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The *FEZ1* Gene Shows No Association to Schizophrenia in Caucasian or African American Populations

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Schizophrenia is a complex psychiatric disorder with both genetic and environmental components and is thought to be in part neurodevelopmental in origin. The *DISC1* gene has been linked to schizophrenia in two independent Caucasian populations. The DISC1 protein interacts with a variety of proteins including FEZ1, the mammalian homolog of the *Caenorhabditis elegans* unc-76 protein, which is involved in axonal outgrowth. Variation at the *FEZ1* gene has been associated with schizophrenia in a large Japanese cohort. In this study, nine SNP markers at the *FEZ1* locus were genotyped in two populations. A North American Caucasian cohort of 212 healthy controls, 178 schizophrenics, 79 bipolar disorder, and 58 with schizoaffective disorder, and an African American cohort of 133 healthy controls, 162 schizophrenics, and 28 with schizoaffective disorder. No association to schizophrenia, bipolar disorder or schizoaffective disorder was found for any of the nine markers typed in these populations at the allelic or the genotypic level. Additionally no association was found in either population between specific haplotypes and any of the psychiatric disorders. Variation at the *FEZ1* locus does not play a significant role in the etiology of schizophrenia, bipolar disorder or schizoaffective disorder in North American Caucasian or African American populations.

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INTRODUCTION

Schizophrenia (OMIM 181500) is debilitating psychiatric disorder that affects more than 29 million individuals worldwide (Barbato, 1998). It is a heritable disorder with a complex transmission pattern as evidenced from family and twin studies (Berry *et al*, 2003). The disorder has been linked to multiple chromosomal regions and several findings now appear to have been widely replicated, including Neuregulin, *COMT*. and *DISC1* (Stefansson *et al*, 2004; Shirts and Nimgaonkar, 2004; Hennah *et al* 2003; Hodgkinson *et al*, 2004).

Both *D*isrupted *i*n *Sc*hizophrenia 1 and 2 (*DISC1* and *DISC2*, OMIM 605210, and OMIM 606271) were observed to be disrupted by a balanced (1;11) (q42.1;q14.3) translocation in a large Scottish family displaying a broad spectrum of psychiatric disorders, in particular, schizophrenia and major depression (Millar *et al*, 2000, 2001; Blackwood *et al*, 2001). Although analysis of other independent Scottish families with schizophrenia and bipolar disorder failed to show significant association between disease and these two genes (Devon *et al*, 2001), association to schizophrenia was shown in a Finnish population (Hennah *et al*, 2003) and to schizophrenia, schizoaffective disorder and bipolar disorder in a North American Caucasian population (Hodgkinson *et al*, 2004). The region containing the two DISC genes also showed linkage to schizophrenia and schizoaffective disorder in Taiwanese families (Hwu *et al*, 2003).

The *DISC1* gene codes for a large (854 amino acid) protein of unknown function, with no homology to known proteins (Millar *et al*, 2000). DISC1 has been shown to occupy a variety of subcellular compartments and to exist in multiple isoforms generated by alternative splicing of the mRNA transcript (Millar *et al*, 2003; Morris *et al*, 2003; Ozeki *et al*, 2003; Brandon *et al*, 2004; James *et al*, 2004). Two-hybrid experiments in yeast systems have shown the DISC1 protein to interact with a large number of different proteins from a wide variety of different protein (Morris *et al*, 2003; Ozeki *et al*, 2003; Brandon *et al*, 2004; Miyoshi *et al*, 2004). The DISC2 gene is thought to encode a nontranslated mRNA

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antisense to *DISC1*, and may have a regulatory function (Millar *et al*, 2000).

FEZ1 protein (OMIM 604825), was identified as a DISC1 interacting partner in a yeast 2-hybrid screen of an adult human brain library (Miyoshi *et al*, 2003). FEZ1 is the ortholog of the *Caenorhabditis elegans* unc-76 gene (Horvitz, 1997). Worms carrying mutations in the *unc-76* gene show severe abnormalities in movement and in elongation of axons along other axonal surfaces (but not non-neuronal surfaces) during development. This process, known as fasciculation, enables axons to associate in specific bundles and is likely to play a major role in determination of neural structures.

