Molecular Psychiatry (2017) 22, 944–953

www.nature.com/mp

REVIEW

The schizophrenia risk gene *ZNF804A*: clinical associations, biological mechanisms and neuronal functions

H Chang[1,2], X Xiao[1,2] and M Li[1]

ZNF804A (zinc-finger protein 804A) has been recognized as a schizophrenia risk gene across multiple world populations. Its intronic single-nucleotide polymorphism (SNP) rs1344706 is among one of the strongest susceptibility variants that have achieved genome-wide significance in genome-wide association studies (GWAS) for schizophrenia and has been widely and intensively studied. To elucidate the biological mechanisms underlying the genetic risk conferred by rs1344706, we retrospectively analyzed the progresses in brain gene expression quantitative trait loci (eQTL) analyses, *ZNF804A*-induced pathway alterations in neural cells and changes in synaptic phenotypes associated with *ZNF804A* expression. Based on these data, we hypothesize a potential biological mechanism for a genetic risk allele of *ZNF804A* in schizophrenia pathogenesis. We also review the efforts being made to characterize the affected intermediate phenotypes using neuroimaging and neuropsychological approaches. We then discuss additional common and rare *ZNF804A* variants in schizophrenia susceptibility and the potential genetic heterogeneity of these genomic loci between Europeans and Asians. This review for we believe the first time systematically presents the evidence for *ZNF804A*, describing its discovery and likely roles in brain development and schizophrenia pathogenesis. We believe that this work has summarized this information with a systemic and broad assessment of recent findings.

Molecular Psychiatry (2017) **22,** 944–953; doi:10.1038/mp.2017.19; published online 14 March 2017

INTRODUCTION

Schizophrenia, a severe neuropsychiatric disorder with complex etiology, has a worldwide lifetime prevalence of ~1% and remains a significant public health problem.[1] Among its multiple etiological hypotheses, the importance of genetic components in addition to other developmental and environmental influences has been consistently demonstrated by family, twin and adoption studies.[2–4] From early linkage and association analyses[5–8] to recent large-scale genome-wide association studies (GWAS),[9–18] multiple risk candidates with strong evidence have been identified. Particularly, given that the GWAS approach provides opportunities to study common genetic variations across the entire genome without any *a priori* hypotheses, many novel but seemingly less relevant risk variants with functions beyond the known disease biology have been discovered.[19] One example is the first genetic variant that achieved genome-wide level of statistical significance in schizophrenia GWAS: rs1344706 in zinc-finger protein 804A (*ZNF804A*).[9] This gene was subsequently studied with replicative and explorative analyses, which have enhanced our understanding of its involvement in schizophrenia.[20–22]

However, despite the substantial genetic evidence and preliminary understanding of the molecular and neuronal mechanisms of the *ZNF804A* risk allele in schizophrenia susceptibility, a systemic synthesis of the current evidence to depict the potential use of this gene in future prevention and therapies is lacking. For this purpose, we have examined recent progresses on the roles of *ZNF804A* in schizophrenia biology revealed by genetic, molecular biology and neuroscience research. Potential mechanisms for disease progression and recommendations for future research are proposed.

IDENTIFICATION OF A GENOME-WIDE SIGNIFICANT VARIANT RS1344706 IN *ZNF804A* FOR SCHIZOPHRENIA IN EUROPEAN POPULATIONS

In 2008, O'Donovan *et al.*[9] performed a GWAS in a UK sample of 479 schizophrenia patients and 2937 controls followed by replication analyses of top risk loci in 16 726 additional subjects. This GWAS study found that a single-nucleotide polymorphism (SNP) rs1344706 (in the intron 2 of *ZNF804A*) exhibited the strongest statistical association with schizophrenia in a meta-analysis of all samples ($P = 1.61 \times 10^{-7}$ in 7308 cases and 12 834 controls). The significance was further enhanced when both schizophrenia and bipolar disorder were considered as the associated phenotypes ($P = 9.96 \times 10^{-9}$ in 9173 cases and 12 834 controls).[9] In addition to this GWAS, several following replication studies each provided independent support for rs1344706 in populations of European ancestry (Table 1). For example, Steinberg *et al.*[21] observed a nominal significant association of rs1344706 with schizophrenia and bipolar disorder in large-scale samples mainly from Europe ($P = 0.00065$ in 5164 schizophrenia patients, 609 cases with bipolar disorder and 20 709 controls); however, they showed a relatively smaller effect size compared with that of O'Donovan's GWAS,[9] probably due to the 'winner's curse' effect.[23–25] In addition, Riley *et al.*[20] replicated the

[1]Key Laboratory of Animal Models and Human Disease Mechanisms of The Chinese Academy of Sciences and Yunnan Province, Kunming Institute of Zoology, Kunming, China. Correspondence: Professor M Li, Key Laboratory of Animal Models and Human Disease Mechanisms of The Chinese Academy of Science, Kunming Institute of Zoology, East 32 Jiao-Chang Road, No. 32 Jiao-Chang Donglu, Kunming, Yunnan 650223, China.
E-mail: limingkiz@mail.kiz.ac.cn
[2]These authors contributed equally to this work.
Received 28 September 2016; revised 2 January 2017; accepted 9 January 2017; published online 14 March 2017

Table 1. Published association results for rs1344706 with schizophrenia in Europeans

Study	*Area*	*No. of case*	*No. of control*	P-*value*	*OR*	*References*
O'Donovan *et al*. (2008)	UK and others	7308	12 834	1.61×10^{-7}	1.12	9
ISC (2009)	ISC minus Dublin and Bulgaria	2519	2110	0.029	1.08	13
Shi *et al*. (2009)	EA+AA	3967	3624	0.0262	1.09	14
Steinberg *et al*. (2010)	Multiple Area	5077	20 506	0.0029	1.08	21
Riley *et al*. (2010)	ICCSS	1021	626	0.0113	1.20	20
Williams *et al*. (2011)	Multiple Area	18 945	38 675	2.50×10^{-11}	1.10	22
Schanze *et al*. (2011)	Germany	937	585	0.31	1.08	108
Zhang *et al*. (2011)	Multiple Area	2343	2680	0.004	1.12	75
PGC2 (2014)	Multiple Area	34 241	45 604	1.27×10^{-10}	1.07	10

Abbreviations: AA, African American; EA, European American; ICCSS, Irish Case–Control Study of Schizophrenia; ISC, International Schizophrenia Consortium, OR, odds ratio.

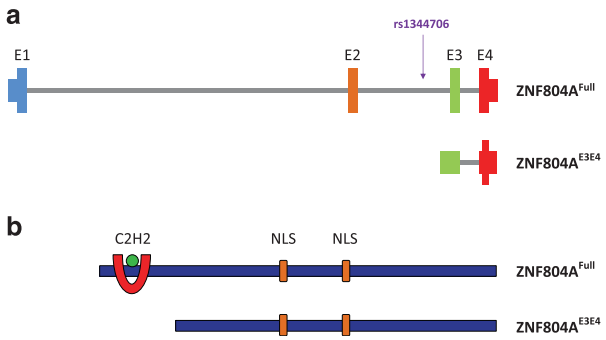

Figure 1. (**a**) Schematic of mRNA structure of *ZNF804A* isoform. (**b**) Schematic of domain structure of predicted ZNF804A protein isoforms. NLS, nuclear localization sequence.

association in an Irish sample of 1021 schizophrenia cases and 626 controls ($P=0.0227$). The association between rs1344706 and schizophrenia was further confirmed by Williams *et al*.[22] through a meta-analysis in 21 274 cases (schizophrenia and bipolar disorder) and 38 675 controls ($P=4.10\times10^{-13}$). Finally, in the latest PGC2 GWAS of schizophrenia (including 34 241 cases and 45 604 controls at the discovery stage), rs1344706 was genome-wide significantly associated with the disease ($P=1.27\times10^{-10}$).[10] These cumulative data provided strong and consistent evidence that rs1344706 is an authentic risk variant for schizophrenia in European populations, making it a highly promising candidate for future studies.[26]

