

Psychosis Susceptibility Gene *ZNF804A* and Cognitive Performance in Schizophrenia

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Context: The Zinc Finger Protein 804A gene (*ZNF804A*) has been implicated in schizophrenia susceptibility by several genome-wide association studies. *ZNF804A* is brain expressed but of unknown function.

Objective: To investigate whether the identified risk allele at the disease-associated single nucleotide polymorphism rs1344706 is associated with variation in neuropsychological performance in patients and controls.

Design: Comparison of cases and controls grouped according to *ZNF804A* genotype (AA vs AC vs CC) on selected measures of cognition in 2 independent samples.

Setting: Unrelated patients from general adult psychiatric inpatient and outpatient services and unrelated healthy participants from the general population were ascertained.

Participants: Patients with DSM-IV–diagnosed schizophrenia and healthy participants from independent samples of Irish (297 cases and 165 controls) and German (251 cases and 1472 controls) nationality.

Main Outcome Measures: In this 2-stage study, we tested for an association between *ZNF804A* rs1344706

and cognitive functions known to be impaired in schizophrenia (IQ, episodic memory, working memory, and attention) in an Irish discovery sample. We then tested significant results in a German replication sample.

Results: In the Irish samples, the *ZNF804A* genotype was associated with differences in episodic and working memory in patients but not in controls. These findings replicated in the same direction in the German samples. Furthermore, in both samples, when patients with a lower IQ were excluded, the association between *ZNF804A* and schizophrenia strengthened.

Conclusions: In a disorder characterized by heterogeneity, a risk variant at *ZNF804A* seems to delineate a patient subgroup characterized by relatively spared cognitive ability. Further work is required to establish whether this represents a discrete molecular pathogenesis that differs from that of other patient groups and whether this also has consequences for nosologic classification, illness course, or treatment.

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SCHIZOPHRENIA HAS A LIFETIME risk of approximately 1% and is a major cause of global disability.¹ Despite its substantial heritability (~80%),² identifying the genetic variations responsible for schizophrenia has proved challenging, as with other nonpsychiatric complex disorders.^{3,4} A recent genome-wide association study (GWAS)⁵ identified the single nucleotide polymorphism (SNP) rs1344706 located at gene *ZNF804A* (OMIM 612282) as achieving genome-wide significance for psychosis (9.96×10^{-9} [odds ratio, 1.12]). Despite being relatively underpowered to replicate such a modest effect, 2 of 3 recently reported large schizophrenia GWASs⁶⁻⁸ supported association with the same A risk allele.

The SNP rs1344706 is located in an intron of *ZNF804A* that maps to chromosome 2q32.1. The human *ZNF804A* gene consists of 4 exons that transcribe a protein of 1210 amino acids with a predicted molecular weight of 137 kDa. The encoded protein is uncharacterized, but analysis of the protein sequence shows a zinc finger domain at the N-terminal end, suggesting that it may bind DNA and have a role in regulating gene expression. The Allen Mouse Brain Atlas indicates that the mouse orthologue Zfp804A is widely expressed in the brain.⁹ Lim et al¹⁰ demonstrated using a yeast 2-hybrid system that *ZNF804A* bound ataxin-1, which is encoded by *ATXN1* (OMIM 601556). Mutations in this gene cause spinocerebellar

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ataxia-1, and it has been implicated, albeit inconclusively, in schizophrenia by several small studies (<http://www.schizophreniaforum.org/res/sczgene/geneoverview.asp?geneid=354>).

In their schizophrenia GWAS, Stefansson et al⁶ identified an association with genes involved in brain development and cognition. Neurocognitive deficits are core features of schizophrenia and may better represent the underlying pathogenesis than clinical diagnostic categories.¹¹ Regardless of whether the measurement of these deficits increases power to detect an association with psychiatric risk genes,¹² they have the unique advantage of enabling in vivo functional investigation of candidate genes at the level of brain behavior in large samples of patients and healthy participants. The utility of such an approach has been demonstrated by findings with existing candidate genes for schizophrenia (including *DISC1*, *NRG1*, *DTNBP1*, *DAOA[G72]*, and *RGS4*, discussed in the study by O'Donovan et al¹³). No neuropsychological investigation of *ZNF804A* has occurred to date, to our knowledge, although evidence that *ZNF804A* is likely to affect brain function derives from a recent study by Esslinger et al.¹⁴ This study, investigating the same risk allele at rs1344706, identified an association with altered connectivity in healthy participants within and between regions that included the dorsolateral prefrontal cortex (DLPFC) and the hippocampus. No behavioral sequelae of this altered connectivity were associated with this finding, although the sample size (n=115) may have been underpowered to detect such differences.