Association between SNP polymorphisms in the *FEZ1* gene and schizophrenia has been shown in a Japanese cohort (Yamada *et al*, 2004). This association was shown not to have arisen due to population admixture. In this study, we have looked at two ethnically distinct North American populations for association of schizophrenia to the *FEZ1* locus. In both of these populations, linkage of the FEZ-interacting partner DISC1 to schizophrenia was observed (Hodgkinson *et al*, 2004 and unpublished results), data that replicated findings in a Finnish cohort (Hennah *et al*, 2003).

MATERIALS AND METHODS

Subject Recruitment and Diagnosis

Subjects were recruited from the clinical services of the Zücker Hillside Hospital, a division of the North Shore—Long Island Jewish Health System (NSLIJHS), in Glen Oaks, NY, USA, and from the Psychiatry Service, Department of Veterans Affairs, New Jersey Health Care System in East Orange, NJ, USA. These studies were performed in a manner that fully complies with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the relevant Institutional Review Boards. After providing written informed consent to participate in the study, each subject was assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders using method previously described (Hodgkinson *et al*, 2004). The Caucasian sample of 521 individuals was comprised of 212 healthy controls, 178 schizophrenics, 79 bipolar disorder patients, and 58 patients with schizoaffective disorder. The African American sample, totaling 323 individuals, contained 133 healthy controls, 162 diagnosed schizophrenics, and 28 with schizoaffective disorder.

Genotyping

Nine SNP loci spanning the 61 kb *FEZ1* gene region were genotyped by 5′ exonuclease assay, using the primer-probe sets available as Taqman® Assays-on-Demand (Applied Biosystems, Foster City, CA, USA). Genomic DNA (5 ng) was amplified on a 9700 thermocycler (ABi) using a program with an initial incubation at 95°C for 10 min followed by 40 cycles of 92°C (15 s) and 60°C (1 min). At the end point of amplification, genotypes were discriminated using SDS 2.0 software on an Applied Biosystems 7900 Analyzer. Genotype completion rates for all markers were $\geqslant$98.9%. Genotyping accuracy was assessed by regenotyping one in six samples, randomly selected, revealing an overall accuracy $>$99%. Haplotype block structure was determined using the HAPLOVIEW program (Barrett *et al*, 2005). Blocks were defined according to the criteria of Gabriel *et al* (2002) but the criterion for pairwise LD between markers was relaxed from $D'>95\%$ to $D'>85\%$ within a block. Haplotypes were assigned to individuals using PHASE 2.02 (Stephens *et al*, 2001; Stephens and Donnelly, 2003).

Statistical Methods

Nonparametric testing for significance values for allelic and genotypic association was performed using a standard χ^2-test. Haplotype association was evaluated using the more stringent Fisher Exact Test because observed haplotype frequencies sometimes equaled zero. Deviation from Hardy–Weinberg distribution of alleles was determined using the Haploview program and the *p*-values are shown in Table 1. Logistic regression was used to test for interaction between genotypes for each FEZ1 SNP and *DISC1* risk/protective haplotypes as described in Cordell (2002) and Norton *et al* (2006). Individuals were assigned a score of 1, 0.5, or 0 according to the number of copies of *DISC1* haplotypes significantly associated with schizophrenia and/or schizoaffective disorders in Hodgkinson *et al* (2004). Analysis were conducted separately for each diagnostic category and for each of the three *DISC1* haploblocks previously linked to schizophrenia and/or schizoaffective disorders.

RESULTS

No *FEZ1* SNP showed association to either schizophrenia or schizoaffective disorder in Caucasians (Table 1) or to schizophrenia in African Americans (Table 2), at either the allelic or genotypic level. The markers tested include rs559668 and rs597570, both of which had shown genotypic association in the Japanese study. Also, none of these markers showed association to bipolar disorder in Caucasians. All nine *FEZ1* markers are in strong linkage disequilibrium and reside in a single haplotype block (Figure 1). As expected there was increased haplotype diversity in the African American population compared to the Caucasian group. Moreover the minor allele frequencies differed greatly between the populations (Table 3). There was no significant association between schizophrenia and any haplotype in either population (Table 4). Nor was there any association to schizoaffective disorder or bipolar disorder in Caucasians. In the Japanese population, schizophrenia was associated with homozygosity of the A allele at the rs559668 and rs597570 loci. The frequency of these alleles was higher in Caucasians (18%) and African Americans (29 and 21%) than in the original Japanese cohort (2%) and in an American Asian group (2%). In the Japanese study, association to schizophrenia was found to homozygosity for the minor alleles of the two tightly linked markers which are separated by over 200 kb. In that study, seven affected individuals but no controls were homozygous for the two markers. In our African American cohort, we found nine of 178 diagnosed schizophrenics and 13 of 212