CIS-ACTING EFFECTS OF THE GENOME-WIDE SIGNIFICANT VARIANT RS1344706 IN *ZNF804A*

The discovery of the schizophrenia risk SNP rs1344706 in *ZNF804A* is intriguing. However, the molecular mechanism by which the risk allele contributes to disease etiology remains to be determined. It was hypothesized that schizophrenia risk alleles were enriched in brain gene expression quantitative trait loci (eQTL).[27,28] As such, rs1344706 might affect the expression of *ZNF804A* or even other genes. Based on this idea, researchers have conducted eQTL analyses to investigate the risk mechanisms of rs1344706.[29,30] In a small sample set, Hill *et al*.[29] used allelic expression assays and found that the rs1344706 genotype had a significant effect on *ZNF804A* allelic expression in second trimester fetal brain, with the schizophrenia risk (A) allele predicting reduced *ZNF804A* gene-level expression. In the subsequent independent study with a much larger sample, including healthy controls and psychiatric patients, Tao *et al*.[30] identified a previously uncharacterized, brain abundantly expressed and developmentally regulated truncated *ZNF804A* transcript (*ZNF804A*^{E3E4}) using next-generation sequencing and PCR-based methods (Figure 1a). Interestingly, they found that rs1344706 influenced expression of *ZNF804A*^{E3E4} mRNA only in fetal brain, and the risk (A) allele indicated reduced expression.[30] *ZNF804A*^{E3E4} expression was also significantly reduced in patients with schizophrenia compared with healthy controls,[30] suggesting that lower expression of this transcript was likely a risk factor. These studies converge on the conclusion that schizophrenia risk SNP rs1344706 has a *cis*-acting effect on *ZNF804A* expression in the brain during the fetal age, a critical period in neurodevelopment and probably schizophrenia onset.

Although various studies in addition to these two have also demonstrated *cis*-effects of rs1344706 on *ZNF804A* expression in brains,[22,29–33] the direction of allelic effects remains controversial. In addition, given that rs1344706 is an intronic SNP, the molecular mechanisms causing altered *ZNF804A* expression by the risk allele remain poorly understood. Although Hill *et al*.[34] proposed that rs1344706 was a functional polymorphism that affected DNA–protein interaction through an electrophoretic mobility shift assay, further validation studies using ChIP-Seq and reporter gene assays are still lacking. In addition, other possibilities, that is, rs1344706 altered the secondary structure of *ZNF804A* mRNA, or was in linkage disequilibrium (LD) with the causative mutations, cannot be excluded.

BIOLOGICAL FUNCTIONS OF *ZNF804A*

Given that the strong association between rs1344706 in *ZNF804A* and schizophrenia is reproducible and compelling, the possible roles of *ZNF804A* in schizophrenia pathogenesis have been intensively studied to provide novel insights into disease biology. The progress to date remains limited, but researchers have gained some hints through recent efforts. Consisting of four exons and transcribing a protein of 1210 amino acids, ZNF804A is expressed in the brain and contains a C2H2-type domain associated with the zinc-finger protein family (Figure 1b). However, the exact function of its protein product is currently unknown. Previous studies of proteins with this zinc-finger domain originally identified these proteins as DNA-binding molecules with a role in transcription. However, these proteins exhibit diverse interactions with numerous other molecules, including RNA and proteins.[35–39] As a result, *ZNF804A* likely has pivotal roles in cell physiology. Indeed, knockdown of *ZNF804A* in human neural progenitor cells (hNPCs) or in developing neurons derived from human-induced pluripotent stem cells resulted in altered expression of genes involved in cell adhesion, neurite outgrowth, synapse formation and cytokine signaling.[40,41] On the other hand, overexpression of *ZNF804A* in rat neural progenitor cells affects the expression of several genes associated with schizophrenia.[42] This latter study further localized the rat homolog of *ZNF804A*, zfp804A, to the nucleus of rat neural progenitor cells, supporting its potential roles in gene expression regualtion.[42]

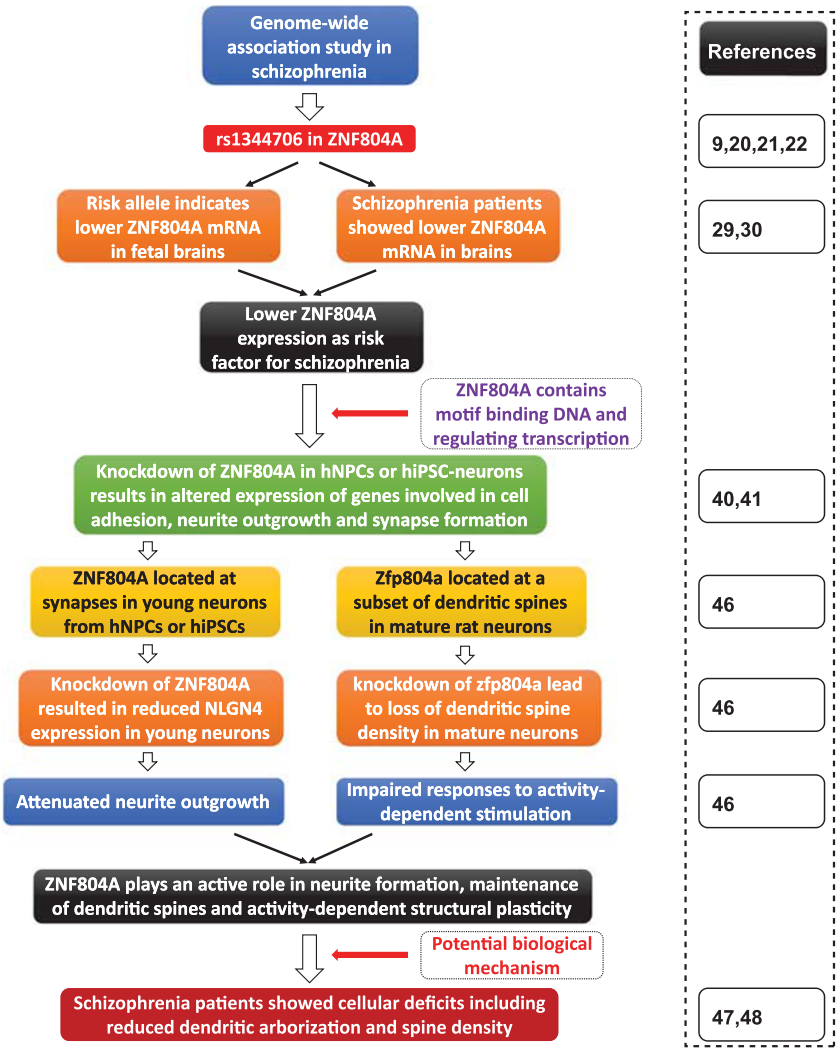

Figure 2. A hypothesized biological mechanism for rs1344706 in schizophrenia pathogenesis, hNPC, human neural progenitor cell; hiPSC, human-induced pluripotent stem cell; NLGN4, neuroligin-4; *ZNF804A*, zinc-finger protein 804A.

Recent studies on zfp804a have provided additional information regarding its function. For example, zfp804a has recently emerged as a target for HOXC8,[43] a major transcription factor known to promote nerve growth, suggesting its involvement in the regulation of early neurodevelopment. Further, Hinna *et al.*[44] demonstrated that zfp804a expression was increased in the rat brain at the time of birth, coinciding with neuronal differentiation. They also showed that zfp804a was localized to growth cones of growing neurites, implicating the role of zfp804a in growth cone function and neurite elongation.[44] Moreover, Chang *et al.*[45] identified changes in zfp804a expression in the rat hippocampus, frontal cortex, and thalamus across postnatal neurodevelopment, implying its possible roles in the development of these brain regions that are substantially affected in schizophrenics. These lines of evidence implicate the potential importance of *ZNF804A* (and zfp804a) in neurodevelopment, although its impact on neuronal phenotypes and mechanisms in psychiatric disease development were unclear until a recently published study.[46]

This landmark study was conducted to characterize the neuronal function of *ZNF804A* by Deans *et al.*[46] They first examined the subcellular localization of ZNF804A protein in diverse neurons derived from hNPCs or human-induced pluripotent stem cells or in primary rat cortical neurons. They showed that endogenous ZNF804A protein localized to somatodendritic compartments and colocalized with the putative synaptic markers (PSD-95) in developing neurons derived from hNPCs and human-induced pluripotent stem cells. In mature rat neurons, zfp804a was present in a subset of dendritic spines and colocalized with synaptic proteins in specific nanodomains. These data suggested that *ZNF804A* affected local signaling during neural development rather than having general gene expression regulatory roles in neurons. They then analyzed its functions in neurite formation, maintenance of dendritic spine morphology and responses to activity-dependent stimulations. Interestingly, young neurons with suppressed expression of *ZNF804A* exhibited attenuated neurite outgrowth potentially through reducing neuroligin-4 expression. In mature rat neurons, knockdown of zfp804a resulted in loss of dendritic spine density and impaired responses to activity-dependent stimulation.[46] Obviously, *ZNF804A* (zfp804a) has a functional role in synaptic development, probably via influencing local signaling of neuron synapses. To the best of our knowledge, this study for the first time described detailed localization of ZNF804A, and proposed the compelling hypothesis that this protein contributed to psychiatric disorders though alteration of neuronal and synaptic structures.