In this study, we investigated the effect on cognition of the A risk allele at rs1344706, the variant showing strongest evidence of association in the GWAS by O'Donovan et al.⁵ Neuropsychological assessment was designed to measure cognitive functions known to be impaired in schizophrenia: IQ, working memory, episodic memory, and attention. The neuropsychological tests examined in the different samples were selected a priori to be as equivalent as possible. To enable a clear investigation of the effects of *ZNF804A* variation on cognition, we focused on a single statistically significantly strong risk variant, used a large discovery sample, and implemented a study design that allowed replication of findings in an independent data set.

METHODS

SAMPLE CHARACTERISTICS

Irish Patient and Control Samples (Discovery Samples)

These samples consisted of 297 cases and 165 controls. Seventy-one of the case participants underwent genotyping as part of the previous GWAS,⁵ and the remaining 226 case participants and all the controls were independent of that study. Cases consisted of clinically stable patients with a *DSM-IV* diagnosis of schizophrenia recruited from 5 sites across Ireland. The inclusion criteria required that participants were aged 18 to 65 years, had no history of substance abuse in the preceding 6 months, and had no previous head injury with loss of consciousness or a history of seizures. Diagnosis was confirmed by trained psy-

chiatrists using the *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)*.¹⁵ Additional diagnostic details and clinical sample characteristics ascertained at the time of interview included symptom severity (Scale for the Assessment of Negative Symptoms/Scale for the Assessment of Positive Symptoms¹⁶) and medication dosage.

The control sample was recruited on the basis of responses to local media advertisements. Control participants were included only if they were aged 18 to 65 years and satisfied, based on clinical interview, the criteria of having no history of major mental health problems, intellectual disability, or acquired brain injury and no history of substance misuse in the preceding 6 months based on self-report. Control participants were also excluded from the study if they reported having a first-degree relative with a history of psychosis. All patient and control assessments were conducted in accordance with the relevant ethics committee approval from each participating site. All patients and controls were of Irish ancestry (ie, 4 grandparents born in Ireland), and all provided written informed consent.

German Patient and Control Samples (Replication Samples)

The German samples consisted of 251 clinically stable patients with a *DSM-IV* diagnosis of schizophrenia and up to 1472 controls, all of whom underwent genotyping as part of the previous study.⁵ Patients were ascertained from mental health services in the Munich area, and all the participants provided written informed consent. The inclusion criteria were a diagnosis of schizophrenia (>6-month symptom duration) and age 18 to 65 years. The exclusion criteria included a history of head injury or neurologic diseases. Detailed medical and psychiatric histories were collected, including data from a clinical interview using the *SCID*,¹⁵ to evaluate lifetime Axis I and II diagnoses. Four physicians and 1 psychologist rated the *SCID* interviews, and all the measurements were independently rated by a senior researcher. Participants were also rated for symptoms using the Positive and Negative Syndrome Scale.¹⁷ In cases, 68% were of German descent (all 4 grandparents born in Germany), and the other 32% were German white. Of the 251 participants with schizophrenia, 241 completed the full Wechsler Adult Intelligence Scale-Revised (WAIS-R) assessment and 235 completed a comprehensive neuropsychological battery.

Control participants of German descent (all 4 grandparents German) were randomly selected from the general population of Munich. Participants were contacted and invited to participate by mail. The address, sex, and age of potential participants were supplied by the municipal registration office, which enabled equal numbers of males and females and people of different ages (in decades) to be approached. Controls for this study were included only if aged 18 to 65 years. To exclude individuals with central neurologic diseases and psychotic disorders or those who had first-degree relatives with psychotic disorders, several screenings were conducted before the volunteers were enrolled in the study. First, individuals who responded were initially screened by telephone for the absence of neuropsychiatric disorders. Second, detailed medical and psychiatric histories were assessed for participants and their first-degree relatives by using a semistructured interview. Third, if no exclusion criteria were fulfilled, they were invited to a comprehensive interview including the *SCID*¹⁵ to validate the absence of any lifetime psychotic disorder. In addition, the Family History Assessment Module¹⁸ was conducted to exclude psychotic disorders in their first-degree relatives. A neurologic examination was also conducted to exclude individuals with current central nervous system impairment. In the case of volunteers older than 60 years, the Mini-Mental-Status-Test¹⁹ was performed to exclude individuals with possible cognitive impairment. Of the 1472 control participants, 1470 completed the full

WAIS-R assessment and 367 completed tests from a further extensive neuropsychological battery.

