RASD2, *MYH9*, and *CACNG2* Genes at Chromosome 22q12 Associated with the Subgroup of Schizophrenia with Non-Deficit in Sustained Attention and Executive Function

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Background: In a previous linkage study of schizophrenia that included Taiwanese samples, the marker D22S278 (22q12.3) was significantly linked to schizophrenia ($p = .001$).

Methods: We conducted fine mapping of the implicated genomic region, with 47 validated single nucleotide polymorphism (SNP) markers around 1 Mb of D22S278, in a Taiwanese sample of 218 pedigrees with at least 2 siblings affected with schizophrenia. We examined the association of these SNPs and their haplotypes with schizophrenia and with subgroups defined by the presence and absence of deficits in sustained attention as assessed by undegraded and degraded continuous performance tests (CPTs). We also examined subgroups defined by deficits in categories achieved in the Wisconsin Card Sort Test (WCST).

Results: Three of five candidate vulnerability genes (*RASD2, APOL5, MYH9, EIF3S7,* and *CACNG2*), which had marginally significant associations with schizophrenia, had significant associations with schizophrenic patients who did not have deficits in sustained attention on the undegraded CPT (*RASD2* gene SNP rs736212; $p = .0008$ with single locus analysis) and the degraded CPT (*MYH9* gene haplotype 1-1-1-1 of SNP rs3752463 - rs1557540 - rs713839 - rs739097; $p = .0059$ with haplotype analysis). We also found a significant association for patients who showed no deficits in executive function as measured by categories achieved in the WCST (*CACNG2* gene haplotype 2-1-1-1 of SNP rs2267360 - rs140526 - rs1883987 - rs916269; $p = .0163$ with haplotype analysis).

Conclusions: The genes *RASD2*, *MYH9*, and *CACNG2* might be vulnerability genes for neuropsychologically defined subgroups of schizophrenic patients.

Key Words: *CACNG2*, candidate gene, endophenotype, *MYH9*, *RASD2*, schizophrenia

Schizophrenia is a complex disorder with a heritability of .7–.85 (1). The long arm of chromosome 22 has been reported to harbor several susceptibility regions for schizophrenia (2–6). On chromosome 22, genetic markers that show significant linkage to schizophrenia include D22S278 (22q12.3) (7–9), D22S283 (22q12.3) (10,11), D22S279 (22q13.1) −276 (22q13.2) (12), and D22S683 (22q12.3) (5). The Schizophrenia Collaborative Linkage Group analyses, which included some Taiwanese samples, found significant linkage evidence ($p = .001$) to schizophrenia for the D22S278 marker on chromosome 22q12.3 (7). This suggested that there are schizophrenia vulnerability genes in the 22q12.3 region near D22S278.

Given the heterogeneous nature of the disorder and inconsistent findings from linkage studies of schizophrenia, the use of endophenotypes to refine the schizophrenia phenotype has been advocated (13). Both sustained attention deficit and executive dysfunction have substantial empirical evidence as potential endophenotypic markers. First, sustained attention deficits measured by the continuous performance test (CPT) (14) have been shown to be present not only in schizophrenic patients but also in subjects with schizotypal personality disorder and in nonpsychotic relatives of schizophrenic patients (15,16). The d′ score is a CPT measure of sustained attention ability. In prior work, schizophrenia patients with a Z score below −2.5 were categorized as having deficits in sustained attention. For these schizophrenic patients, the recurrence risk ratio for schizophrenia among relatives of all schizophrenic patients is approximately three times more than those with non-deficit group (17,18).

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Table 1. Distribution of Families by the Number of Siblings and Parents Genotyped

	Parents Genotyped/Family			
Sibs Genotyped/Family	0	1	2	Total Families
1	0	0	2	2
2	9	15	74	98
3	8	78	17	103
4	2	9	2	13
5	0	1	1	2
Total Families	19	103	96	218

Sibs, siblings.

Executive functioning as measured by the Wisconsin Card Sorting Test (WCST) (19) is known to be impaired in schizophrenic patients (20,21) and their first degree relatives (22). Given these data, we hypothesized that CPT and WCST test performance would be useful as endophenotypes for schizophrenia and might be helpful in addressing the heterogeneity of the disorder in genetic studies.