Table 1 Allelic and Genotypic Association of FEZ1 SNPs in Caucasians, Comparing Healthy Controls (HC), Schizophrenics (SZ), Schizoaffective Disorder (SA), and Bipolar Disorder (BP)

Marker	NCBI position (Build 35)	Samples	Allele		*p*-value	Genotype			*p*-value	HW variation *p*-value
rs2702009	124 870 051		C	T		C/C	C/T	T/T		
		HC	314 (0.67)	156 (0.33)		110 (0.52)	85 (0.40)	17 (0.08)		0.909
		SZ	256 (0.72)	100 (0.28)	0.994	94 (0.53)	68 (0.38)	16 (0.09)	0.900	
		SA	84 (0.74)	30 (0.26)	0.711	31 (0.54)	22 (0.39)	4 (0.07)	0.934	
		BP	109 (0.69)	49 (0.31)	0.485	38 (0.48)	33 (0.42)	8 (0.10)	0.779	
rs559668	124 862 986		C	T		C/C	C/T	T/T		
		HC	77 (0.18)	345 (0.82)		8 (0.04)	61 (0.29)	142 (0.67)		0.901
		SZ	68 (0.19)	286 (0.81)	0.732	8 (0.05)	52 (0.29)	117 (0.66)	0.927	
		SA	19 (0.16)	97 (0.84)	0.642	0 (0.00)	19 (0.33)	39 (0.67)	0.297	
		BP	27 (0.17)	131 (0.83)	0.746	1 (0.01)	25 (0.32)	53 (0.67)	0.515	
rs597570	124 856 682		A	T		A/A	A/T	T/T		
		HC	75 (0.18)	345 (0.82)		7 (0.03)	61 (0.29)	142 (0.68)		1.0
		SZ	69 (0.19)	287 (0.81)	0.586	9 (0.05)	51 (0.29)	118 (0.66)	0.696	
		SA	19 (0.16)	97 (0.84)	0.711	0 (0.00)	19 (0.33)	39 (0.67)	0.342	
		BP	25 (0.16)	133 (0.84)	0.564	2 (0.03)	21 (0.27)	56 (0.71)	0.848	
rs10893385	124 854 131		A	G		A/A	A/G	G/G		
		HC	222 (0.53)	200 (0.47)		57 (0.27)	108 (0.51)	46 (0.22)		0.862
		SZ	180 (0.51)	174 (0.49)	0.625	49 (0.28)	82 (0.46)	46 (0.26)	0.551	
		SA	65 (0.56)	51 (0.44)	0.512	18 (0.31)	29 (0.50)	11 (0.19)	0.799	
		BP	79 (0.50)	79 (0.50)	0.576	22 (0.28)	35 (0.44)	22 (0.28)	0.481	
rs1365410	124 844 322		C	G		C/C	C/G	G/G		
		HC	1 (0.002)	423 (0.998)		0 (0.00)	1 (0.005)	211 (0.99)		1.0
		SZ	3 (0.01)	353 (0.99)	0.237	0 (0.00)	3 (0.02)	175 (0.98)		
		SA	1 (0.01)	115 (0.99)	0.325	0 (0.00)	1 (0.02)	57 (0.98)		
		BP	1 (0.01)	115 (0.99)	0.467	0 (0.00)	1 (0.01)	78 (0.99)		
rs12223186	124 836 849		A	G		A/A	A/G	G/G		
		HC	179 (0.42)	245 (0.58)		37 (0.17)	105 (0.50)	70 (0.33)		0.575
		SZ	132 (0.38)	218 (0.62)	0.203	27 (0.15)	78 (0.45)	70 (0.40)	0.363	
		SA	46 (0.40)	70 (0.60)	0.620	10 (0.17)	26 (0.45)	22 (0.38)	0.767	
		BP	57 (0.36)	101 (0.64)	0.180	11 (0.14)	35 (0.44)	33 (0.42)	0.367	
rs2241514	124 831 236		C	T		C/C	C/T	T/T		
		HC	173 (0.41)	251 (0.59)		35 (0.17)	103 (0.49)	74 (0.35)		0.76
		SZ	137 (0.38)	219 (0.62)	0.510	27 (0.15)	83 (0.47)	68 (0.38)	0.788	
		SA	46 (0.40)	70 (0.60)	0.824	10 (0.17)	26 (0.45)	22 (0.38)	0.875	
		BP	58 (0.37)	100 (0.63)	0.369	11 (0.14)	36 (0.46)	32 (0.41)	0.654	
rs2907228	124 821 283		A	T		A/A	A/T	T/T		
		HC	372 (0.88)	52 (0.12)		161 (0.76)	50 (0.24)	1 (0.005)		0.762
		SZ	305 (0.86)	51 (0.14)	0.804	134 (0.77)	37 (0.21)	4 (0.02)	0.259	
		SA	103 (0.89)	11 (0.11)	0.441	46 (0.81)	11 (0.19)	0 (0.00)	0.765	
		BP	133 (0.84)	25 (0.16)	0.940	59 (0.78)	15 (0.20)	2 (0.02)	0.235	