COGNITIVE ASSESSMENT

This study was designed so that identical or near-identical tests of the cognitive domains of IQ, episodic memory, working memory, and attention were used for the Irish discovery samples and the German samples. The number of individual tests in each domain of cognition was limited to minimize multiple testing effects. The Irish discovery sample was used to test for genotypic associations with these tests. Where significant ($P \leq .05$) associations were detected, these phenotypes were taken forward to the German sample for replication.

IQ was measured in the Irish sample using selected subtests (vocabulary, similarities, block design, and matrix reasoning) from the WAIS, third edition,²⁰ yielding a full-scale verbal and performance IQ. For the German sample, IQ was indexed using the German version of the WAIS-R²¹ and all 11 verbal and performance subtests (vocabulary, comprehension, information, digit span, arithmetic, similarities, block design, picture completion, picture arrangement, object assembly, and digit symbol and coding). Episodic memory was assessed in the Irish samples using the logical memory immediate and delayed from the Wechsler Memory Scale, third edition (WMS-III),²² and in the German sample using the logical memory immediate and delayed from the German version of the WMS-Revised.^{23,24}

Verbal and spatial working memory were assessed in the Irish samples using the Wechsler Letter Number Sequencing task (WMS-III)²² and the spatial working memory task from the Cambridge Neuropsychological Test Automated Battery.²⁵ In the German samples, working memory was measured using the digit span from the WAIS-R²¹ and the spatial span from the WMS-R.^{23,24} Vigilant attention was assessed in the Irish patient samples using the Continuous Performance Test (CPT), identical pairs version,²⁶ and in the German samples using the CPT 3-7 version.²⁷ Insufficient numbers of Irish controls completed this task, making it unavailable for this group. The memory and attention tasks used herein have been described in detail elsewhere.²⁸

GENOTYPING

The SNP rs1344706 was genotyped in the German sample and in a proportion of the Irish sample using the Sequenom iPLEX Gold system (further details are provided by O'Donovan et al³). The call rate for the iPLEX genotyping was greater than 95% in the Irish sample and greater than 99% in the German sample. Both case and control samples were in Hardy-Weinberg equilibrium ($P > .05$). The remainder of the Irish sample ($n=529$) underwent genotyping using a TaqMan SNP Genotyping Assay on a 7900HT Sequence Detection System (Applied Biosystems Inc, Foster City, California). The call rate for the TaqMan genotyping was greater than 95%, and both case and control samples were in Hardy-Weinberg equilibrium ($P > .05$). Along with the Irish samples, several HapMap CEU DNA samples ($n=90$ [http://www.hapmap.org]) and duplicates ($n=60$) were genotyped for rs1344706 for quality control purposes. All the genotypes were found to be concordant with either the available online HapMap data or each other for this SNP.

STATISTICAL ANALYSES

To inform appropriate adjustments in the primary cognitive analyses, the association between ZNF804A rs1344706 and demographic variables was investigated using 1-way analysis of variance. In the case of symptom severity, a PCA (principal components analysis) was undertaken separately in each of the

3 samples based on Scale for the Assessment of Negative Symptoms/Scale for the Assessment of Positive Symptoms scores in the Irish sample and Positive and Negative Syndrome Scale scores in the German sample (see eTable 1 and eTable 2 for factor descriptions; http://www.archgenpsychiatry.com); differences associated with genotype were analyzed using multivariate analysis of covariance in which age and sex were included as covariates.

Associations between ZNF804A rs1344706 and the phenotypes of IQ, episodic memory, working memory, and attention were tested using a general factorial design in a statistical software program (SPSS 14).²⁹ In the original GWAS there was no difference in genotypic vs allelic model; because there was no evidence on which to test a specific dominant or recessive model and as sample sizes allowed, the analysis was based on a comparison of all 3 genotype groups. ZNF804A genotype (AA vs AC vs CC) and diagnosis (cases vs controls) were entered as fixed effects. In a series of analyses of variance, scores for each neuropsychological subtest were entered as dependent variables, with age and sex included as covariates as appropriate. Significant interaction effects were further explored by examining simple effects in cases and controls. Tests showing significant results in the Irish samples were then taken forward to the same analyses in the German samples.