This study was designed to assess evidence of association with schizophrenia of single nucleotide polymorphism (SNP) located near the D22S278 region. Our first hypothesis was that SNPs in functional genes near the D22S278 that were expressed in the brain would be significantly associated with schizophrenia. The second hypothesis was that any association of SNPs or haplotypes with schizophrenia would become more significant in subgroups of patients selected for neuropsychological endophenotypes.

Methods and Materials

Subjects

This research project was approved by the Institutional Review Board of National Taiwan University Hospital. After the study subjects provided written informed consent, they underwent a diagnostic assessment, and blood samples were collected for the extraction of genomic DNA. The subjects were recruited from two programs: the multidimensional psychopathology study of schizophrenia (MPSS) (23) from 1993 to 2001, and the Taiwan schizophrenia linkage study (TSLS) (24) from 1998 to 2002. The 86 families from the MPSS project were interviewed by research psychiatrists with the Psychiatrist Diagnostic Assessment (PDA) (25). The 132 families from the TSLS project were interviewed by research assistants with the Mandarin Chinese version of the Diagnostic Interview for Genetic Studies (26). The final diagnoses of both MPSS and TSLS subjects were made by integrating either the PDA or Diagnostic Interview for Genetic Studies data and clinical information from the medical chart records with the Specialist Diagnostic Assessment Sheet, based on the criteria of the DSM-IV. The study samples included 218 schizophrenic nuclear families with at least two affected siblings. A total of 864 subjects were genotyped (Table 1). Within these 218 families, 216 had at least two siblings genotyped, 103 had one parent genotyped, and 96 had both parents genotyped. There were a total of 461 patients with schizophrenia; their mean age was 34.5 (± 9.4 SD) years, and 62.5% were men. The mean age at onset was 22.2 (± 6.2 SD) years. The mean age of the unaffected subjects was 52.6 (± 15.3 SD) years, and 47.5% were men. All subjects were Han Chinese.

Of the 864 individuals in this study, 579 underwent an undegraded CPT test and 555 underwent a degraded CPT test. Meanwhile, 554 subjects underwent a WCST assessment; 172 families (78.9%) received an undegraded CPT test, and 166 families (76.2%) received a degraded CPT and WCST.

The heritabilities, as calculated by the Quantitative Transmission Disequilibrium Test (QTDT) (27) were .48 ($p = .005$) for the undegraded d′ score and .42 ($p = .01$) for the degraded d′ score. The heritability for categories achieved (CAT) on the WCST was 0 ($p = 1$). The average Z scores for both the CPT and WCST scores in affected individuals were between −2 and −2.5. As the cutoff for the adjusted Z score decreased from −2.5 to −3.0, the risk ratio increased for both the undegraded d′ score (from 10.1 to 18.8 for parents and from 10.0 to 16.7 for siblings) and the degraded d′ score (from 12.4 to 102.7 for parents and from 8.6 to 72.0 for siblings) (18). Therefore, we set the cutoff at −2.5 to create a binary classification of the family as "deficit" or "non-deficit" (Table 2).

Neuropsychological Assessment

CPT. A CPT machine from Sunrise System (v. 2.20; Pembroke, Massachusetts) was used to assess sustained attention. The procedure has been described in detail elsewhere (28). Briefly, numbers from 0 to 9 were randomly presented for 50 msec each at a rate of one/sec. Each subject underwent 2 CPT sessions: the undegraded 1-9 task and the 25% degraded 1-9 task. Subjects were asked to respond whenever the number "9" was preceded by the number "1" on the screen. During the 25% degraded session, a pattern of snow was used to toggle the background and foreground so that the image was visually distorted. We used the d′ score as our measure of the individual's ability to discriminate target stimuli from non-target stimuli. This was derived from the hit rate (probability of the response to target trials) and the false-alarm rate (probability of response to non-target trials) (29).

In this study, the Z score of d′ on the CPT was used as the endophenotype indicator for schizophrenia: if one of the affected siblings in the family had a CPT deficit, the family was classified as a CPT deficit family. If no affected siblings in the family had a Z score of $d' < -2.5$, the family was classified as CPT non-deficit. We found CPT deficits in 454 (96 families) subjects for the undegraded group and in 487 subjects (103 families) for the degraded group. We did not find CPT deficits in 345 (75 families) subjects for the undegraded group and in 287 (62 families) subjects for the degraded group.

