the Haplotype Analysis of Polymorphic Markers program; this method has a very low error rate and compares favorably with other programs.[60] Logistic regression was used to evaluate associations of *DISC1* and *TRAX* haplotypes with diagnostic status, entering age, sex, substance use disorder, and parental social class as covariates and controlling for the dependency of observations within twin pairs using generalized estimating equations. Differences in haplotype frequency were modeled at the level of independent meioses (ie, each individual entered twice). Only 1 co-twin from healthy and concordant MZ pairs was included in analyses of associations with diagnosis, thereby correcting for ascertainment bias in MZ pairs concordant for diagnostic status.

Our analyses strategy used a hierarchical approach to hypothesis testing to protect against type I error. We first tested each haplotype (HEP1, HEP2, and HEP3) for association with diagnostic status. Given that these 3 haplotypes were independently associated with schizophrenia in the report by Hennah et al,[6] they were treated as independent tests in the present study (ie, critical value of $P<.05$ in each case). If no evidence of association was detected assuming a dominant mode of transmission, association assuming a recessive model was then tested. At this stage, the critical value for significance was $P<.05/2$ or $P=.025$. Only those haplotypes that survived the first stage of analysis were examined for association with the quantitative phenotypes.

Association analyses of the *DISC1* and *TRAX* haplotypes with neurocognitive and magnetic resonance imaging measures were performed using the QTDT program (Linkage Disequilibrium Analyses for Quantitative and Discrete Traits),[61] which uses a variance components framework incorporating information from all available siblings that is not biased in the presence of linkage or familiality. All models tested the significance of the haplotype effect after controlling for the effects of age, sex, handedness, zygosity, social class, substance use disorder, and schizophrenia diagnosis. Because of the likelihood of pleiotropic effects across different cognitive phenotypes, each analysis was considered an independent test, and associations that reached the $P<.05$ level of significance were tested for robustness using 1000 randomized sample replicates. For analyses involving magnetic resonance imaging data, this statistical model was applied at each voxel in the 3D cortical surface maps, and nominal significance ($P<.05$) was tested for robustness to multiple comparisons through permutation testing.[28,57]

RESULTS

ASSOCIATION WITH SCHIZOPHRENIA

Of the 3 associating haplotypes identified in our previous family study,[6] only HEP1 showed suggestive evidence of association with schizophrenia in the present sample ($\chi^2=3.6$ [$P=.06$]; odds ratio [OR], 1.7; 95% confidence interval [CI], 0.9-2.9). The HEP1 haplotype (ie, TCG) defines a 3-SNP segment located near the translocation break point of *DISC1* (Figure 1). Consistent with our previous study,[6] this haplotype was observed to have the highest frequency in both the affected and control populations (ie, 75.4% and 63.9%, respectively). Such a pattern is unlikely under a dominant mode of inheritance. When a recessive mode of transmission was assumed, the HEP1 haplotype was significantly more frequent among affected individuals (61.0%; $\chi^2=6.8$ [$P=.02$]; OR, 2.6; 95% CI, 1.2-5.6) but not among their nonschizophrenic co-twins (49.1%; $\chi^2=0.8$ [$P=.38$]). This effect was significant after correction for multiple hypothesis testing (ie, critical $P=.05/2$ or $P=.025$; observed, $P=.02$).

Neither of the 2 haplotypes found to be undertransmitted to affected individuals in our previous family study (ie, HEP2 and HEP3) was significantly associated with schizophrenia in the present sample, assuming a dominant or recessive mode of inheritance ($P>.68$ for all). Modeling of the linkage disequilibrium structure of these SNP markers suggested that HEP2 and HEP3 may not be segregating independently in this sample. To test for possible interaction of these haplotypes in relation to diagnostic status, the 2 segments were combined into a single haplotype block composed of 4 SNPs. In this case, the Bonferroni-corrected critical value of P was .05/4 or $P=.0125$ for a particular haplotype, but 8 haplotypes of the combined segment were observed, so the Bonferroni-corrected critical value is $P=.0125/8$ or $P=.00156$. As shown in **Table 2**, a rare haplotype for this region (ie, AATG, with a frequency of 1.1% in the control population) was observed to be significantly overrepresented among individuals with schizophrenia ($\chi^2=10.6$ [$P=.001$]; OR, 13.0; 95% CI, 2.8-62.1), with a trend toward overrepresentation among their nonschizophrenic co-twins ($\chi^2=7.3$ [$P=.008$]; OR, 8.8; 95% CI, 1.7-43.8).