Table 1 Continued

Marker	NCBI position (Build 35)	Samples	Allele		*p*-value	Genotype			*p*-value	HW variation *p*-value
rs10893380	124 816 884		A	G		A/A	A/G	G/G		
		HC	47 (0.12)	355 (0.88)		1 (0.005)	45 (0.22)	155 (0.77)		0.908
		SZ	47 (0.13)	309 (0.87)	0.536	4 (0.02)	39 (0.22)	135 (0.76)	0.450	
		SA	10 (0.09)	104 (0.91)	0.380	0 (0.00)	10 (0.18)	47 (0.82)	0.627	
		BP	20 (0.13)	138 (0.87)	0.742	2 (0.03)	16 (0.20)	61 (0.77)	0.783	

Table 2 Allelic and Genotypic Association of FEZ1 SNPs in African Americans Comparing Healthy Controls (HC), and Schizophrenics (SZ)

Marker	NCBI position (Build 35)	Samples	Allele		*p*-value	Genotype			*p*-value	HW variation *p*-value
rs2702009	124 870 051		C	T		C/C	C/T	T/T		
		HC	212 (0.62)	128 (0.38)		67 (0.39)	78 (0.46)	25 (0.15)		0.498
		SZ	193 (0.60)	127 (0.40)	0.962	56 (0.35)	81 (0.51)	23 (0.14)	0.363	
rs559668	124 862 986		C	T		C/C	C/T	T/T		
		HC	98 (0.28)	244 (0.72)		14 (0.08)	74 (0.43)	85 (0.49)		0.515
		SZ	98 (0.31)	220 (0.69)	0.411	12 (0.08)	74 (0.47)	73 (0.46)	0.369	
rs597570	124 856 682		A	T		A/A	A/T	T/T		
		HC	78 (0.23)	262 (0.77)		8 (0.05)	62 (0.36)	100 (0.59)		0.632
		SZ	75 (0.24)	243 (0.76)	0.858	10 (0.06)	55 (0.35)	94 (0.59)	0.812	
rs10893385	124 854 131		A	G		A/A	A/G	G/G		
		HC	97 (0.29)	241 (0.71)		17 (0.10)	63 (0.37)	89 (0.53)		0.267
		SZ	85 (0.27)	235 (0.73)	0.450	11 (0.07)	63 (0.39)	86 (0.54)	0.262	
rs1365410	124 844 322		C	G		C/C	C/G	G/G		
		HC	28 (0.08)	306 (0.92)		2 (0.01)	24 (0.14)	141 (0.84)		0.553
		SZ	27 (0.08)	293 (0.92)	0.576	2 (0.01)	23 (0.14)	135 (0.84)	0.531	
rs12223186	124 836 849		A	G		A/A	A/G	G/G		
		HC	88 (0.28)	250 (0.74)		11 (0.07)	66 (0.39)	92 (0.54)		0.937
		SZ	88 (0.28)	228 (0.72)	0.877	12 (0.08)	64 (0.41)	82 (0.52)	0.835	
rs2241514	124 831 236		C	T		C/C	C/T	T/T		
		HC	91 (0.27)	245 (0.73)		12 (0.07)	67 (0.40)	89 (0.53)		0.825
		SZ	88 (0.28)	232 (0.72)	0.911	12 (0.08)	64 (0.40)	84 (0.53)	0.964	
rs2907228	124 821 283		A	T		A/A	A/T	T/T		
		HC	313 (0.93)	25 (0.07)		146 (0.86)	21 (0.12)	2 (0.01)		0.456
		SZ	285 (0.91)	27 (0.09)	0.848	131 (0.84)	23 (0.15)	2 (0.01)	0.982	
rs10893380	124 816 884		A	G		A/A	A/G	G/G		
		HC	21 (0.06)	307 (0.94)		0 (0.00)	21 (0.13)	143 (0.87)		1.0
		SZ	26 (0.08)	290 (0.92)	0.716	2 (0.01)	22 (0.14)	134 (0.85)	0.924	