WCST. We used a computerized version of the WCST (30) that had been used in a previous study in a Taiwanese popula-

Table 2. Descriptive Data of the Performances of the Neuropsychological Tests Expressed as Adjusted Z Scores

	Affected Individuals *n* (mean ± SD)	Unaffected Individuals *n* (mean ± SD)	All Individuals *n* (mean ± SD)
Undegraded CPT	311 (−2.2956 ± 2.1371)	268 (−1.0227 ± 1.7572)	579 (−1.7064 ± 2.0687)
Degraded CPT	299 (−2.2286 ± 1.6198)	256 (−1.2340 ± 1.5582)	555 (−1.7698 ± 1.6659)
CAT of WCST	297 (−3.0816 ± 1.0807)	257 (−1.7311 ± 1.3881)	554 (−2.4551 ± 1.4041)

CPT, continuous performance test; CAT, categories achieved; WCST, Wisconsin card sorting test.

tion (31). During the WCST, subjects were required to match 128 response cards to 4 stimulus cards in one of three dimensions (color, form, or number) by pressing one of the one to four number keys on the computer keyboard. Subjects were not informed of the correct sorting principle and were not told when the principle would shift during the test, but they were given feedback ("right" or "wrong") on the screen after each trial. In this study, the measure of the WCST (32) for genetic association analyses was CAT: the number of times that 10 consecutive correct responses were made, reflecting overall success. This indicator has been found to be impaired in schizophrenic probands (20,21) and in first-degree relatives of schizophrenic probands (22). On the basis of familial distributions of CAT indicators in this study sample, schizophrenic patients with a Z score on the CAT of < -2.5 were considered to have a deficit.

Families in which one of the affected siblings had a CAT deficit were classified into the WCST deficit group. Families in which none of the affected siblings had CAT deficits were classified into the WCST non-deficit group. The WCST deficit group (CAT < -2.5) included 637 subjects from 138 families. The WCST non-deficit group (defined by CAT ≥ -2.5) included 133 subjects from 28 families.

SNP Selection Criteria and Validation

A total of 94 SNPs for each brain-expressed gene were selected in the 2-centimorgan (cM) region around D22S278 from the UCSC Genome Bioinformatics database (http://genome.ucsc.edu/index.html?org=Human&db=hg17&hgsid=100327650) and from SNP Finder (http://snpper.chip.org/bio/snpper-enter). The inter-SNP marker distance ranged from 6.7 to 405 kb, with an average of 34 kb. According to the relative position of the brain-expressed functional genes, we first selected SNPs from exons (including the 5′-untranslated and 3′-untranslated regions) and then from promoter regions (CpG island). If such SNPs were available, we selected SNPs from introns within functional genes. We used 31 trios and 2 independent individuals for a total of 94 individuals to validate the 94 SNPs from a public database (http://snpper.chip.org/bio/snpper-enter).

SNP Genotyping

All SNP genotyping was performed by using the robust method of matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) (33,34). Primers and probes flanking the SNPs were designed with SpectroDESIGNER software (Sequenom, San Diego, California). A DNA fragment (100–300 bp) encompassing the SNP site was amplified with polymerase chain reaction (PCR) (GeneAmp 9700 thermocycler; Applied Biosystems, Foster City, California) according to the manufacturer's instructions.

After unincorporated deoxynucleotide triphosphate was removed from the PCR product and the shrimp alkaline phosphatase (SAP) was inactivated, primer extension was performed by adding the probe (Thermo Sequenase; Amersham Pharmacia, Piscataway, New Jersey) and appropriate dideoxynucleotide triphosphate/deoxynucleotide triphosphate mixture, followed by 55 cycles of denaturing at 94°C for 5 sec, annealing at 52°C for 5 sec, and extension at 72°C for 5 sec. Different extension products were differentiated by mass through MALDI-TOF.

Statistical Analysis

To check data quality, PEDCHECK version 1.1 (35) and UNKNOWN version 5.23 (36) were used to check Mendelian inheritance. The procedure ALLELE in SAS/GENETICS release 8.2 (37) was used to test for Hardy-Weinberg equilibrium. Linkage disequilibrium of inter-markers was measured with the coefficient D′ (38), which was also used to define haplotype blocks. A graphic presentation of the block pattern was completed with HAPLOVIEW software (39). An individual's haplotype was inferred with SimWalk2 version 2.86 (40–42), which uses the Markov Chain Monte Carlo algorithm.