Table 2. Haplotype Frequencies for a 4-SNP Block of Markers Spanning the *DISC1* and *TRAX* Genes and Tests of Association With Diagnostic Group*

Haplotype	Frequency, %			χ^2 Test	*z* Score	*P* Value
	Patients (n = 59)	Co-twins (n = 53)	Controls (n = 90)			
AACA	11.0	12.3	17.8	1.92	–1.11	.27
AACG	6.8	8.5	7.2	0.11	–0.30	.77
AATA	2.5	1.0	1.1	0.85	0.95	.35
AATG	9.3	7.6	1.1	14.00	–5.34	<.001
CCCA	2.5	4.7	5.0	0.62	–0.64	.52
CCCG	12.7	11.3	8.3	0.50	0.66	.51
CCTA	5.1	2.8	6.7	1.11	–1.02	.32
CCTG	48.3	50.0	52.2	0.20	–0.40	.69

Abbreviations: *DISC1*, disrupted-in-schizophrenia 1 gene; SNP, single-nucleotide polymorphic; *TRAX*, translin-associated factor X gene.
*Gene frequencies were modeled at the level of independent meioses (each subject contributes 2 genotypes). Haplotypes with frequencies of less than 1% were excluded. Parameters were estimated controlling for dependency of observations from twin pairs using generalized estimating equations.

ASSOCIATION WITH NEUROANATOMICAL MEASURES

Figure 2 shows 3D anatomical brain atlases indexing tests of genetic association of the disease-related *DISC1* and *TRAX* haplotypes with regional cortical gray matter density. These maps used a pattern-matching algorithm that adjusts for individual differences in the cortical folding pattern and in overall brain size, thus ensuring that regional variation in gray matter volume was assessed in the same anatomical reference locations across subjects. Homozygous HEP1 haplotype was significantly associated with small, focal reductions of gray matter in the superior and inferior frontal gyri (Figure 2A). The rare AATG haplotype of the combined HEP2/HEP3 segment was significantly associated with small, focal reductions in gray matter density in the superior and middle frontal gyri, as well as portions of superior temporal gyrus and superior parietal cortex (Figure 2B). The probabilities for the 2 largest regions with multiple contiguous significantly associating voxels in the prefrontal cortex were $P<8.61\times10^{-31}$ and $P<1.21\times10^{-8}$. We also evaluated a measure of hippocampal volume, derived from the same magnetic resonance images as described previously,[29] for association with both haplotypes. Whereas the rare HEP2/HEP3 AATG segment was unrelated to hippocampal volume ($P=.58$), there was suggestive evidence of association of homozygous HEP1 haplotype with hippocampal volume reduction ($\chi^2_1=3.42$; $P=.06$; empirically derived *P* value on 1000 permutations, .07). The regions identified in these maps as affected by *DISC1* and *TRAX* haplotypes have previously been shown to be highly heritable in normal twins[57] and sensitive to degree of genetic relationship to an affected individual in twins discordant for schizophrenia.[28,29]

ASSOCIATION WITH NEUROCOGNITIVE MEASURES

As shown in **Table 3**, homozygous HEP1 haplotype was significantly negatively associated with semantic clustering of items during verbal learning and memory and with verbal learning and memory generally, but not with any of the other measures. The rare AATG haplotype of the combined HEP2/HEP3 segment was significantly negatively associated with visuospatial working memory, significantly positively associated with reaction time to visual targets, and significantly negatively associated with verbal learning and memory. These genetic associations were independent of the effects of psychiatric diagnosis, substance use disorder, zygosity, sex, handedness, age at examination, and social class, and statistical significance was confirmed by permutation testing based on 1000 randomized sample replicates (Table 3).

INTERRELATIONSHIPS OF COGNITIVE AND ANATOMICAL MEASURES

A volumetric measure of prefrontal cortex volume correlated significantly with spatial working memory ($r=0.12$ [$P=.04$]) and choice reaction time ($r=-0.18$ [$P<.001$]), whereas a volumetric measure of hippocampal volume correlated with verbal learning and memory ($r=0.14$ [$P=.02$]) and semantic clustering ($r=0.13$ [$P=.03$]).