Overall, these studies found that the risk allele at rs1344706 is associated with reduced *ZNF804A* mRNA in human brain,

indicating its decreased expression as a likely risk factor for schizophrenia. Indeed, reduced *ZNF804A* expression in neurons resulted in aberrant neurite growth and loss of dendritic spine density, which was consistent with the clinical observations in the brains of schizophrenia patients.[47,48] The defined effects of *ZNF804A* on neurite growth and dendritic spines were also consistent with the previous findings that schizophrenia susceptibility genes often affect synaptic development and functions.[49–51] The hypothesized potential biological mechanism underlying the genetic risk of rs1344706 in schizophrenia and the logic of evidence are summarized in Figure 2.

NEUROIMAGING STUDIES OF *ZNF804A*

In addition to investigating the physiological outcome of genetic modification of *ZNF804A* in cell cultures and animals, analyzing changes in regional brain structures and functions may provide more information regarding the biological roles of *ZNF804A* in schizophrenia. In fact, these brain structural alterations, which are named intermediate phenotypes, are believed to better represent underlying pathophysiology than clinical diagnostic categories.[52,53] These intermediate phenotypes are assumed to involve the same biological pathways as the illness but exhibit a simpler etiologic background and are more closely related to relevant gene effects.[54,55] Although measuring these readouts may or may not directly increase power to detect schizophrenia risk genes,[54] they allow stratified delineation of the effects of particular risk alleles on brain structures and functions rather than that of simply the diagnostic phenotypes. This approach was previously validated in the studies of several schizophrenia candidate genes.[56–59]

In 2009, Esslinger *et al*.[60] investigated the influence of *ZNF804A* rs1344706 on functional connectivity between brain regions that were often associated with dysfunction in schizophrenia during working memory (N-back task) performance in a healthy sample. Notably, the authors observed reduced connectivity in the dorsolateral prefrontal cortex (DLPFC) between hemispheres and increased connectivity between the right DLPFC and left hippocampal formation (HF) during the working memory task.[60] In a follow-up study, the same imaging sample was reanalyzed to understand how the effects of rs1344706 generalize across different experimental settings.[61] This study revealed that the reduced interhemispheric DLPFC connectivity at higher rs1344706 risk status persisted in both resting state and cognitive states induced by an emotion recognition.[61] Contrarily, the increase in prefrontal–hippocampal connectivity was exclusively observed during working memory engagement.[61] Such changes in functional coupling between the right DLPFC and HF in the context of the working memory task were later replicated by Paulus *et al*.[62] in an independent healthy sample, albeit with weaker effects compared with original study.[60] These studies served as the initial evidence that rs1344706 affected brain function and thus memory formation.

This contention was further supported by Walter *et al*.[63] using a sample that overlapped with that reported in Esslinger *et al*.[60] They investigated cortical activation and connectivity associated with rs1344706 during performance on a theory of mind task (which measured participant's ability to infer mental state) in healthy subjects. A significant risk allele dose effect was observed for activation of regions implicated in theory of mind function: the dorsomedial prefrontal cortex and the temporoparietal cortex.[63] The authors also observed differences in activation of the left inferior prefrontal associated with the *ZNF804A* risk allele, and this brain region is attributed to general social information processing difficulties.[63] Later, in an independent healthy sample, Mohnke *et al*.[64] observed reduced activity of the left temporoparietal junction, dorsomedial prefrontal cortex and the posterior cingulate cortex with increasing numbers of rs1344706 risk alleles during theory of mind tasks, confirming the results in the study by Walter *et al*.[63] Mohnke *et al*.[64] further reported negative genotypic effects in the left dorsomedial prefrontal cortex and the temporal and parietal regions, highlighting the importance of *ZNF804A* in social cognition.

Given that *ZNF804A* is important in cognitive function in healthy individuals, researchers then analyzed its roles in such traits in schizophrenia patients. In an independent sample including normal controls, schizophrenia patients and their unaffected siblings, Rasetti *et al*.[65] found that siblings and patients exhibited abnormal DLPFC functional coupling with the HF during working memory tasks. *ZNF804A* rs1344706 significantly modulated right DLPFC coupling with the HF in the control group, which was further confirmed in siblings and patients.[65] Later, Thurin *et al*.[66] explored the role of rs1344706 on functional connectivity measures related to cognitive control (using the modified Flanker task that includes response inhibition). The rs1344706 allele loaded the effect on right DLPFC and anterior cingulate cortex functional coupling, with risk allele carriers exhibiting increased coupling. Taken together, these data provided further evidence that *ZNF804A* modulated cortical network connectivity during executive cognition.

In addition to brain function, efforts were also made to understand the effects of rs1344706 on brain structure. In contrast to the fruitful and relatively reproducible functional magnetic resonance imaging results for rs1344706 across samples, this schizophrenia risk SNP exhibited more variable effects on brain structures. Cousijn *et al*.[67] showed that genetic variations in *ZNF804A*, including the genome-wide significant risk SNP rs1344706, did not affect either total or regional brain volumes in 892 healthy young adults. In another study including 335 individuals with schizophrenia spectrum disorders and 198 healthy volunteers, Wassink *et al*.[68] observed significant effects of rs1344706 on total and frontal white matter volumes in the patient group, and the pattern of effects was concordant with risk allele carriers having larger volumes than non-risk homozygotes. In the healthy control group, risk allele homozygotes exhibited increased total white matter volume compared with non-risk allele carriers, replicating a previously reported association.[69] Further, in an independent sample, Voineskos *et al*.[70] found that individuals who were homozygous for the risk allele had reduced cortical gray matter thickness in the superior temporal gyrus and the anterior and posterior cingulate cortices compared with non-risk allele carriers. Those risk allele homozygotes also demonstrated reduced attention control, aligning with findings in the anterior cingulate cortex. These data of *ZNF804A* in brain structure modification were less consistent compared with its role in brain function. However, the data are not completely contradictory, as no difference in total brain volume could be attributed to simultaneous increases and decreases of certain brain regions. In addition, the effects of rs1344706 could differ in schizophrenic individuals with different behavioral defects. As a result, although we can tentatively conclude that *ZNF804A* SNP rs1344706 probably confers schizophrenia risk via augmenting white matter volume but reducing the bulk of matter volume, further stratified research analyzing its effects on specific structures of the brain according to the detailed behavioral phenotypes are needed.

NEUROCOGNITIVE STUDIES OF *ZNF804A*

As previously mentioned, one important characteristic of schizophrenia patients is the impairment of cognitive function. Hence, the neurocognitive analyses of *ZNF804A* rs1344706 were critical and compelling. One study by Walters *et al*.[71] on the neuropsychological effects of rs1344706 offered a likely explanation of *ZNF804A*'s effect on cognition. This study sought to investigate neuropsychological performance in patients and healthy controls on cognitive functions typically impaired in schizophrenia, that is,

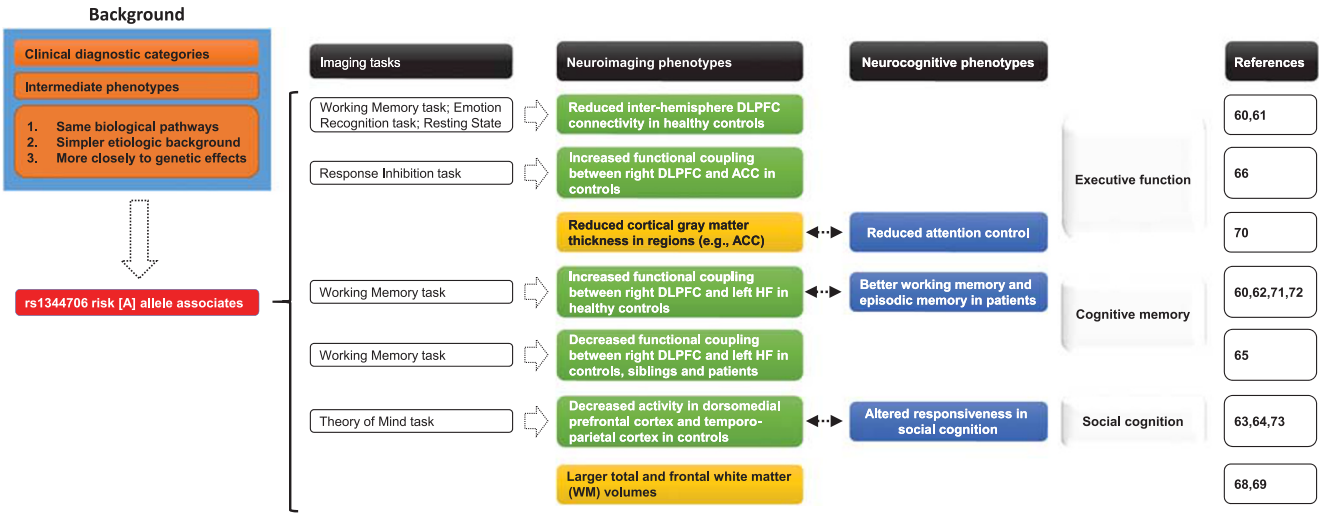

Figure 3. A summary of rs1344706's results in neuroimaging and neurocognitive studies. ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; HF, hippocampal formation.