RESULTS

ZNF804A AND DEMOGRAPHIC AND CLINICAL VARIABLES

Demographic and clinical characteristics by rs1344706 genotype appear in **Table 1**. In the Irish sample, no differences were observed in age, years of education, or sex between the genotype groups for either the full sample or when patients and controls were considered separately. In terms of clinical symptom severity, no difference was observed between genotype groups for PCA-derived negative or disorganized symptoms. For positive symptom severity, a trend-level difference between groups was observed ($F=2.31$, $P=.06$); mean values for the 3 genotype groups suggested that the homozygous carriers of the A risk allele presented somewhat higher positive scores than the other genotype groups. This trend was observed in the absence of any association between genotype and medication dose.

For the German sample, no significant differences were apparent in age, sex distribution, or years of education by genotype in cases or controls (Table 1). In terms of clinical severity, a significant difference was observed for the PCA-derived depressive factor ($F=4.61$, $P=.01$). Pairwise comparisons revealed that the CC genotype scored higher on this depressive factor than the AC ($t=2.19$, $P=.03$) and AA ($t=3.06$, $P=.002$) genotype groups. Genotype was not associated with any other symptom factor score, and neither were any differences in medication dosage by genotype observed.

COGNITIVE ANALYSIS OF ZNF804A

Mean scores for each of the 4 cognitive domains of IQ, working memory, episodic memory, and attention by ZNF804A genotype group for cases and controls in the Irish discovery sample are given in **Table 2**. As expected, patients performed significantly below controls

Table 1. Sample Characteristics According to ZNF804A Genotype of Cases and Controls for the Irish and German Samples

Variable	Cases					Healthy Participants				
	AA	AC	CC	F Value/ χ^2	P Value	AA	AC	CC	F Value/ χ^2	P Value
Irish sample	n=134	n=127	n=36			n=61	n=77	n=27		
Age, mean (SD), y	42.2 (12.4)	40.8 (11.3)	40.2 (11.7)	0.64	.53	36.8 (12.3)	38.0 (13.0)	37.1 (12.7)	0.152	.86
Female sex, %	34.3	23.6	25.0	3.90	.14	45.0	51.9	57.7	1.33	.52
Education, mean (SD), y	13.1 (2.4)	13.3 (2.6)	12.7 (2.3)	0.78	.46	16.0 (2.2)	15.7 (2.1)	15.8 (2.8)	0.364	.70
Medication, mean (SD), mg	442.6 (401.0)	444.3 (356.3)	444.1 (379.3)	0.01	>.99	NA	NA	NA	NA	NA
German sample	n=85	n=125	n=41			n=512	n=707	n=253		
Age, mean (SD), y	38.8 (10.8)	36.0 (10.1)	36.8 (11.1)	1.93	.15	44.6 (14.2)	44.5 (14.2)	44.4 (14.5)	0.022	.98
Female sex, %	44.7	31.2	39.0	4.039	.13	54.5	55.7	58.5	1.103	.58
Education, completing high school, %	76.5	60.0	65.4	6.354	.17	80.1	80.9	77.9	3.158	.53
Medication, mean (SD), mg	666 (738)	696 (696)	821 (794)	0.587	.56	NA	NA	NA	NA	NA

Abbreviation: NA, not applicable.

Table 2. Cognitive Analysis by ZNF804A Genotype in the Irish Samples

Cognitive Function	Test or Subscale	Sample	Participants, No.	Mean (SD)			$F_{Cases vs Controls}$	P Value	$F_{Main Effect}$	P Value	$F_{Interaction Effect}$	P Value	$F_{Simple Effect}$	P Value
				AA	AC	CC								
IQ	Abbreviated full-scale IQ	Cases	288	90.5 (19.0)	88.5 (15.8)	85.0 (14.0)	361.0	<.001	0.78	.46	1.96	.14		
		Controls	164	122 (14.4)	119.6 (14.4)	125.2 (12.7)								
Working memory ^a	LN sequence	Cases	276	7.7 (3.6)	7.4 (3.2)	6.0 (2.5)	295.2	<.001	0.11	.90	4.20 ^b	.02 ^b	4.781 ^b	.009 ^b
		Controls	163	13.1 (3.7)	13.2 (3.2)	14.3 (2.8)								
	CANTAB SWM	Cases	287	-0.81 (1.2)	-1.1 (1.3)	-1.8 (1.5)	136.4	<.001	2.6	.08	5.04 ^b	.007 ^b	7.159 ^b	.001 ^b
		Controls	153	0.25 (0.90)	0.26 (0.78)	0.37 (0.59)								
Episodic memory ^a	Logical memory immediate	Cases	283	6.44 (3.6)	6.42 (3.4)	4.59 (2.6)	361.3	<.001	0.35	.70	6.53 ^b	.002 ^b	4.586 ^b	.01 ^b
		Controls	161	12.5 (2.6)	12.1 (2.7)	13.7 (2.8)								
	Logical memory delayed	Cases	283	7.24 (3.4)	7.15 (3.1)	6.18 (2.6)	344.9	<.001	0.12	.89	3.26 ^b	.04 ^b	1.552	.21
		Controls	160	12.5 (2.7)	12.1 (2.7)	13.9 (2.5)								
Vigilant attention	CPT-IP (3 letters)	Cases	192	1.9 (1.1)	2.0 (1.0)	1.9 (0.9)	NA	NA	0.145	.87	NA	NA	NA	NA
		Controls	0	NA	NA	NA								