healthy controls homozygous for the same two A alleles. In the Caucasian group, we found eight of 178 diagnosed schizophrenics to be homozygous for the same two A alleles, seven of 212 healthy controls, one of 70 diagnosed with bipolar disorder and 0 of 58 diagnosed with schizoaffective disorder. Thus, we found no increase in homozygosity. Analysis of homozgosity at the diplotype level showed no association in either the Caucasian or

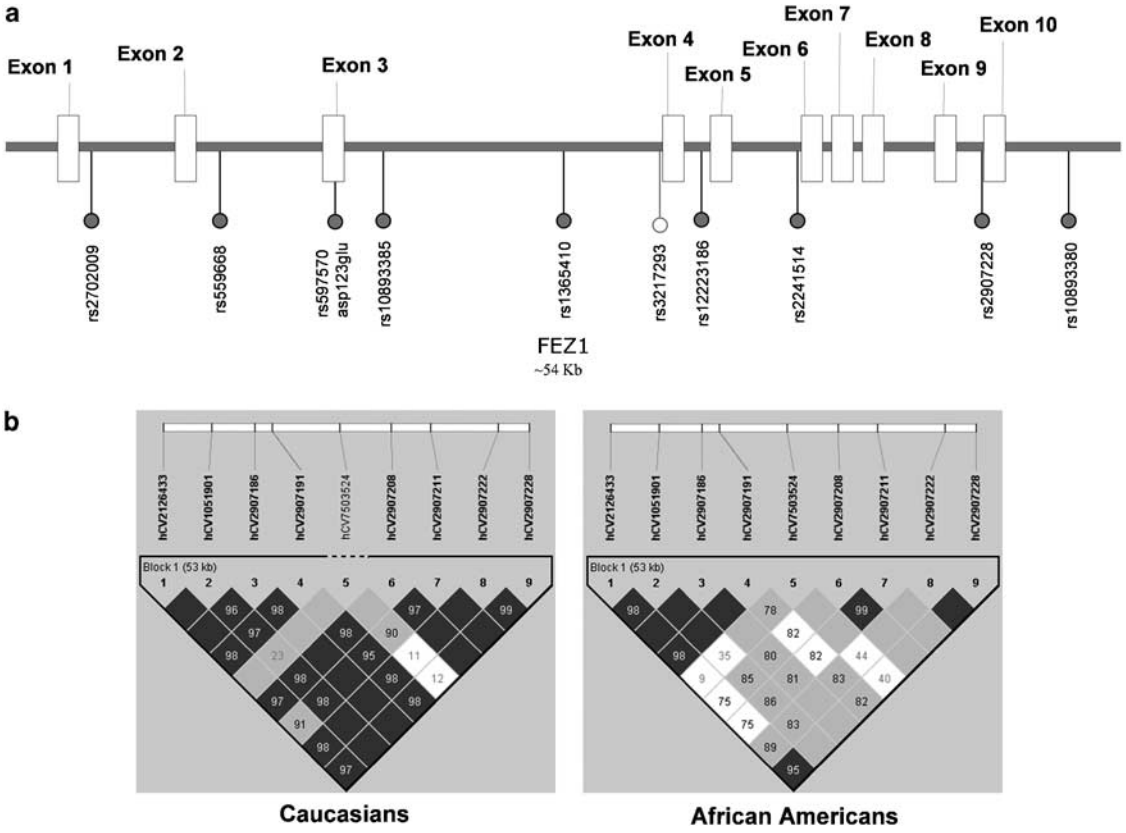

Figure 1 (a) Diagram of the human *FEZ1* gene showing the relative positions of exons and the SNP markers used (shaded circles). Marker rs3217293 from Yamada *et al* (*Biol Psychiatry* 2004; **56**: 683–690.) shown with open circle. (b) Haplotype block structure of the FEZ1 locus in Caucasians and African Americans.

African American populations by Fisher Exact test (data not shown). Analysis of a small group of African Americans diagnosed with schizoaffective disorder ($n = 28$) did show a genotype association ($p = 0.038$) at marker rs559668 and a haplotype association ($p = 0.025$) for the 112222212 haplotype. Neither of these associations remained significant after correction for multiple testing.

The failure to detect association of schizophrenia to FEZ1 haplotypes is unlikely to arise due to lack of power in the data set. For schizophrenics both the Caucasian and African American datasets have sufficient power to detect significance ($p = 0.05$) for frequency differences of 1.2 at 90% confidence, and for frequency differences of 1.6 at 99% confidence. For schizoaffective disorder the Caucasian dataset has sufficient power to detect significance ($p = 0.05$) for frequency differences of 2.1 at 90% confidence, and of 2.8 at 99% confidence.