intelligence quotient (IQ), episodic memory, working memory and attention control. Carriers of the risk allele exhibited significantly 'better' cognitive performance (e.g., working memory and episodic memory) compared with non-risk allele carriers only in patients but not healthy controls.[71] Of note, the affected cognitive functions implicated precisely those cortical regions affected by rs134706: DLPFC and HF.[60,65] In addition, Walters *et al.*[71] also found that the association between rs1344706 and schizophrenia was strengthened in patients with high IQ, indicating potential interaction effects between the risk variant rs1344706 and IQ. This interaction among cognitive functions (i.e., working memory and executive functions) was later confirmed in a Chinese sample by Chen *et al.*[72] but only in schizophrenia patients. Specifically, the schizophrenia risk allele was associated with poorer cognitive function in patients with high IQ but better cognitive function in patients with low IQ.[72] Chen *et al.*[72] reported that the association between rs1344706 and schizophrenia was modulated by IQ, with a stronger association among individuals with relatively high IQ. These converging lines of evidence suggest a possible modulating effect of IQ on the roles of rs1344706 in the etiology of schizophrenia. Further, the counterintuitive response, that is, rs1344706, affected cognition only in patients and not in healthy participants, suggesting that *ZNF804A* may be a risk factor for a subgroup of schizophrenia in which cognitive performance was relatively less impaired.

Following the recent 'theory of mind' study,[63] Hargreaves *et al.*[73] tested the hypothesis that the risk of rs1344706 was partially mediated through affecting social cognition. They tested this hypothesis based on behavioral measures of two constructs (The 'Eyes of the Mind' task, which indexes mental state decoding, and the 'Hinting task', which measures mental state reasoning) widely investigated in schizophrenia. They indexed attribution style when interpreting positive and negative events using the 'Interpersonal social attributions questionnaire'. They found that rs1344706 was significantly associated with variation in interpersonal attributions in healthy participants but not in patients.[73] Combining these results with those from the Walter *et al.*[63] imaging study, the *ZNF804A* risk allele was clearly associated with negatively altered responsiveness in social cognition in healthy participants.

Despite the consistency between the studies discussed above, the effect of *ZNF804A* was not always consistent, and negative results have also been observed. In 1507 healthy young men undergoing induction to military training, Stefanis *et al.*[74] sought to investigate whether common *ZNF804A* variants (e.g., rs1344706) affect psychosis-related intermediate phenotypes, such as cognitive performance dependent on prefrontal and frontotemporal brain function, schizotypal traits and attenuated psychotic experiences. However, they did not observe significant associations through central indexes of sustained attention or working memory performance. Instead, the psychosis risk variants were associated with a refined positive schizotypy phenotype characterized primarily by self-rated paranoia/ideas of reference. This phenotype was previously suggested to reflect genetic tendency to psychosis (the high likelihood to 'misinterpret otherwise neutral social cues and perceptual experiences in one's immediate environment, as personally relevant and significant information').[74] As a result, the fact that this study did not arrive at a significant observation did not reject the previous conclusion, as clues of *ZNF804A*'s impact on cognition were presented. In addition, the negative results could be attributed to the biased sample selection, as all participants were young males experiencing military activities.

Overall, these neuroimaging and neurocognitive studies implied that the *ZNF804A* rs1344706, as a genome-wide significant variant, may display pleiotropic effects on the intermediate phenotypes of schizophrenia, and a summary of the results is presented in Figure 3.

EXPANDING *ZNF804A* COMMON VARIANTS IN SCHIZOPHRENIA AMONG EUROPEANS

Although demonstrating genome-wide significant association in GWAS,[9] no direct evidence suggested that rs1344706 was the strongest genetic variant within *ZNF804A*. Although Williams *et al.*[22] performed fine-mapping analyses in the UK sample and suggested that rs1344706 was among the strongest associations signals, phenotypic and genetic heterogeneity still exist among different populations. For example, Riley *et al.*[20] replicated the association at rs1344706 and extended the analyses to 11 additional LD-tagging SNPs that captured common variations across *ZNF804A* in an Irish sample. Intriguingly, the GWAS SNP rs1344706 was not exclusively significant in this study.[20] An additional SNP, rs7597593, which was in moderate LD with rs1344706 in Europeans ($r^2 = 0.40$), exhibited a stronger association with schizophrenia. Similarly, Zhang *et al.*[75] performed an

Table 2. Published association results for rs1344706 with schizophrenia in Asians

Study	*Area*	*No. of case*	*No. of control*	P-*value*	*OR*	*References*
O'Donovan *et al*. (2008)	Shanghai, China	1034	1034	0.332	1.063	9
Yue *et al*. (2011)	Beijing, China	650	1340	0.301	1.112	17
Shi *et al*. (2011)	Multiple Area	3750	6468	0.713	1.014	15
Zhang *et al*. (2011)	Shaanxi01, China	566	574	0.00083	1.324	94
	Shaanxi02, China	101[a]	—	0.058	1.198	94
Li *et al*. (2011)	Yuxi, China	488	694	0.880	1.013	96
	Kunming, China	403	604	0.490	0.939	96
Liou *et al*. (2012)	Taiwan, China	522	973	0.584	1.047	99
Li *et al*. (2012)	Singapore	885	976	0.389	1.056	104
Chen *et al*. (2012)	Shandong, China	570	448	0.038	1.254	72
Yang *et al*. (2013)	Xinxiang, China	1025	977	0.087	1.116	109
Wong *et al*. (2013)	Sichuan, China	1086	1060	0.118	0.909	100
Lan *et al*. (2013)	Guangdong, China	250	201	0.025	0.734	97
Schwab *et al*. (2013)	Indonesia	1067	1111	0.019	1.155	95
Aberg *et al*. (2013)	Multiple Area	579[b]	—	0.289	0.930	110
Saito *et al*. (2014)	Japan	1032	993	0.145	1.104	111
Stepanov *et al*. (2015)	Kazakhstan	101	189	0.910	0.980	112
Wang *et al*. (2016)	Jiangsu, China	1284	990	0.497	0.961	98

Abbreviation: OR, odds ratio. [a]In Zhang *et al*.,[75,94] the Shaanxi02 sample is a family-based sample including 101 probands. [b]In Aberg *et al*.,[110] the Asian sample includes 2296 individuals from 579 families.

association analysis of rs7597593 in four GWAS cohorts of European ancestry and found that rs7597593 was significantly associated with schizophrenia in the combined samples. Rs1344706 was also significant in the study by Zhang *et al*.[75] but was less consistent than rs7597593 across samples. More recently, in the PGC2 schizophrenia GWAS,[10] a newly identified SNP rs11693094 exhibited the strongest association within the *ZNF804A* region ($P = 1.53 \times 10^{-12}$; Figure 1), although rs1344706 and rs7597593 were also genome-wide significantly associated with schizophrenia in this GWAS ($P = 1.27 \times 10^{-10}$ and 1.47×10^{-9}, respectively). These results suggest that there are (at least partially) independent association signals for schizophrenia within *ZNF804A* in Europeans.