Abbreviations: CANTAB SWM, spatial working memory task from the Cambridge Neuropsychological Test Automated Battery; CPT-IP, Continuous Performance Test, identical pairs version; LN, letter-number; NA, not applicable.

^aTests with significant results that were taken forward for replication.

^bStatistically significant.

on all cognitive tests administered in the Irish and German samples ($P < .001$ for all).

Irish Discovery Sample

For the Irish samples, a significant interaction between ZNF804A genotype and case or control status revealed associations with variance on both working memory tasks in patients but not in controls (verbal working memory: $F = 4.2$, $P = .02$; spatial working memory: $F = 5.04$, $P = .007$) (Table 2). Effect size estimates (partial η^2) indicated that in cases, genotype explains 2.8% of verbal working memory and 4.4% of spatial working memory. Tukey post hoc analyses within the patient group revealed that the homozygous risk AA genotype performed significantly better than the homozygous CC genotype group (verbal working memory: $H = 1.53$, $P = .046$; spatial working memory: $H = 11.38$, $P = .045$). Finally, although a small trend for a main effect of genotype on spatial working memory was

apparent, this seemed to be primarily driven by cases; separate analysis of controls revealed no such trend.

A significant association between ZNF804A genotype and verbal episodic memory was also observed in patients and not in controls for immediate and, to a lesser extent, delayed verbal memory. Effect size estimates indicated that in cases, genotype explains 2.7% of immediate logical memory scores and 1.1% of delayed verbal memory scores (Table 2). For immediate verbal episodic memory, Tukey post hoc analysis revealed that this difference was driven by homozygous ($H = 1.86$, $P = .01$) and heterozygous ($H = 1.83$, $P = .02$) risk carriers, again performing significantly better than homozygous non-risk carriers. For delayed verbal episodic memory, the effect of genotype was smaller, and post hoc analysis did not reveal specific between-group differences.

Finally, scores for vigilant attention (the CPT task) were available for patients but not for controls. Based on analysis of covariance, again with age and sex used as co-

Table 3. Cognitive Analysis by ZNF804A Genotype in the German Samples

Cognitive Function	Test or Subscale	Sample	Participants No.	Mean (SD)			$F_{\text{Cases vs Controls}}$	P Value	$F_{\text{Main Effect}}$	P Value	$F_{\text{Interaction Effect}}$	P Value	$F_{\text{Simple Effect}}$	P Value
				AA	AC	CC								
Working memory	Digit span	Cases	237	14.5 (4.0)	13.2 (3.3)	13.6 (3.5)	32.70	<.001	3.71 ^a	.02 ^a	4.00 ^a	.02 ^a	3.73 ^a	.02 ^a
		Controls	1836	14.4 (4.0)	14.4 (3.8)	14.3 (4.0)							0.037	.96
	WMS spatial	Cases	243	15.8 (3.1)	15.0 (3.2)	14.3 (3.0)	115.20	<.001	3.25 ^a	.04 ^a	3.24 ^a	.04 ^a	4.18 ^a	.02 ^a
		Controls	374	17.3 (3.6)	17.2 (3.3)	17.3 (2.5)							0.159	.85
Episodic memory	Logical memory immediate	Cases	239	25.4 (8.4)	24.4 (8.0)	21.5 (6.3)	156.50	<.001	1.95	.14	3.32 ^a	.04 ^a	3.20 ^a	.04 ^a
		Controls	376	30.7 (6.7)	31.0 (6.2)	32.0 (5.0)							0.398	.67
	Logical memory delayed	Cases	239	28.3 (10.4)	26.8 (9.7)	23.1 (9.1)	155.80	<.001	2.42	.09	4.69 ^a	.01 ^a	3.60 ^a	.03 ^a
		Controls	376	34.2 (7.9)	34.8 (6.4)	35.8 (6.2)							0.718	.49

Abbreviations: WM, working memory; WMS, Wechsler Memory Scale.
^aStatistically significant.