COMMENT

Our findings, based on a highly phenotypically detailed sample of Finnish twins, associate sequence variations in the *DISC1* and *TRAX* genes with increased risk for schizophrenia and with multiple quantitative trait deficits marking processes thought to be involved in the pathophysiology of the illness. These findings indicate a high likelihood that the *DISC1* and *TRAX* genes are responsible for previous evidence of linkage of the 1q42 region with schizophrenia and suggest that these associations are mediated through disruptive effects on the structure and function of the prefrontal cortex and other brain regions, effects that are consistent with involvement of these genes in processes affecting neurite outgrowth, neuronal migration, synaptogenesis, and glutamatergic neurotransmission.

These findings partially replicate those obtained in multiplex schizophrenia families by Hennah et al[6] in re-

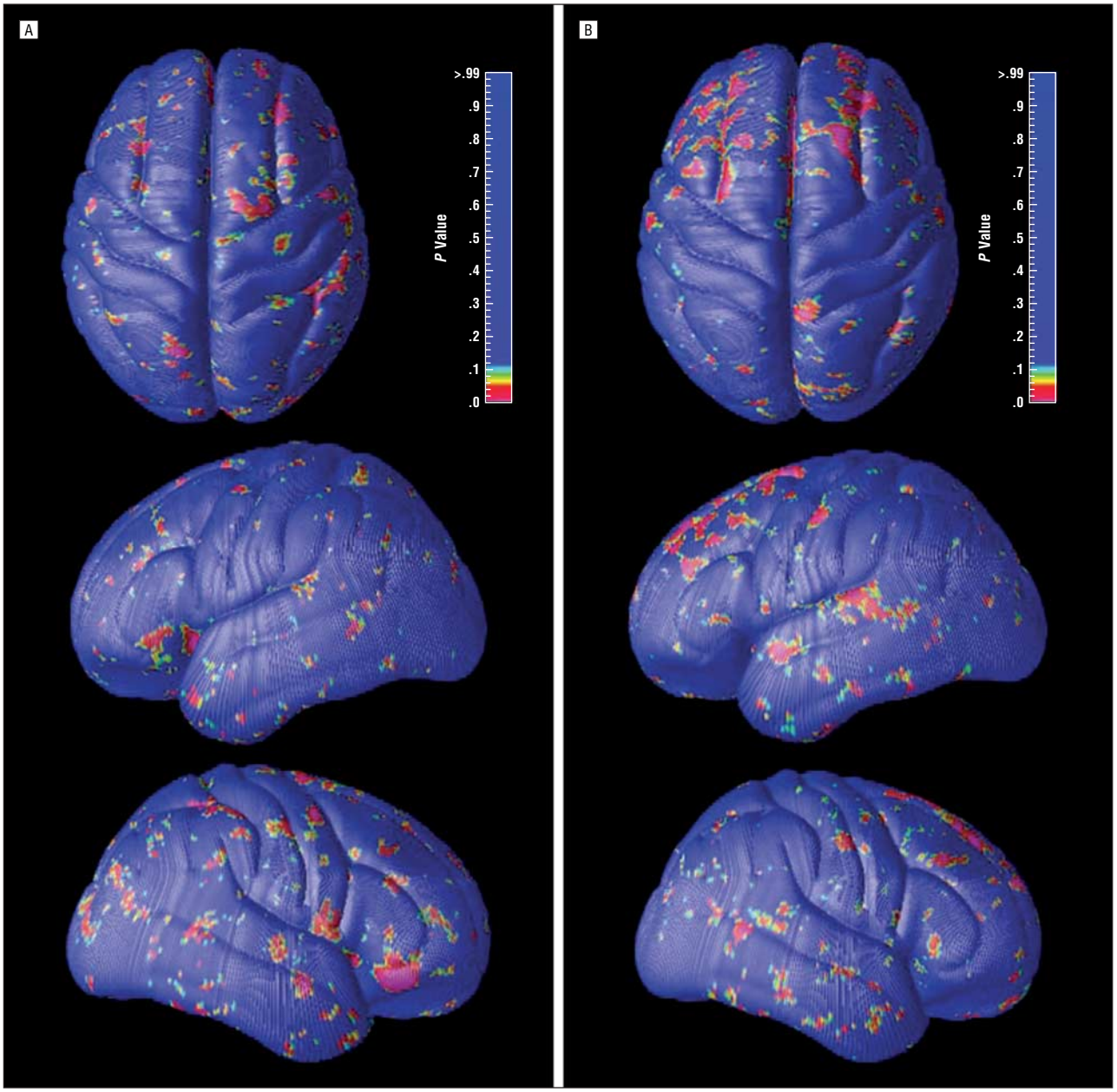

Figure 2. Statistical anatomical maps of areas of the cortical surface in which significant reductions in gray matter density are associated with a common haplotype (HEP1; TCG) of a 3–single-nucleotide polymorphic (SNP) block of markers located near the translocation break point on the disrupted-in-schizophrenia 1 (*DISC1*) gene (A) and a rare haplotype (AATG) of a 4-SNP block of markers spanning the *DISC1* and translin-associated factor X (*TRAX*) genes (B). Top, Left, and right views of each map are displayed. Haplotype associations were tested using the QTDT program (Linkage Disequilibrium Analyses for Quantitative and Discrete Traits),[61] controlling for the effects of age, sex, handedness, zygosity, social class, and psychiatric diagnosis and adjusting for dependency of observations among co-twins using generalized estimating equations. Maps are statistically thresholded to display regions showing association with gray matter density reductions at $P<.05$, the significance of which was confirmed through permutation testing. The *P* values for the 2 largest regions with multiple contiguous significantly associating voxels in the prefrontal cortex were $P<8.61\times10^{-31}$ and $P<1.21\times10^{-8}$ for the rare *DISC1/TRAX* haplotype (AATG).