Family-based transmission disequilibrium tests were applied to test linkage disequilibrium. Both single-locus and haplotype-based association analyses were carried out with two programs for nuclear family data: haplotype Family Based Association Test (FBAT) version 1.4.1 for affected offspring association analyses (43–45), and TRANSMIT version 2.5.4 for parent to affected offspring association analyses (46). These analyses were performed with the entire sample of schizophrenia subjects and for the subgroups of schizophrenia defined by deficit or non-deficit of neuropsychological functions on the CPT and WCST.

Multiple tests were considered necessary. However, because the SNP markers used in this study were in linkage disequilibrium with one another, the application of Bonferroni's procedure would have been too conservative. Instead, we used Merlin software (47) to simulate the pedigree 1000 times, assuming no linkage/no association on the interested SNP marker identified with the TRANSMIT and FBAT programs. Each empirical p value was adjusted by using the false discovery rate (FDR) algorithm.

Results

SNP Validation

An SNP was considered valid if the minor allele frequency was $> 10\%$. Forty-seven of the 94 originally selected SNPs met the validity criteria. These validated SNPs spanned a 1747-kb SNP from location 33978687 (rs2235145) to 35643996 (rs2899280) around D22S278 marker. They covered 20 known central nervous system–expressed functional genes (*HMG2L1, TOM1, HMOX1, MCM5, RASD2, APOL6, APOL5, RBM9, APOL2, APOL1, MYH9, TXN2, FLJ23322, EIF3S7, CACNG2, RABL4, PVALB, NCF4, CSF2RB*, and *TST*) (Figure 1 in Supplement 1). Forty-five of the 47 validated SNPs were in Hardy-Weinberg equilibrium. The 2 exceptions were rs875400 and rs2899280.

Single-Locus Association Analysis

Analyses were conducted with either a narrow model (DSM-IV schizophrenia only) or broad model (DSM-IV schizophrenia, schizoaffective disorder, and other nonaffective psychotic disorders). Single-locus association analyses with FBAT version 1.4.1 (43,44) showed that three SNP variants in two genes (*RASD2* and *CACNG2*) exhibited a marginally significant association with schizophrenia (Table 3). With the computer program TRANSMIT version 2.5.4 (46), which includes families when parental genotypes were unknown, we found a greater significance for the RASD2 SNP marker rs736212 ($p = .0067$ for the narrow model and $p = .0097$ for the broad model of schizophrenia).

Haplotype-Based Association Analysis

Nine SNP haplotype blocks were identified with two criteria: 1) a significant inter-marker association on the basis of the χ^2 test, and 2) a coefficient $D' > .8$. The nine blocks covered the following SNPs for each gene: rs2235145 - rs1053593 - rs737755 - rs741995 (*HMG2L1*), rs4466 - rs138795 - rs743810 (*TOM1*), rs743813 - rs875400 - rs2252709 (*HMOX1, MCM5*), rs1540297 - rs2899256 - rs2076671 - rs879680 (*APOL5*), rs2481 - rs875726 - rs1009150

Table 3. Single Locus of *RASD2*, and *CACNG2* Associated with Narrow and Broad Phenotype Models of Schizophrenia

	Transmit						FBAT					
	Narrow Model			Broad Model			Narrow Model			Broad Model		
Gene Primer ID	*n*	χ^2	*p*	*n*	χ^2	*p*	*n*	*Z*	*p*	*n*	*Z*	*p*
RASD2 rs736212 (Exon 3)	216	7.360	.0067[a]	218	6.681	.0097[a]	78	2.202	.0276[a]	78	1.976	.0481[a]
CACNG2 rs2283986 (Intron 1)	215	2.485	.1149	218	2.556	.1099	86	1.972	.0486[a]	88	1.997	.0458[a]
CACNG2 rs2092662 (Intron 1)	215	.951	.3295	218	1.761	.1845	63	−1.909	.0561	67	−2.229	.0257[a]

FBAT, Family Based Association Test.
[a] p value $< .05$.

(*MYH9*), rs3752463 - rs1557540 - rs713839 - rs739097 (*MYH9*), rs3747163 - rs1000427 - rs760718 (*TXN2, FLJ23322*), rs140002 - rs2142824 (*EIF3S7*), and rs2267360 - rs140526 - rs1883987 - rs916269 (*CACNG2*) (Figure 2 in Supplement 1).