RARE GENETIC VARIANTS AT *ZNF804A* AND RISK OF SCHIZOPHRENIA

In addition to the risk SNPs identified by GWAS, there are other types of rare genetic variants accounting for the disease risk of specific genes. In the case of schizophrenia, both common and rare variants could contribute to its genetic risk.[76] Based on this hypothesis, Steinberg *et al*.[21] investigated copy number variants (CNVs) at the *ZNF804A* locus in psychiatric samples, including schizophrenia, bipolar disorder, depression and anxiety. They identified three CNVs spanning at least part of *ZNF804A* after screening 5408 psychiatric patients, and none of these CNVs were present in the 39 481 controls ($P = 0.0016$).[21] These CNVs included a deletion in an individual with schizophrenia, a deletion in an individual with anxiety and a duplication in an individual with bipolar disorder. Although this result provided important evidence regarding the involvement of CNVs in the disease risk conferred by *ZNF804A*, caution is also required as other genome-wide CNV studies of schizophrenia and bipolar disorder have failed to identify additional carriers of CNVs affecting *ZNF804A*.[77–85]

To understand whether rare (frequency ~ 0.001%) coding variants in *ZNF804A* are associated with schizophrenia, Dwyer *et al*.[86] screened the coding regions of the gene in 517 schizophrenic cases and 501 controls and further genotyped rare nonsynonymous variants in an independent sample (692 cases and 1456 controls). This sample had sufficient power to detect associations with rare alleles with an effect size (odds ratio) of 5.00. However, no single rare nonsynonymous variant was associated with schizophrenia in their study or the burden test. The negative results were then supported by the current exome-wide or genome-wide sequencing analyses of rare exonic mutations in schizophrenia.[87–91] As such, rare non-synonymous variants at the *ZNF804A* locus are unlikely involved in schizophrenia susceptibility.

RELEVANCE TO CLINICAL INTERVENTION

With all the evidence for its association with schizophrenia risk, rs1344706 influences the response of positive symptoms to antipsychotics in schizophrenia patients.[92] Specifically, the risk genotype AA of rs1344706 led to a poorer response of positive symptoms in patients.[92] In another study, Zhang *et al*.[93] found that rs1344706 was associated with a positive response to atypical antipsychotic treatment in a group of first-episode schizophrenia patients, and the risk allele carriers exhibited significantly less improvement in total Positive and Negative Syndrome Scale scores and positive subscores after treatment compared with G homozygotes. These studies indicated that *ZNF804A* rs1344706 does not only influence the development of schizophrenia but also prognostic response to therapies, making it a potential target for future intervention development. However, this proposal is still under debate, as the OR (~1.1) conferred by rs1344706 is only considered modest.

COMMON VARIANTS IN *ZNF804A* AND RISK OF SCHIZOPHRENIA IN ASIANS

To date, converging data suggest that *ZNF804A* is undoubtedly a risk gene for schizophrenia in populations of European ancestry. However, in the genetically divergent Asian population, a significant association of rs1344706 with schizophrenia was only replicated in several cohorts,[72,94,95] whereas negative results were observed in most additional samples (Table 2).[96–98] In addition, rs1344706 was not associated with schizophrenia in recent Han Chinese GWASs, suggesting that it is likely not a susceptibility variant for schizophrenia in some Asian populations.[15,17,99,100] Researchers have attempted to prove this hypothesis through larger meta-analyses but could not obtain consistent results.[101–103] We previously compared the LD patterns of the genomic region covering *ZNF804A* between Asians and Europeans and observed sharp differences,[104] supporting the

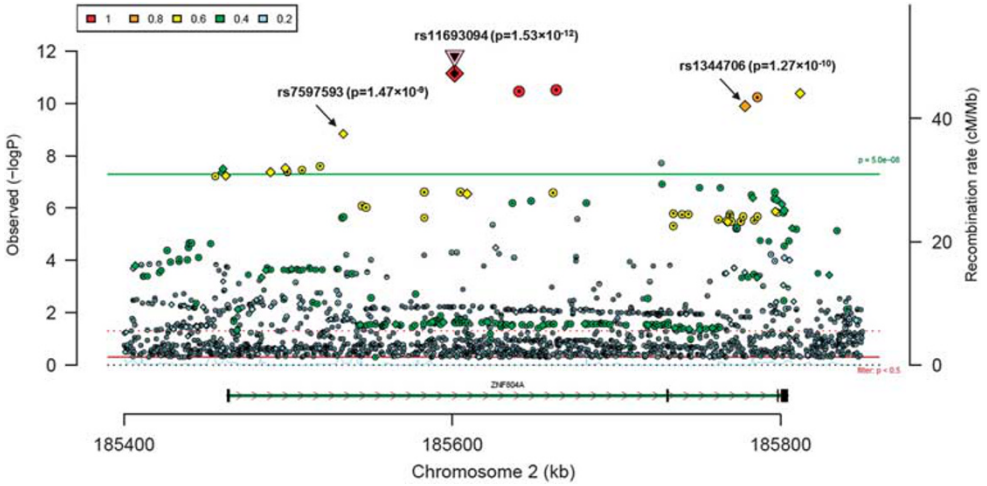

Figure 4. Associations of *ZNF804A* common variants with schizophrenia in PGC2 genome-wide association studies (GWAS).[10]

Table 3. Published association results for rs1366842 with schizophrenia in Asians

Study	*Area*	*No. of case*	*No. of control*	P-*value*	*OR*	*References*
Yue *et al*. (2011)	Beijing01, China	746	1599	0.917	0.991	17
Yue *et al*. (2011)	Beijing02, China	1703	1373	0.152	1.110	17
Xiao *et al*. (2011)	Xinxiang, China	498	450	0.469	1.094	113
Zhang *et al*. (2012)	Shaanxi, China	492	516	0.025	1.306	105
Li *et al*. (2012)	Yuxi, China	497	570	0.053	1.271	104
Li *et al*. (2012)	Singapore	885	976	0.141	1.138	104
Aberg *et al*. (2013)	Multiple Area	579[a]	—	0.793	0.978	110
Li *et al*. (2013)	Meta-analysis	4323	5034	0.004	1.130	106
Huang *et al*. (2016)	Meta-analysis	5400	5484	0.00996	1.095	103

Abbreviation: OR, odds ratio. [a]In Aberg *et al*.,[110] the Asian sample includes 2296 individuals from 579 families.

hypothesis that rs1344706 is unlikely a causative-linked variant for schizophrenia in Asians. On the other hand, the differences of rs1344706 in association with schizophrenia between Europeans and Asians likely reflect the genetic heterogeneity often observed in the genetic association analyses for complex diseases, probably as a result of differential population histories. Other population specific factors, such as diet, culture or environmental exposure, may also contribute to this inconsistency.

In addition to rs1344706, several studies have also analyzed the associations of rs7597593 with schizophrenia in Asian populations. However, only Schwab *et al*.[95] successfully replicated the associations in Indonesian populations, whereas other studies, including the overall meta-analysis, failed to achieve any significant associations.[17,100,104]

In contrast to these two European positive SNPs, we previously identified a functional SNP rs359895 in the promoter region of *ZNF804A* as significantly associated with schizophrenia in Southern Han Chinese populations. Further *in vitro* analysis showed that the risk SNP could affect transcription factor Sp1 binding affinity and promoter activity.[96] These results confirmed *ZNF804A* as a susceptibility gene for schizophrenia in Asian populations. However, rs359895 is in low LD with either rs1344706 or rs7597593 in either population, implying that the association signals are likely independent.

Another risk SNP rs1366842 has also been reported in Asians by Zhang *et al*.[105] in a small Han Chinese case–control sample. This SNP locates in the exon region of *ZNF804A* and results in an amino-acid change from threonine to lysine. Further meta-analyses confirmed that this SNP was significantly associated with schizophrenia (Table 3).[103,106]

In sum, although not implicated in Asian schizophrenia GWAS, these collective results suggest that *ZNF804A* common variants may still confer a risk of schizophrenia in this population, with distinct association signals compared with those in Europeans. Future research addressing the questions regarding which variant (s) within *ZNF804A* is causal for schizophrenia and what are the relevant biological mechanisms is needed.