Table 4. Associations Between ZNF804A and Schizophrenia (Allelic and Genotypic) in the Irish Samples According to IQ

IQ Cutoff Value	Controls/Cases, No.	Odds Ratio (95% CI)	Allelic		Genotypic	
			χ^2	P Value	χ^2	P Value
All	165/297	1.37 (0.95-1.98)	2.88	.09	4.69	.10
≥70	164/256	1.49 (1.02-2.18)	4.29	.04	4.79	.09
≥80	162/186	1.74 (1.14-2.65)	6.76	.009	4.43	.11
≥90	136/161	2.29 (1.41-3.72)	11.47	.001	8.99	.01
≥100	154/68	4.59 (2.81-9.71)	18.39	<.001	18.24	<.001
≥110	40/126	6.10 (2.11-17.54)	13.70	<.001	9.10	.01
≥120	88/14	9.70 (1.26-76.90)	6.90	.009	6.92	.03

Abbreviation: CI, confidence interval.

variates, we found no effect of ZNF804A genotype on CPT in terms of the 2- and 3-letter conditions (Table 2).

German Replication Sample

The significant results from the Irish samples were taken forward to the replication samples (Table 3). The results from the Irish sample replicated in the German sample cases for all the cognitive tests: verbal and spatial working memory and episodic memory. Furthermore, the allelic direction of effect was the same in that those with AA genotype performed better than AC and CC genotypes on all significant tests. For spatial and episodic memory, Tukey post hoc analysis confirmed that this was mainly driven by a significant difference between AA and CC genotypes (spatial working memory: $H=2.39$, $P=.047$; immediate episodic memory: $H=2.81$, $P=.02$; delayed episodic memory: $H=3.12$, $P=.009$). In the case of verbal working memory, inter-genotype group differences were observed between homozygous risk carriers and heterozygous risk carriers only ($H=2.67$, $P=.02$). Effect size estimates, again based on partial η^2 , indicated that in cases, genotype explains 3.3% of the variance in spatial working memory, 3.1% in verbal working memory, and 3% in immediate and delayed episodic memory.

ANALYSIS OF WHETHER THE ZNF804A-SCHIZOPHRENIA ASSOCIATION IS MODERATED BY COGNITION

Given the counterintuitive evidence that carriers of the ZNF804A risk genotype presented less impaired cognitive

performance than did noncarriers, we tested the post hoc hypothesis that ZNF804A was delineating a subgroup of patients characterized by relatively intact cognitive performance. To do so, we used χ^2 statistics to calculate the association between ZNF804A and schizophrenia in subsamples with higher cognitive ability. We selected IQ rather than memory performance for this analysis so as to provide a more general index of cognitive ability than that provided by memory function. Higher cognitive ability was based on IQ scores of at least 70, at least 80, at least 90, at least 100, at least 110, and at least 120. In the Irish and German samples, as the phenotype was narrowed to individuals with an IQ in the average range, the association between ZNF804A and schizophrenia became more statistically significant (Table 4, Table 5, and the Figure). For example, in the Irish samples, as the minimum IQ for inclusion approaches 90 (the range for normal IQ), the odds ratio of the allelic association between ZNF804A and schizophrenia increases from 1.37 (when all samples are included) to 2.29 (95% confidence interval, 1.41-3.72). In the German sample, the same trend of increasing association between ZNF804A and schizophrenia also emerges, becoming statistically significant for patients with high average IQ ($IQ > 110$; odds ratio, 1.63; 95% confidence interval, 1.12-2.38). Conducting this analysis based on memory scores instead of IQ revealed the same pattern of results.

COMMENT

Regarding its credibility as a risk variant, the SNP at ZNF804A is the first variant to have achieved genome-

Table 5. Associations Between *ZNF804A* and Schizophrenia (Allelic and Genotypic) in the German Samples According to IQ

IQ Cutoff Value	Controls/Cases, No.	Odds Ratio (95% CI)	Allelic		Genotypic	
			χ^2	P Value	χ^2	P Value
All	1462/251	1.00 (0.82-1.21)	0	.99	0.283	.87
≥70	1460/225	0.96 (0.79-1.18)	0.124	.72	0.196	.91
≥80	1457/207	1.02 (0.83-1.26)	0.048	.83	0.119	.94
≥90	1394/169	1.05 (0.83-1.32)	0.162	.69	0.164	.92
≥100	1236/126	1.16 (0.89-1.52)	1.20	.27	1.44	.49
≥110	913/70	1.63 (1.12-2.38)	6.75	.009	6.83	.03
≥120	563/37	2.20 (1.28-3.80)	8.48	.004	8.68	.01

Abbreviation: CI, confidence interval.