Given the biological evidence of interaction between *DISC1* and *FEZ1*, logistic regression was performed to test whether variation at *FEZ1* contributed to the risk of schizophrenia and/or schizoaffective disorders depending on *DISC1* disease-associated haplotypes. For schizophrenia no significant interaction was observed for any FEZ1 SNP to *DISC1* haplotypes for Haploblocks 1, 2, or 3. Significant *p*-values were obtained for interaction of rs2702009 ($p = 0.001$) and rs10893385 ($p = 0.03$) with the common protective *DISC1* haplotype previously shown to be under represented in Caucasian women with schizoaffective disorder. These data, however, should be treated with extreme caution due to the relatively low number of affected individuals in the analysis ($n = 57$) and the elevated number of statistical tests performed ($n = 54$). Based on these data it appears unlikely that any significant GXG interaction between FEZ1 and DISC1 exists.

DISCUSSION

An important genetic component in the etiology of schizophrenia is thought to be a neurodevelopmental defect (Lewis and Levitt, 2002) that either occurs in latent form early in development (Marenco and Weinberger, 2000) or at a later stage during brain maturation in adolescence (Feinberg, 1982), the time at which early symptoms begin to appear. FEZ1 when expressed in *unc-76* mutant worms can partially rescue the locomotor phenotype suggestive of a shared developmental function (Horvitz, 1997) and suggesting that these sequence-similar proteins are orthologs. Studies in primates and rodents demonstrate that FEZ1 and DISC1 have overlapping spatial and temporal expression patterns (Austin *et al*, 2004; Honda *et al*, 2004; Inoue *et al*, 2004; Schurov *et al*, 2004). Both proteins are expressed in the pyramidal neurons of the developing hippocampus, the cerebral neocortex and the olfactory bulb. Moreover disruption of the DISC1/FEZ1 interaction inhibits DISC1-stimulated neurite outgrowth in PC12 cells (Miyoshi *et al*, 2003). Together these data make *FEZ1* a compelling candidate gene. Our data, however, indicates no strong role of variation at the *FEZ1* locus in schizophrenia in Caucasian