CONCLUSIONS

In this review, we have outlined the compelling research showing that *ZNF804A* is a significant factor in the onset of schizophrenia. Ever since the identification of *ZNF804A*, the first genome-wide associated common variant for schizophrenia and bipolar disorder, additional risk genes have been discovered,[10–12] yet *ZNF804A* is still one of the most intriguing and promising risk genes with substantial supporting evidence for schizophrenia and the broader psychosis phenotype.[20–22] Previous clues of the gene's neurobiological function have been gathered from neuroimaging and neurocognitive studies in which *ZNF804A* rs1344706 is associated with altered functional connectivity, relatively less impaired neuropsychological performance and reduced activation during measures of social cognition.[60,63,65,66,68,71,73] More importantly, recent studies showed that the development and maturation of neurons in embryonic and adult stem cells appear to be sensitive to the expression of *ZNF804A*, with downregulation of *ZNF804A* in neurons causing aberrant neurite growth and decreased dendritic

spine density.[46] Taken together, this protein has a significant function in schizophrenia that may help with our understanding and control of this disease and other conditions where dysregulation of this gene or its pathways are involved. However, more exploration is required to reach this goal. For example, the genes regulated by *ZNF804A*[40–42,107] remain to be investigated in neurodevelopment and schizophrenia onset, and pathway analyses have demonstrated their involvement in several aspects of nervous system function and development associated with schizophrenia, including cell adhesion, neurite outgrowth and synapse formation.[40,41] In addition, as a transcription factor, the binding motif of ZNF804A protein on DNA sequence is unclear; thus, the genome-wide prediction of ZNF804A targets remains difficult. Further functional experiments together with bioinformatics analyses might answer this question. In addition, elucidating the biological roles of *ZNF804A* in animal and human studies are important next steps in understanding schizophrenia pathophysiology.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

This work was supported by CAS Pioneer Hundred Talents Program (to ML).

REFERENCES

1 Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. *PLoS Med* 2005; **2**: e141.
2 Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry* 2003; **60**: 1187–1192.
3 Kendler KS, Diehl SR. The genetics of schizophrenia: a current, genetic–epidemiologic perspective. *Schizophr Bull* 1993; **19**: 261–285.
4 Maki P, Veijola J, Jones PB, Murray GK, Koponen H, Tienari P *et al.* Predictors of schizophrenia—a review. *Br Med Bull* 2005; **73-74**: 1–15.
5 Luo XJ, Li M, Huang L, Steinberg S, Mattheisen M, Liang G *et al.* Convergent lines of evidence support CAMKK2 as a schizophrenia susceptibility gene. *Mol Psychiatry* 2014; **19**: 774–783.
6 Li M, Mo Y, Luo XJ, Xiao X, Shi L, Peng YM *et al.* Genetic association and identification of a functional SNP at GSK3beta for schizophrenia susceptibility. *Schizophr Res* 2011; **133**: 165–171.
7 Zhang W, Xiao MS, Ji S, Tang J, Xu L, Li X *et al.* Promoter variant rs2301228 on the neural cell adhesion molecule 1 gene confers risk of schizophrenia in Han Chinese. *Schizophr Res* 2014; **160**: 88–96.
8 Huffaker SJ, Chen J, Nicodemus KK, Sambataro F, Yang F, Mattay V *et al.* A primate-specific, brain isoform of KCNH2 affects cortical physiology, cognition, neuronal repolarization and risk of schizophrenia. *Nat Med* 2009; **15**: 509–518.
9 O'Donovan MC, Craddock N, Norton N, Williams H, Peirce T, Moskvina V *et al.* Identification of loci associated with schizophrenia by genome-wide association and follow-up. *Nat Genet* 2008; **40**: 1053–1055.
10 Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014; **511**: 421–427.
11 Ripke S, O'Dushlaine C, Chambert K, Moran JL, Kahler AK, Akterin S *et al.* Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat Genet* 2013; **45**: 1150–1159.
12 Ripke S, Sanders AR, Kendler KS, Levinson DF, Sklar P, Holmans PA *et al.* Genome-wide association study identifies five new schizophrenia loci. *Nat Genet* 2011; **43**: 969–976.
13 Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF *et al.* Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* 2009; **460**: 748–752.
14 Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I *et al.* Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature* 2009; **460**: 753–757.
15 Shi Y, Li Z, Xu Q, Wang T, Li T, Shen J *et al.* Common variants on 8p12 and 1q24.2 confer risk of schizophrenia. *Nat Genet* 2011; **43**: 1224–1227.
16 Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D *et al.* Common variants conferring risk of schizophrenia. *Nature* 2009; **460**: 744–747.
17 Yue WH, Wang HF, Sun LD, Tang FL, Liu ZH, Zhang HX *et al.* Genome-wide association study identifies a susceptibility locus for schizophrenia in Han Chinese at 11p11.2. *Nat Genet* 2011; **43**: 1228–1231.
18 Bergen SE, O'Dushlaine CT, Ripke S, Lee PH, Ruderfer DM, Akterin S *et al.* Genome-wide association study in a Swedish population yields support for greater CNV and MHC involvement in schizophrenia compared with bipolar disorder. *Mol Psychiatry* 2012; **17**: 880–886.
19 Manolio TA. Genomewide association studies and assessment of the risk of disease. *N Engl J Med* 2010; **363**: 166–176.
20 Riley B, Thiselton D, Maher BS, Bigdeli T, Wormley B, McMichael GO *et al.* Replication of association between schizophrenia and ZNF804A in the Irish case–control study of Schizophrenia sample. *Mol Psychiatry* 2010; **15**: 29–37.
21 Steinberg S, Mors O, Borglum AD, Gustafsson O, Werge T, Mortensen PB *et al.* Expanding the range of ZNF804A variants conferring risk of psychosis. *Mol Psychiatry* 2011; **16**: 59–66.
22 Williams HJ, Norton N, Dwyer S, Moskvina V, Nikolov I, Carroll L *et al.* Fine mapping of ZNF804A and genome-wide significant evidence for its involvement in schizophrenia and bipolar disorder. *Mol Psychiatry* 2011; **16**: 429–441.
23 Zollner S, Pritchard JK. Overcoming the winner's curse: estimating penetrance parameters from case–control data. *Am J Hum Genet* 2007; **80**: 605–615.
24 Nci-Nhgri Working Group on Replication in Association Studies, Chanock SJ, Manolio T, Boehnke M, Boerwinkle E, Hunter DJ *et al.* Replicating genotype–phenotype associations. *Nature* 2007; **447**: 655–660.
25 Clarke R, Xu P, Bennett D, Lewington S, Zondervan K, Parish S *et al.* Lymphotoxin-alpha gene and risk of myocardial infarction in 6,928 cases and 2,712 controls in the ISIS case-control study. *PLoS Genet* 2006; **2**: e107.
26 Donohoe G, Morris DW, Corvin A. The psychosis susceptibility gene ZNF804A: associations, functions, and phenotypes. *Schizophr Bull* 2010; **36**: 904–909.
27 Richards AL, Jones L, Moskvina V, Kirov G, Gejman PV, Levinson DF *et al.* Schizophrenia susceptibility alleles are enriched for alleles that affect gene expression in adult human brain. *Mol Psychiatry* 2012; **17**: 193–201.
28 Bacanu SA, Chen J, Sun J, Richardson K, Lai CQ, Zhao Z *et al.* Functional SNPs are enriched for schizophrenia association signals. *Mol Psychiatry* 2014; **19**: 276–277.
29 Hill MJ, Bray NJ. Evidence that schizophrenia risk variation in the ZNF804A gene exerts its effects during fetal brain development. *Am J Psychiatry* 2012; **169**: 1301–1308.
30 Tao R, Cousijn H, Jaffe AE, Burnet PW, Edwards F, Eastwood SL *et al.* Expression of ZNF804A in human brain and alterations in schizophrenia, bipolar disorder, and major depressive disorder: a novel transcript fetally regulated by the psychosis risk variant rs1344706. *JAMA Psychiatry* 2014; **71**: 1112–1120.
31 Guella I, Sequeira A, Rollins B, Morgan L, Myers RM, Watson SJ *et al.* Evidence of allelic imbalance in the schizophrenia susceptibility gene ZNF804A in human dorsolateral prefrontal cortex. *Schizophr Res* 2014; **152**: 111–116.
32 Guella I, Vawter MP. Allelic imbalance associated with the schizophrenia risk SNP rs1344706 indicates a *cis*-acting variant in ZNF804A. *Schizophr Res* 2014; **153**: 243–245.
33 Schultz CC, Nenadic I, Riley B, Vladimirov VI, Wagner G, Koch K *et al.* ZNF804A and cortical structure in schizophrenia: *in vivo* and postmortem studies. *Schizophr Bull* 2014; **40**: 532–541.
34 Hill MJ, Bray NJ. Allelic differences in nuclear protein binding at a genome-wide significant risk variant for schizophrenia in ZNF804A. *Mol Psychiatry* 2011; **16**: 787–789.
35 Klug A. The discovery of zinc fingers and their applications in gene regulation and genome manipulation. *Annu Rev Biochem* 2010; **79**: 213–231.
36 Klug A, Rhodes D. Zinc fingers: a novel protein fold for nucleic acid recognition. *Cold Spring Harb Symp Quant Biol* 1987; **52**: 473–482.
37 Brown RS. Zinc finger proteins: getting a grip on RNA. *Curr Opin Struct Biol* 2005; **15**: 94–98.
38 Berg JM. Zinc fingers and other metal-binding domains. Elements for interactions between macromolecules. *J Biol Chem* 1990; **265**: 6513–6516.
39 Laity JH, Lee BM, Wright PE. Zinc finger proteins: new insights into structural and functional diversity. *Curr Opin Struct Biol* 2001; **11**: 39–46.
40 Hill MJ, Jeffries AR, Dobson RJ, Price J, Bray NJ. Knockdown of the psychosis susceptibility gene ZNF804A alters expression of genes involved in cell adhesion. *Hum Mol Genet* 2012; **21**: 1018–1024.
41 Chen J, Lin M, Hrabovsky A, Pedrosa E, Dean J, Jain S *et al.* ZNF804A transcriptional networks in differentiating neurons derived from induced pluripotent stem cells of human origin. *PLoS One* 2015; **10**: e0124597.
42 Girgenti MJ, LoTurco JJ, Maher BJ. ZNF804a regulates expression of the schizophrenia-associated genes PRSS16, COMT, PDE4B, and DRD2. *PLoS One* 2012; **7**: e32404.
43 Chung HJ, Lee JY, Deocaris CC, Min H, Kim SH, Kim MH. Mouse homologue of the schizophrenia susceptibility gene ZNF804A as a target of Hoxc8. *J Biomed Biotechnol* 2010; **2010**: 231708.