The results of haplotype-based association analyses, which were carried out with both the TRANSMIT (46) and FBAT (45) programs, are shown in Table 4. Five haplotypes in four genes showed a marginally significant association with schizophrenia: *APOL5* (rs1540297 - rs2899256 - rs2076671 - rs879680), *MYH9* (rs2481 - rs875726 - rs1009150 and rs3752463 - rs1557540 - rs713839 - rs739097), *EIF3S7* (rs140002 - rs2142824), and *CACNG2* (rs2267360 - rs140526 - rs1883987 - rs916269) (Figure 2 in Supplement 1). Significant associations with these haplotypes were observed for both the narrow and broad models of the schizophrenia phenotype. However, only the haplotype (1-1-2-2) in the *CACNG2* gene exhibited a marginally significant association for the narrow model of schizophrenia with both analysis programs. This haplotype also showed a transmission preference for the narrow model of schizophrenia (transmit to non-transmit ratio of 1.824, $p = .0231$).

The five haplotype structures in this study were compared with those in other populations of Japanese, Chinese, Caucasians, and Africans in HapMap through visualization linkage disequilibrium and haplotype maps (39,48). The haplotype structures were very similar to those of the Japanese and Chinese populations but were different from those of the whites and Africans (data not shown).

Association Analysis with Endophenotype Indicators of CPT or WCST

Single-Locus SNP Association Analysis. Five SNP markers were significantly associated with the subgroup of schizophrenia without deficit in sustained attention as measured by the undegraded CPT (Table 5). One SNP (rs2076671) from the *APOL5* gene was significantly associated ($p = .0073$) with the subgroup of schizophrenia with deficit in sustained attention endophenotype as defined by the undegraded CPT. The association of rs736212 of the *RASD2* gene was highly significant ($p = .0008$; $p = .002$ with empirical multiple testing correction). Additionally, six SNPs had a significant association with the subgroup of schizophrenia without deficits in sustained attention as measured by the degraded CPT. Three of these six SNPs from the *MYH9* gene had significant *p* values (range: .0035–.0059; *p* value ranged from .007 to .009 with empirical multiple testing correction). No SNP marker was significantly associated with the subgroup of schizophrenia with attention deficit as measured by the degraded

Table 4. Haplotype Frequencies of *APOL5, MYH9, EIF3S7*, and *CACNG2* Genes Associated with Narrow and Broad Phenotype Models of Schizophrenia

		Transmit (n = 215–216)					FBAT						
			Narrow Model		Broad Model			Narrow Model			Broad Model		
Gene (Haplotype Combination)	HP	HF	χ^2	*p*	χ^2	*p*	HF	*n*	*Z*	*p*	*n*	*Z*	*P*
APOL5													
(rs1540297 - rs2899256 - rs2076671 - rs879680)	1-2-2-1	.061	3.918	.0478−	3.306	.0690–	.060	24	−1.179	.2384–	25	−.925	.3552–
(Promoter-Intron1-Exon 3-3′-end)	2-1-2-2	.014	4.120	.0424+	3.365	.0666+	.014	5	[a]	[a]	6	[a]	[a]
MYH9													
(rs2481 - rs875726 - rs1009150) (Exon 41-Intron 25-Intron 16)	1-2-2	.016	4.618	.0316+	4.972	.0258+	.016	8	[a]	[a]	8	[a]	[a]
MYH9													
(rs3752463 - rs1557540 - rs713839 - rs739097) (Intron 9-Intron 3-Intron 3-Intron 1)	1-1-1-1	.830	4.105	.0428–	2.428	.1192–	.833	47	−1.439	.1501–	48	−.855	.3926–
EIF3S7													
(rs140002 - rs2142824) (Promoter-Promoter)	2-1	.100	3.449	.0633–	3.042	.0812–	.098	35	−2.566	.0102–	35	−2.505	.0122–
CACNG2													
(rs2267360 - rs140526 - rs1883987 - rs916269) (Intron 1-Intron 1-Intron 1-Intron 1)	1-1-2-2	.029	6.435	.0112+	4.728	.0297+	.029	12	2.222	.0262+	12	1.706	.088+

+ indicates risk effect; – indicates protective effect.
HP, haplotype; HF, haplotype frequencies; FBAT, Family Based Association Test.
[a] Not analyzed due to insufficient number of families for study.