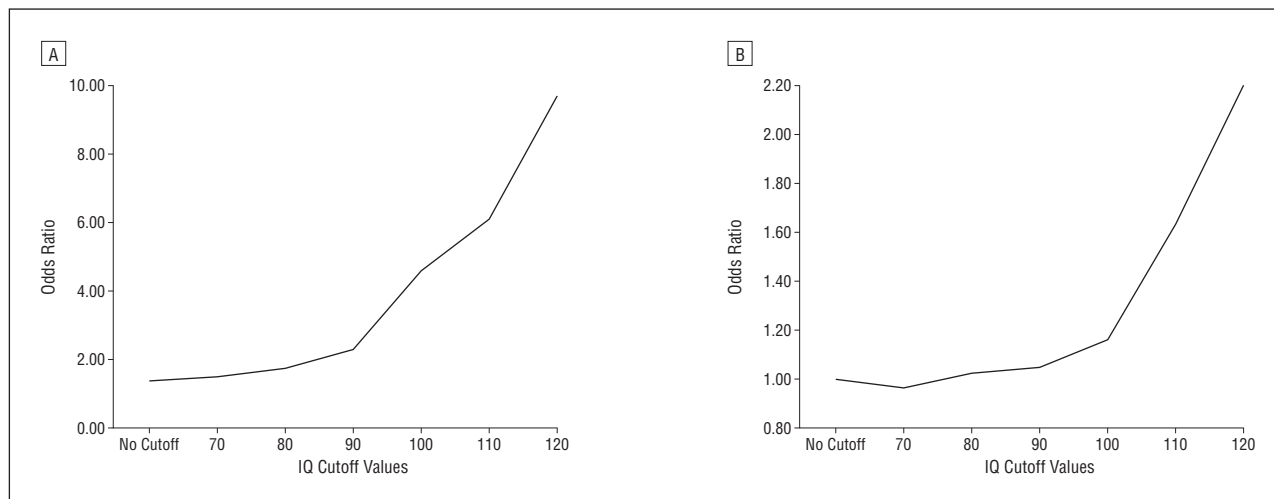


Figure. Changes in associated odds ratios for *ZNF804A* and schizophrenia according to IQ in the Irish (A) and German (B) samples.

wide significance for psychosis, with the association replicating in multiple independent samples. Despite the modest effect size, 2 independent GWAS^{7,8} have provided support for an association with the same risk allele. Although this finding may have a very small effect on disease risk, it is potentially important to our understanding of the genetic mechanisms and pathways that contribute to susceptibility. Little is known about the function of *ZNF804A*, and this study sought to elucidate the phenotypic effects of the identified risk allele on indices of neuropsychological function. The design of this study sought to overcome weaknesses of earlier gene cognition studies (eg, small sample size and high multiple testing burden) by investigating a single GWAS significant variant and then seeking to replicate significant findings in a large independent data set using comparable cognitive tests. In this study, carrying the risk allele at the SNP rs1344706 was associated with variation in cognitive performance in patients. Specifically, schizophrenia carriers of the AA risk genotype performed relatively better on measures of episodic memory and working memory based on 2 independent Irish and German samples that had contributed to the original GWAS finding.

Although the observed association with cognition observed may seem counterintuitive, it is important to note that the risk allele at *ZNF804A* is not so much associated with better cognitive performance in the pres-

ent study as with less impaired cognitive performance. We interpret these data to mean that *ZNF804A* is delineating an illness susceptibility pathway that is independent of an effect on cognition and, hence, is characterized by relatively spared cognitive ability compared with other patient subgroups whose pathway into illness is being mediated by a greater burden of more cognitively deleterious gene variants.³⁰ Support for this view derives from the following: first, the association is seen only for cases; if *ZNF804A* was having a positive effect on cognitive performance, this should also be apparent in controls, but this is not the case; and second, in the association analysis between *ZNF804A* and schizophrenia, when cases with lower cognitive ability are excluded, the association signal strengthens, indicating that the relationship between *ZNF804A* and psychosis is particularly apparent in those with relatively intact cognitive function. This finding that *ZNF804A* may encode for a cognitively spared psychosis subtype complements earlier evidence in the original GWAS⁵ that inclusion of bipolar patients (a patient group typically associated with less severe cognitive impairments³¹) also led to a strengthening of its association with psychosis. The fact that the association is found in these 2 independently collected samples of individuals with schizophrenia also counteracts the argument that *ZNF804A* is, in fact, a gene for bipolar disorder.