44 Hinna KH, Rich K, Fex-Svenningsen A, Benedikz E. The rat homolog of the schizophrenia susceptibility gene ZNF804A is highly expressed during brain development, particularly in growth cones. *PLoS One* 2015; **10**: e0132456.
45 Chang EH, Kirtley A, Chandon TS, Borger P, Husain-Krautter S, Vingtdeux V *et al.* Postnatal neurodevelopmental expression and glutamate-dependent regulation of the ZNF804A rodent homologue. *Schizophr Res* 2015; **168**: 402–410.
46 Deans MPJ, Raval P, Sellers JK, Gatford JFN, Halai S, Duarte RRR *et al.* Psychosis risk candidate ZNF804A localizes to synapses and regulates neurite formation and dendritic spine structure. *Biol Psychiatry* 2016; doi:10.1016/j.biopsych.2016.08.038.
47 Penzes P, Cahill ME, Jones KA, VanLeeuwen JE, Woolfrey KM. Dendritic spine pathology in neuropsychiatric disorders. *Nat Neurosci* 2011; **14**: 285–293.
48 Konopaske GT, Lange N, Coyle JT, Benes FM. Prefrontal cortical dendritic spine pathology in schizophrenia and bipolar disorder. *JAMA Psychiatry* 2014; **71**: 1323–1331.
49 Hattori T, Shimizu S, Koyama Y, Yamada K, Kuwahara R, Kumamoto N *et al.* DISC1 regulates cell–cell adhesion, cell-matrix adhesion and neurite outgrowth. *Mol Psychiatry* 2010; **15**: 798–809.
50 Ito H, Morishita R, Shinoda T, Iwamoto I, Sudo K, Okamoto K *et al.* Dysbindin-1, WAVE2 and Abi-1 form a complex that regulates dendritic spine formation. *Mol Psychiatry* 2010; **15**: 976–986.
51 Ochs SM, Dorostkar MM, Aramuni G, Schon C, Filser S, Poschl J *et al.* Loss of neuronal GSK3beta reduces dendritic spine stability and attenuates excitatory synaptic transmission via beta-catenin. *Mol Psychiatry* 2015; **20**: 482–489.
52 Meyer-Lindenberg A, Weinberger DR. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nat Rev Neurosci* 2006; **7**: 818–827.
53 Rasetti R, Weinberger DR. Intermediate phenotypes in psychiatric disorders. *Curr Opin Genet Dev* 2011; **21**: 340–348.
54 Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* 2003; **160**: 636–645.
55 Greenwood TA, Braff DL, Light GA, Cadenhead KS, Calkins ME, Dobie DJ *et al.* Initial heritability analyses of endophenotypic measures for schizophrenia: the consortium on the genetics of schizophrenia. *Arch Gen Psychiatry* 2007; **64**: 1242–1250.
56 Meyer-Lindenberg A, Nichols T, Callicott JH, Ding J, Kolachana B, Buckholtz J *et al.* Impact of complex genetic variation in COMT on human brain function. *Mol Psychiatry* 2006; **11**: 867–877.
57 Nicodemus KK, Luna A, Vakkalanka R, Goldberg T, Egan M, Straub RE *et al.* Further evidence for association between ErbB4 and schizophrenia and influence on cognitive intermediate phenotypes in healthy controls. *Mol Psychiatry* 2006; **11**: 1062–1065.
58 Eisenberg DP, Ianni AM, Wei SM, Kohn PD, Kolachana B, Apud J *et al.* Brain-derived neurotrophic factor (BDNF) Val(66)Met polymorphism differentially predicts hippocampal function in medication-free patients with schizophrenia. *Mol Psychiatry* 2013; **18**: 713–720.
59 Papaleo F, Burdick MC, Callicott JH, Weinberger DR. Epistatic interaction between COMT and DTNBP1 modulates prefrontal function in mice and in humans. *Mol Psychiatry* 2014; **19**: 311–316.
60 Esslinger C, Walter H, Kirsch P, Erk S, Schnell K, Arnold C *et al.* Neural mechanisms of a genome-wide supported psychosis variant. *Science* 2009; **324**: 605.
61 Esslinger C, Kirsch P, Haddad L, Mier D, Sauer C, Erk S *et al.* Cognitive state and connectivity effects of the genome-wide significant psychosis variant in ZNF804A. *Neuroimage* 2011; **54**: 2514–2523.
62 Paulus FM, Krach S, Bedenbender J, Pyka M, Sommer J, Krug A *et al.* Partial support for ZNF804A genotype-dependent alterations in prefrontal connectivity. *Hum Brain Mapp* 2013; **34**: 304–313.
63 Walter H, Schnell K, Erk S, Arnold C, Kirsch P, Esslinger C *et al.* Effects of a genome-wide supported psychosis risk variant on neural activation during a theory-of-mind task. *Mol Psychiatry* 2010; **16**: 462–470.
64 Mohnke S, Erk S, Schnell K, Schutz C, Romanczuk-Seiferth N, Grimm O *et al.* Further evidence for the impact of a genome-wide-supported psychosis risk variant in ZNF804A on the Theory of Mind Network. *Neuropsychopharmacology* 2014; **39**: 1196–1205.
65 Rasetti R, Sambataro F, Chen Q, Callicott JH, Mattay VS, Weinberger DR. Altered cortical network dynamics: a potential intermediate phenotype for schizophrenia and association with ZNF804A. *Arch Gen Psychiatry* 2011; **68**: 1207–1217.
66 Thurin K, Rasetti R, Sambataro F, Safrin M, Chen Q, Callicott JH *et al.* Effects of ZNF804A on neurophysiologic measures of cognitive control. *Mol Psychiatry* 2013; **18**: 852–854.
67 Cousijn H, Rijpkema M, Harteveld A, Harrison PJ, Fernandez G, Franke B *et al.* Schizophrenia risk gene ZNF804A does not influence macroscopic brain structure: an MRI study in 892 volunteers. *Mol Psychiatry* 2012; **17**: 1155–1157.
68 Wassink TH, Epping EA, Rudd D, Axelsen M, Ziebell S, Fleming FW *et al.* Influence of ZNF804a on brain structure volumes and symptom severity in individuals with schizophrenia. *Arch Gen Psychiatry* 2012; **69**: 885–892.
69 Lencz T, Szeszko PR, DeRosse P, Burdick KE, Bromet EJ, Bilder RM *et al.* A schizophrenia risk gene, ZNF804A, influences neuroanatomical and neurocognitive phenotypes. *Neuropsychopharmacology* 2010; **35**: 2284–2291.
70 Voineskos AN, Lerch JP, Felsky D, Tiwari A, Rajji TK, Miranda D *et al.* The ZNF804A gene: characterization of a novel neural risk mechanism for the major psychoses. *Neuropsychopharmacology* 2011; **36**: 1871–1878.
71 Walters JT, Corvin A, Owen MJ, Williams H, Dragovic M, Quinn EM *et al.* Psychosis susceptibility gene ZNF804A and cognitive performance in schizophrenia. *Arch Gen Psychiatry* 2010; **67**: 692–700.
72 Chen M, Xu Z, Zhai J, Bao X, Zhang Q, Gu H *et al.* Evidence of IQ-modulated association between ZNF804A gene polymorphism and cognitive function in schizophrenia patients. *Neuropsychopharmacology* 2012; **37**: 1572–1578.
73 Hargreaves A, Morris DW, Rose E, Fahey C, Moore S, Cummings E *et al.* ZNF804A and social cognition in patients with schizophrenia and healthy controls. *Mol Psychiatry* 2012; **17**: 118–119.
74 Stefanis NC, Hatzimanolis A, Avramopoulos D, Smyrnis N, Evdokimidis I, Stefanis CN *et al.* Variation in psychosis gene ZNF804A is associated with a refined schizotypy phenotype but not neurocognitive performance in a large young male population. *Schizophr Bull* 2013; **39**: 1252–1260.
75 Zhang F, Chen Q, Ye T, Lipska BK, Straub RE, Vakkalanka R *et al.* Evidence of sex-modulated association of ZNF804A with schizophrenia. *Biol Psychiatry* 2011; **69**: 914–917.
76 Owen MJ, Craddock N, O'Donovan MC. Suggestion of roles for both common and rare risk variants in genome-wide studies of schizophrenia. *Arch Gen Psychiatry* 2010; **67**: 667–673.
77 Xu B, Roos JL, Levy S, van Rensburg EJ, Gogos JA, Karayiorgou M. Strong association of *de novo* copy number mutations with sporadic schizophrenia. *Nat Genet* 2008; **40**: 880–885.
78 International Schizophrenia Consortium. Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature* 2008; **455**: 237–241.
79 Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM *et al.* Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science* 2008; **320**: 539–543.
80 Stefansson H, Rujescu D, Cichon S, Pietilainen OP, Ingason A, Steinberg S *et al.* Large recurrent microdeletions associated with schizophrenia. *Nature* 2008; **455**: 232–236.
81 Vacic V, McCarthy S, Malhotra D, Murray F, Chou HH, Peoples A *et al.* Duplications of the neuropeptide receptor gene VIPR2 confer significant risk for schizophrenia. *Nature* 2011; **471**: 499–503.
82 Ikeda M, Aleksic B, Kirov G, Kinoshita Y, Yamanouchi Y, Kitajima T *et al.* Copy number variation in schizophrenia in the Japanese population. *Biol Psychiatry* 2010; **67**: 283–286.
83 Li Z, Chen J, Xu Y, Yi Q, Ji W, Wang P *et al.* Genome-wide analysis of the role of copy number variation in schizophrenia risk in Chinese. *Biol Psychiatry* 2016; **80**: 331–337.
84 Kushima I, Aleksic B, Nakatochi M, Shimamura T, Shiino T, Yoshimi A *et al.* High-resolution copy number variation analysis of schizophrenia in Japan. *Mol Psychiatry* 2017; **22**: 430–440.
85 Szatkiewicz JP, O'Dushlaine C, Chen G, Chambert K, Moran JL, Neale BM *et al.* Copy number variation in schizophrenia in Sweden. *Mol Psychiatry* 2014; **19**: 762–773.
86 Dwyer S, Williams H, Holmans P, Moskvina V, Craddock N, Owen MJ *et al.* No evidence that rare coding variants in ZNF804A confer risk of schizophrenia. *Am J Med Genet B* 2010; **153B**: 1411–1416.
87 Purcell SM, Moran JL, Fromer M, Ruderfer D, Solovieff N, Roussos P *et al.* A polygenic burden of rare disruptive mutations in schizophrenia. *Nature* 2014; **506**: 185–190.
88 Fromer M, Pocklington AJ, Kavanagh DH, Williams HJ, Dwyer S, Gormley P *et al.* *De novo* mutations in schizophrenia implicate synaptic networks. *Nature* 2014; **506**: 179–184.
89 Girard SL, Gauthier J, Noreau A, Xiong L, Zhou S, Jouan L *et al.* Increased exonic *de novo* mutation rate in individuals with schizophrenia. *Nat Genet* 2011; **43**: 860–863.
90 Xu B, Roos JL, Dexheimer P, Boone B, Plummer B, Levy S *et al.* Exome sequencing supports a *de novo* mutational paradigm for schizophrenia. *Nat Genet* 2011; **43**: 864–868.
91 Singh T, Kurki MI, Curtis D, Purcell SM, Crooks L, McRae J *et al.* Rare loss-of-function variants in SETD1A are associated with schizophrenia and developmental disorders. *Nat Neurosci* 2016; **19**: 571–577.
92 Mossner R, Schuhmacher A, Wagner M, Lennertz L, Steinbrecher A, Quednow BB *et al.* The schizophrenia risk gene ZNF804A influences the antipsychotic response of positive schizophrenia symptoms. *Eur Arch Psychiatry Clin Neurosci* 2012; **262**: 193–197.
93 Zhang J, Wu X, Diao F, Gan Z, Zhong Z, Wei Q *et al.* Association analysis of ZNF804A (zinc finger protein 804A) rs1344706 with therapeutic response to