Table 5. Significant Association Levels of Single Locus of SNP Markers with the Subgroup of Schizophrenia Defined by the Endophenotype Indicators of CPT and WCST

		CPT			WCST	
Gene	S	UD[a] ≥ −2.5	UD[b] < −2.5	D[c] ≥ −2.5	CAT[d] ≥ −2.5	CAT[e] < −2.5
RASD2	rs736212 (Exon 3)	.0008 + (.002)[f]	ns	ns	ns	.0077 + (.001)[f]
APOL5	rs2076671 (Exon 3)	.0243 − (.029)[f]	.0073 + (.002)[f]	ns	ns	ns
	rs879680 (3′-End)	.0337 − (.037)[f]	ns	ns	ns	ns
	rs1540297 (Promoter)	ns	ns	.0218 + (.018)[f]	ns	ns
MYH9	rs3752463 (Intron 9)	ns	ns	.0059 − (.008)[f]	ns	ns
	rs1557540 (Intron 3)	ns	ns	.0035 − (.009)[f]	ns	ns
	rs713839 (Intron 3)	.0244 − (.034)[f]	ns	.0045 − (.007)[f]	ns	ns
	rs739097 (Intron 1)	ns	ns	.018 − (.023)[f]	ns	ns
CACNG2	rs2092662(Intron 1)	.0141 − (.017)[f]	ns	ns	ns	ns
	rs2283986(Intron 1)	ns	ns	.0413 + (.051)[f]	ns	ns
	rs2267360(Intron 1)	ns	ns	ns	ns	ns

SNP, single nucleotide polymorphism; CPT, continuous performance test; WCST, Wisconsin card sorting test; S, single locus; UD, Undegraded CPT; D, Degraded; +, risk effect; −, protective effect; CAT, categories achieved.

[a]Subgroup of schizophrenia defined by *Z* score of d′ ≥ −2.5 for non-deficit in sustained attention assessed by undegraded CPT.

[b]Subgroup of schizophrenia defined by *Z* score of d′ < −2.5 for deficit in sustained attention assessed by undegraded CPT.

[c]Subgroup of schizophrenia defined by *Z* score of d′ ≥ −2.5 for non-deficit in sustained attention assessed by degraded CPT.

[d]Subgroup of schizophrenia defined by *Z* score of categories achieved ≥ −2.5 for non-deficit in CAT of WCST.

[e]Subgroup of schizophrenia defined by *Z* score of categories achieved < −2.5 for deficit in CAT of WCST.

[f]Empirical *p* value was calculated by use of simulation study.

CPT. rs736212 from *RASD2* was significantly associated with the schizophrenia subgroup defined by CAT < −2.5 ($p = .0077$).

Haplotype Association Analysis. The association data for eight haplotypes of three genes (*APOL5, MYH-9*, and *CACNG2*) in the subgroups of schizophrenia defined by impairment in neuropsychological functions are shown in Table 6. The haplotype (2-1-2) of rs2481 - rs875726 - rs1009150 SNPs and the haplotype (1-1-1-1) of rs3752463 - rs1557540 - rs713839 - rs739097 on *MYH9* had significant levels as low as .0085 and .0059, respectively, in the subgroups of schizophrenia defined by non-deficit in sustained attention assessed by undegraded and degraded CPT.

The subgroups with schizophrenia defined by non-deficit also had significant associations with four- nucleotide haplotype on *CACNG2*. The haplotype 2-1-1-1 comprising rs2267360 - rs140526 - rs1883987 - rs916269 from the *CACNG2* gene had a significance level of .0163; all others had no significance.

The subgroup of schizophrenia defined by the presence of sustained attention deficit (undegraded CPT *Z* score of d′ below −2.5) had only a marginally significant association with two haplotypes on *APOL5* and *MYH9*. The subgroup of schizophrenia defined by deficit in CAT also had only a marginally significant association with the haplotype on *CACNG2*. Apparently there is no haplotype with more than a moderately high significant association for the subgroup of schizophrenia defined by deficits in sustained attention and by deficits in the CAT measure from the WCST.