By elucidating the role of *ZNF804A* in delineating a schizophrenia subtype characterized by relatively intact cognitive performance, this study counters the expectation that it is impaired cognition that will be informative about the relationship between a risk gene and a disease phenotype.³² This finding is not unique, however. Recent studies of *PPP1R1B*, encoding DARPP-32, and *CH13L1* found that the schizophrenia-associated risk alleles at both gene loci were associated with a relatively spared performance.^{30,33} Given the heterogeneity of the schizophrenia syndrome and the fact that it is possible to be schizophrenic and cognitively intact,^{34,35} it is perhaps to be expected that not all identified susceptibility genes will have detrimental effects on broad cognitive abilities.

In contravening the typical expectations for intermediate phenotypes (of not being associated with poorer function), an obvious concern is that the observed associations might spuriously result from 1 or more confounding demographic or clinical variables in the patient group. We examined this possibility using a variety of demographic and clinical indicators, including age, medication, sex, education, and clinical symptom severity. No differences between genotype groups on any of these variables were observed. One factor that might potentially have affected these results was the above-average IQ of the Irish controls. We presume that this bias resulted from the ascertainment strategy of advertising for participants via local media advertisements, which may inadvertently have appealed to higher IQ groups. However, IQ in the German control sample was in the average range, and post hoc analysis of this variable did not reveal significant differences associated with genotype. Furthermore, in the 1 other study²⁸ based on exactly the same samples reported herein, the effect of genotype on cognitive ability was apparent in case and control samples in the Irish and German data sets. The impact of *ZNF804A* variation being apparent only in cases in the Irish and German data sets is, therefore, unlikely to be explainable purely in terms of this effect.

An important context for interpreting these data is provided by the recent imaging study of the same genetic variant reported by Esslinger et al.¹⁴ In a sample of controls, they found that the *ZNF804A* risk genotype was associated with altered connectivity in the DLPFC, the hippocampus, and the amygdala. Altered connectivity within and between these brain regions has been associated with schizophrenia; its association with *ZNF804A* provided the first evidence of the gene's functional involvement in brain activity. The fact that the 2 aspects of cognition implicated in the present study, episodic and working memory, are the aspects of cognition subserved by the brain regions identified by Esslinger et al,¹⁴ the DLPFC and the hippocampus, again implicates *ZNF804A* in biological processes relevant to these regions. However, there are 2 caveats to this interpretation. First, Esslinger et al¹⁴ observed an association between *ZNF804A* and altered brain connectivity in healthy participants but no association between the risk variant and neuropsychological performance in this population. In the present study, we

similarly found no association between *ZNF804A* variation and neuropsychological performance in healthy participants but did find an association in patients. Second, Esslinger et al¹⁴ demonstrated enhanced functional connectivity between the DLPFC and the hippocampus. Although hypothesized to have a deleterious effect on cognition, the true functional significance of this finding for cognition and psychosis is unknown because patients were not included in that study. Speculatively, it is possible that the increased connectivity between the hippocampus and the DLPFC observed by Esslinger et al¹⁴ and previously described by Meyer-Lindenberg et al³⁶ could represent a neural mechanism that spares episodic and working memory in patients by allowing processing of memory information in both structures. Because this is not necessary in controls (in whom these structures are unimpaired), the associated behavioral advantage would be evident in the patient group only, as seen herein. Testing this hypothesis will require imaging-based connectivity analysis in patient groups and, therefore, represents an important next step in linking these brain imaging and neuropsychological findings.

In conclusion, these findings have potential relevance for the nosologic classification of schizophrenia and related psychotic disorders, particularly given that the genetic evidence for traditional clinical dichotomies is a subject of considerable discussion.^{37,38} The results of the present study support the approach of subgrouping patients with schizophrenia to better understand molecular and biological processes, as has been done for other complex genetic diseases (eg, breast cancer³⁹). These findings suggest that individuals with less compromised cognitive functioning may show a different pattern of association or may even be a genetically distinct group worthy of further study in genetic association studies. In light of the stronger association between *ZNF804A* in the combined schizophrenia-bipolar sample in the original GWAS,⁵ the present data suggest that *ZNF804A* is indexing a psychosis pathway defined by cognitive rather than diagnostic characteristics. If confirmed, defining the molecular etiology involved in this group may have important diagnostic, prognostic, and therapeutic implications.

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