or African American populations. The asp[123] residue is conserved between humans and rodents. This residue lies within a region shown to be responsible for the axonal targeting of the unc-76 protein (Horvitz, 1997) and it has been suggested that the glutamate substitution affects the subcellular distribution of the FEZ1 protein (Miyoshi *et al*, 2003). The asp[123] glu transition (rs597970) is a conservative substitution and this residue is not conserved in either *Gallus gallus* (his) or in *C. elegans* (thr) suggesting that it is unlikely to have a functional role in axonal targeting of the mature FEZ1 protein. Our findings do not exclude the possibility that a functional polymorphism unique to the Japanese population exists in strong LD with rs559668 and rs597570 which when present in the homozygous state results in an increased predisposition to the development of schizophrenia. Sequencing of the Japanese schizophrenics homozygous for the two associated markers may identify the relevant polymorphism, which could lie either in the axonal targeting N-terminus, or the DISC1-interacting C-terminus of FEZ1.

Table 3 Minor Allele Frequencies in Three North American Populations

	Minor allele frequency		
Marker	**Caucasian ($n=633$)**	**African American ($n=428$)**	**Asian ($n=44$)**
rs2702009			
C>T	0.28	0.38	0.43
rs559668			
T>C	0.18	0.29	0.02
rs597570			
T>A	0.18	0.21	0.02
rs10893385			
A>G	0.48	0.29*	0.45
rs1365410			
G>C	0.01	0.08	0.02
rs12223186			
G>A	0.39	0.28	0.38
rs2241514			
T>C	0.39	0.28	0.35
rs2907228			
A>T	0.12	0.08	0.36
rs10893380			
G>A	0.12	0.07	0.34

*G>A

Although association has been shown between schizophrenia and *DISC1* in two independent Caucasian populations including the Caucasians studied here, no association was found in a case/control study involving $\geqslant$1000 individuals from Japan (Kockelkorn *et al*, 2004). This suggests that variation at the *DISC1* locus may play no role in the etiology of schizophrenia in the Japanese population. It would, therefore, be hardly surprising that the converse were found for other loci. Schizophrenia and schizophrenia spectrum disorders are complex diseases showing variability in many features in terms of symptoms, age of onset and genetics. Certainly the clinical heterogeneity coupled to the number and diversity of genes reported to be associated with schizophrenia might support the idea that the clinical entity known as schizophrenia could arise from dysregulation of different molecular pathways or by disruption of a common pathway at multiple different points.

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Table 4 Haplotype Associations in African American and Caucasians Comparing Schizophrenics (SZ), Schizoaffective Disorder (SA), and Bipolar Disorder (BP)

	Caucasians							African Americans			
Haplotype	**Controls ($n=212$)**	**SZ ($n=178$)**	***p*-value**	**SA ($n=178$)**	***p*-value**	**BP ($n=79$)**	***p*-value**	**Controls ($n=166$)**	**SZ ($n=161$)**	***p*-value**	**Haplotype**
111222212	73 (0.17)	67 (0.19)	0.575	19 (0.16)	0.890	24 (0.15)	0.618	73 (0.22)	73 (0.23)	0.391	111222212
122122212	46 (0.11)	46 (0.13)	0.375	19 (0.16)	0.109	23 (0.15)	0.248	18 (0.05)	8 (0.02)	0.161	122122212
122121112	169 (0.40)	132 (0.37)	0.460	45 (0.39)	0.915	55 (0.35)	0.292	78 (0.23)	75 (0.23)	0.713	122121112
222222212	65 (0.15)	47 (0.13)	0.414	19 (0.16)	0.774	28 (0.18)	0.525	92 (0.27)	87 (0.27)	0.860	222222212
222222221	52 (0.12)	45 (0.13)	0.913	11 (0.09)	0.514	19 (0.12)	0.999	14 (0.04)	16 (0.05)	0.855	222222221
112222212	—	—	—	—	—	—	—	8 (0.02)	8 (0.02)	0.999	112222212
112212212	—	—	—	—	—	—	—	15 (0.04)	13 (0.04)	0.878	112212212
122222212	—	—	—	—	—	—	—	16 (0.05)	11 (0.03)	0.999	122222212
222212221	—	—	—	—	—	—	—	11 (0.03)	10 (0.03)	0.673	222212221

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