Table 6. Significant Association Levels of Haplotypes with the Subgroup of Schizophrenia Defined by the Endophenotype Indicators of CPT and WCST

		CPT			WCST	
Gene Haplotype Primer ID	H	UD[a] ≥ −2.5	UD[b] < −2.5	D[c] ≥ −2.5	CAT[d] ≥ −2.5	CAT[e] < −2.5
APOL5						
(rs1540297-rs2899256-rs2076671-rs879680)	1-1-1-1	.0322–	.015+	ns	ns	ns
(Promoter-Intron 1-Exon 3-3′-end)	1-2-2-2	.0484+	ns	ns	ns	ns
MYH9						
(rs2481-rs875726-rs1009150)	2-1-2	.0085+	.041–	ns	ns	ns
(Exon 41-Intron 25-Intron 16)	1-2-2	ns	ns	ns	ns	ns
MYH9						
(rs3752463-rs1557540-rs713839-rs739097)	1-1-1-1	.0206–	ns	.0059–	ns	ns
(Intron 9-Intron 3-Intron 3-Intron 1)	2-2-2-2	ns	ns	.018+	ns	ns
CACNG2						
(rs2267360-rs140526-rs1883987-rs916269)	1-1-1-1	ns	ns	ns	ns	ns
(Intron 1-Intron 1-Intron 1-Intron 1)	2-1-1-1	ns	ns	ns	.0163–	ns

+ indicates risk effect; – indicates protective effect.

H, Haplotype composition; other abbreviations as in Table 5.

[a]Subgroup of schizophrenia defined by *Z* score of d′ ≥ −2.5 for non-deficit in sustained attention assessed by undegraded CPT.

[b]Subgroup of schizophrenia defined by *Z* score of d′ < −2.5 for deficit in sustained attention assessed by undegraded CPT.

[c]Subgroup of schizophrenia defined by *Z* score of d′ ≥ −2.5 for non-deficit in sustained attention assessed by degraded CPT.

[d]Subgroup of schizophrenia defined by *Z* score of categories achieved ≥ −2.5 for non-deficit in CAT of WCST.

[e]Subgroup of schizophrenia defined by *Z* score of categories achieved < −2.5 for deficit in CAT of WCST.

In short, these two haplotypes (2-1-2 of SNP rs2481 - rs875726 - rs1009150; 1-1-1-1 of SNP rs3752463 - rs1557540 - rs713839 - rs739097) on *MYH9* had moderately high degrees (p = .0089–.0059) of association with the subgroups of schizophrenia without deficits in sustained attention as assessed by undegraded and degraded CPT, respectively. One haplotype (2-1-1-1 of SNP rs2267360 - rs140526 - rs1883987 - rs916269) from the *CACNG2* gene showed a moderately significant association with the subgroup of schizophrenia without deficit on the basis of CAT of WCST.

Discussion

In this fine mapping study in a two cM region around D22S278, we found that *RASD2*, *MYH-9*, and *CACNG2* were candidate vulnerability genes for subgroups of schizophrenic patients who did not have deficits in our CPT measure of sustained attention or our WCST measure of executive dysfunction. However, we cannot rule out the possibility of additional association outside of the 2-Mb region surrounding D22S278. Of these three implicated genes, we feel that *MYH9* is the most likely candidate vulnerability gene for schizophrenia, not only because of the high statistical significance in the subgroup of schizophrenia with non-deficit CPT but also because of the statistical significance in haplotype association analyses. The significant associations with the non-deficit subgroup of patients defined by CPT demonstrate the heterogeneity of this disease. The subgrouping based on the CAT indicator of WCST showed no consistent findings, and this might be due to the lack of heritability of CAT indicator.

The significant SNP in *RASD2* is located at exon 3, the *APOL5* haplotype covers the whole gene (from the promoter to the 3′-end), and the *MYH9* haplotype has two blocks covering intron 1 to exon 41. Our data for *EIF3S7* implicate the promoter region, and the data for *CACNG2* implicate intron 1.