lation to overtransmission of the HEP1 haplotype to individuals with schizophrenia. In the present sample, this association was significant only when assuming a recessive mode of inheritance. Two other haplotypes in the 1q42 region (HEP2 and HEP3) were observed in our previous study to be significantly undertransmitted to affected individuals (potentially reflecting protective effects). Although neither of these haplotypes was significantly associated with schizophrenia in the present sample, integration of the same SNP markers into a single segment uncovered a rare haplotype that was observed to be significantly overrepresented among individuals with schizophrenia and to a lesser extent among their nonschizophrenic co-twins. Modeling of linkage disequilibrium using only these SNP markers within the present twin sample provided strong evidence that the markers in HEP1 are separable, but the markers in HEP2 and HEP3 were less clearly dissociated from each other, and the overall pattern of linkage disequilibrium suggested that they may be segregating together. The combined HEP2/HEP3 haplotype incorporates markers from both *TRAX* and *DISC1*. That a haplotype block spans 2 differ-

Table 3. Least-Square Means and χ^2 Tests for *DISC1/TRAX* Haplotype Associations With Neurocognitive Measures*

Domain (Source)	3-SNP *DISC1* Haplotype				4-SNP *DISC1/TRAX* Haplotype			
	Other (n = 121)	HEP1 (n = 115)	χ^2 Test	*P* Value	Other (n = 219)	AATG (n = 17)	χ^2 Test	*P* Value
Spatial working memory (Russell,[43] 1975)	13.6 ± 0.5	13.8 ± 0.4	0.8	.37	14.6 ± 0.3	12.8 ± 0.7	6.6	.01
Choice reaction time (Finkelstein et al,[45] 1997	489 ± 17	477 ± 16	0.5	.48	463 ± 10	504 ± 27	9.3	.002
Verbal long-term memory (Delis et al,[46] 1983)	13.6 ± 0.5	12.7 ± 0.5	4.8	.03	13.9 ± 0.3	12.4 ± 0.8	5.5	.02
Semantic clustering (Delis et al,[46] 1983)	18.9 ± 1.5	14.8 ± 1.5	8.2	.006	18.4 ± 0.8	15.3 ± 2.5	2.3	.05
Recall intrusions (Delis et al,[46] 1983)	0.4 ± 0.01	0.4 ± 0.01	0.0	>.99	0.4 ± 0.01	0.5 ± 0.1	2.8	.09
Divided attention (Vilkki et al,[44] 1996)	39.3 ± 1.9	38.7 ± 1.8	0.1	.75	38.2 ± 0.9	39.8 ± 3.3	0.9	.34
Visual long-term memory (Russell,[43] 1975)	27.5 ± 1.0	28.2 ± 1.0	0.6	.44	27.0 ± 0.6	28.7 ± 1.7	0.8	.37
Motor speed (Reitan and Wolfson,[47] 1985)	53.2 ± 1.7	54.8 ± 1.6	0.6	.44	53.5 ± 0.9	54.4 ± 2.8	2.4	.12

Abbreviations: *DISC1*, disrupted-in-schizophrenia 1 gene; SNP, single-nucleotide polymorphic; *TRAX*, translin-associated factor X gene.