In this study, we provide evidence supporting the hypothesis that the degree of association of SNP markers and/or haplotype markers with the subgroups of schizophrenia defined by neuropsychological endophenotypes is higher than that with the whole study sample. We attribute this to the possible heterogeneity of schizophrenia when defined by DSM-IV criteria. This is exemplified by SNP rs736212 in the *RASD2* gene. The p values for SNP rs736212 in the whole sample were .0067 and .0097 (narrow and broad models, respectively; Table 3) and .0008 (Table 5) for the sustained attention non-deficit subgroup of schizophrenia. This was also shown by the significant association of single loci and haplotypes for *MYH9* with the subgroup of schizophrenia defined by lack of deficits in neuropsychological functions. A significant association was observed only for the non-deficit subgroup defined by the CPT score. We predict that other vulnerability genes are responsible for the subgroup of schizophrenia with neuropsychological deficits. We previously reported that *DISC1* (1q42.1) was significantly associated with the subgroup of schizophrenia defined by deficit in the CPT (49). This provides further evidence for the genetic heterogeneity of schizophrenia that can be delineated by the presence or absence of deficit in neuropsychological function.

Several genes located in the 22q chromosome regions have been studied and suggested as candidate genes for schizophrenia, including synaptogyrin 1 (*SYNGR1*; 22q13.1) (3), phosphatidylinositol 4-kinase, catalytic α polypeptide (*PIK4CA*; 22q11.21) (50), synaptosomal-associated protein (29-kDa *SNAP29*; 22q11.21) (51), the adenosine A2a receptor gene (*ADORA2A*; 22q11.23) (52), and the catechol-*O*-methyltransferase gene (*COMT*; 22q11.21) (53). The three schizophrenia vulnerability genes discovered in this study are located in the 22q12.3 region (http://genome.ucsc.edu/cgi-bin/hgTracks). The closest candidate gene to our region is *SYNGR1*, which is located approximately 2.6 cM from the *CACNG2* gene.

The *RASD2* (RASD family, member 2) gene encodes a Ras-related protein that binds to GTP and possesses intrinsic GTPase activity. It belongs to the Ras superfamily of small GTPases and is rich in striatum. The mechanism whereby *RASD2* variants cause schizophrenia in a subgroup of patients without deficits in sustained attention needs to be investigated further.

MYH9 is a non-muscle myosin II heavy chain of the polypeptide 9 isoform belonging to the myosin superfamily (54). This class II myosin is required for cytokinesis, cell motility, cell chemotaxis, cell architecture, and development of non-muscle cells (55). The *MYH9* gene has been associated with an inherited human disease family referred to as *MYH9* disorders, which are characterized by giant platelet, thrombocytopenia, and cytoplasmic granulocyte inclusions (56,57). In *MYH9*-targeted disruption knockout (KO) mice, no *MYH9* homozygous KO mice were able to survive, which suggests that the genetic expression of *MYH9* is required for embryonic development (58).

Our study was the first to find a significant association between *MYH9* and the subgroup of schizophrenic patients having no deficits in sustained attention as assessed by the degraded CPT. The degraded CPT, one of the paradigms for measuring sustained attention, requires controlled information processing to deal with the added interference of a 25% degraded snowball pattern. It is different from the undegraded CPT test, which is mainly automatic information processing. The pathophysiological process of *MYH9* involvement in schizophrenia is likely different from that of the *RASD2* gene, which seems to be a contributory factor in the subgroup of schizophrenia with no deficits in sustained attention as assessed by the undegraded CPT.

The *CACNG2* gene is the γ subunit of neuronal voltage-activated L-type calcium channels, which might stabilize the calcium channel in an inactive state (59). The *CACNG2* protein is similar to the mouse stargazin protein (60,61), which is also implicated in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor trafficking (62,63). The AMPA receptor mediates fast excitatory synaptic transmission in the brain and underlies aspects of synaptic plasticity (63). Mutations in *CACNG2* have been reported to be associated with absence seizure (petit-mal or spike-wave seizures) (64). The DNA copy number in *CACNG2* is altered in both bipolar and schizophrenic patients (65). The related pathophysiological processes of this finding need further study.

In summary, a 2-cM region surrounding the D22S278 marker was screened with SNPs for genetic association with schizophrenia. This research design risked having negative results, because fine mapping was done on a relatively narrow region. However, we did find that: 1) the *RASD2* gene was associated with schizophrenia that occurs without deficits in sustained attention assessed by the undegraded CPT, 2) *MYH9* gene was associated with schizophrenia that occurs without deficits in sustained attention assessed by the degraded CPT, and 3) *CACNG2* was associated with schizophrenia that occurs without deficits in executive function as indicated by categories achieved on the WCST. Of these three candidate genes, we favor *MYH9*, because of its statistical significance associated with schizophrenia across most of the statistical operations applied in this study.

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Supplementary material cited in this article is available online.

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