**P* values refer to empirically derived probabilities for the observed test statistics on 1000 randomized sample replicates. Analyses performed using the QTDT program (Linkage Disequilibrium Analyses for Quantitative and Discrete Traits)[61] with variance components option. The HEP1 haplotype was modeled assuming a recessive mode of inheritance (*df* = 1) and the AATG haplotype was modeled assuming a dominant mode of inheritance (*df* = 2), consistent with the manner in which each haplotype was observed to be associated with schizophrenia. Performance indexes were defined as in Cannon et al.[27] Unless otherwise indicated, data are expressed as mean ± SEM.

ent genes is not unusual when the 2 genes are immediately adjacent and the markers quite proximal, as in this case. Given that splice variants of *DISC1* and *TRAX* interact with each other in vitro,[20] it also appears biologically plausible that there could be interdependency of these genes at the sequence level. The variants observed to be undertransmitted in the family sample (AC and TA) would combine to form a 4-SNP haplotype different from that observed to be overrepresented among affected cases in this study (AATG). The primary difference in the genetic structure of this region between the 2 samples appears to be the lower-than-expected rate of the HEP2 haplotype (AC) in the twin sample, which could be a chance variation due to a relatively small sample size. Nevertheless, taken together, the 2 sets of findings imply that different combinations of SNP markers of the *DISC1* and *TRAX* genes are differentially sensitive to the putative disease-promoting vs disease-protecting sequence variations in this region.

The 2 schizophrenia-related haplotypes in this study were observed to have partially distinct profiles of association with neuroanatomical and cognitive performance measures. Homozygosity of the common haplotype of a block of markers near the translocation break point of *DISC1* (HEP1) was strongly associated with impaired semantic processing in long-term memory and showed a trend toward association with reductions in total hippocampal volume. This set of associations is consistent with the well-established role of the hippocampus in the mediation of long-term memory functions.[31] At the same time, a rare haplotype of another block of markers integrating a more centromeric portion of the *DISC1* gene and a portion of the immediately adjacent *TRAX* gene was associated with impaired spatial working memory, increased reaction time to visual targets, and reduced gray matter predominantly in the superior and middle frontal gyri. This set of associations is provocative in view of the clearly established involvement of the lateral and superior prefrontal cortex in the mediation of spatial working memory functions.[30] Although the cortical surface analyses revealed small regions in the superior frontal sulcus showing association with both haplotypes, the overall pattern of differential associations with quantitative endophenotypic traits is consistent with at least partially distinct contributions of the 2 disease-related polymorphisms in this region in predisposing to schizophrenia. Also supporting this interpretation is the fact that the associations of each haplotype with schizophrenia as well as the aforementioned brain morphological measures and neurocognitive performance indexes remained significant while controlling for the effects of the other haplotype. *DISC1* and *TRAX* are among a number of genes, including the gene for catechol *O*-methytransferase,[62] that may exert their influences on susceptibility to and expression of schizophrenia by affecting the structural and functional integrity of the prefrontal cortex and/or hippocampus and related circuitry. It remains to be determined whether either or both of these polymorphisms are also associated with structural or functional changes, specifically in the dentate gyrus of the hippocampus, a region in which *DISC1* is maximally expressed in rodents and primates[63,64] and in which activity is correlated with working memory and episodic memory processing.[65,66]

In the context of complex inheritance, one would expect nonschizophrenic relatives of patients to manifest some disease-promoting haplotypes to a degree intermediate between that of probands and the general population, a pattern that appeared at the trend level in the case of a rare haplotype of a 4-SNP segment spanning the *DISC1* and *TRAX* genes but that was not significant in the case of a common haplotype of a 3-SNP segment located near the translocation break point of *DISC1*. A further implication of this set of observations is that alleles inherited identical by descent in discordant DZ twins should be related to twin resemblance for the quantitative phenotypes we studied, a pattern that was confirmed for each SNP marker (and, given the limited variability in the modeled identical-by-descent status, to an equivalent degree across markers) in relationship to spatial working memory performance and gray matter volume in the dorsolateral prefrontal cortex ($r = -0.43$

[P=.03] and r=–0.53 [P=.006], respectively). These findings highlight the utility of quantitative trait methods in mapping genes involved in complexly inherited illnesses such as schizophrenia, in that relatives without the illness phenotype nevertheless manifest quantitative trait markers of the illness to varying degrees and are thus informative for tests of genetic linkage and association.

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