atypical antipsychotics in first-episode Chinese patients with schizophrenia. *Compr Psychiatry* 2012; **53**: 1044–1048.
94 Zhang R, Lu SM, Qiu C, Liu XG, Gao CG, Guo TW *et al.* Population-based and family-based association studies of ZNF804A locus and schizophrenia. *Mol Psychiatry* 2011; **16**: 360–361.
95 Schwab SG, Kusumawardhani AA, Dai N, Qin W, Wildenauer MD, Agiananda F *et al.* Association of rs1344706 in the ZNF804A gene with schizophrenia in a case/control sample from Indonesia. *Schizophr Res* 2013; **147**: 46–52.
96 Li M, Luo XJ, Xiao X, Shi L, Liu XY, Yin LD *et al.* Allelic differences between Han Chinese and Europeans for functional variants in ZNF804A and their association with schizophrenia. *Am J Psychiatry* 2011; **168**: 1318–1325.
97 Lan X, Wei L, Wu X, Diao F, Tang X, Li L *et al.* Association analysis of ZNF804A rs1344706 polymorphism and schizophrenia. *Chin J Nerv Ment Dis* 2013; **39**: 213–217.
98 Wang J, Zhao S, Shugart YY, Zhou Z, Jin C, Yuan J *et al.* No association between ZNF804A rs1344706 and schizophrenia in a case-control study of Han Chinese. *Neurosci Lett* 2016; **618**: 14–18.
99 Liou YJ, Wang HH, Lee MT, Wang SC, Chiang HL, Chen CC *et al.* Genome-wide association study of treatment refractory schizophrenia in Han Chinese. *PLoS One* 2012; **7**: e33598.
100 Wong EH, So HC, Li M, Wang Q, Butler AW, Paul B *et al.* Common variants on Xq28 conferring risk of schizophrenia in Han Chinese. *Schizophr Bull* 2014; **40**: 777–786.
101 Li M, Zhang H, Luo XJ, Gao L, Qi XB, Gourraud PA *et al.* Meta-analysis indicates that the European GWAS-identified risk SNP rs1344706 within ZNF804A is not associated with schizophrenia in Han Chinese population. *PLoS One* 2013; **8**: e65780.
102 Sun Y, Hu D, Liang J, Bao YP, Meng SQ, Lu L *et al.* Association between variants of zinc finger genes and psychiatric disorders: systematic review and meta-analysis. *Schizophr Res* 2015; **162**: 124–137.
103 Huang L, Ohi K, Chang H, Yu H, Wu L, Yue W *et al.* A comprehensive meta-analysis of ZNF804A SNPs in the risk of schizophrenia among Asian populations. *Am J Med Genet B* 2016; **171B**: 437–446.
104 Li M, Shi CJ, Shi YY, Luo XJ, Zheng XB, Li ZQ *et al.* ZNF804A and schizophrenia susceptibility in Asian populations. *Am J Med Genet B* 2012; **159B**: 794–802.
105 Zhang R, Yan JD, Valenzuela RK, Lu SM, Du XY, Zhong B *et al.* Further evidence for the association of genetic variants of ZNF804A with schizophrenia and a meta-analysis for genome-wide significance variant rs1344706. *Schizophr Res* 2012; **141**: 40–47.
106 Li M, Su B. Meta-analysis supports association of a non-synonymous SNP in ZNF804A with schizophrenia. *Schizophr Res* 2013; **149**: 188–189.
107 Umeda-Yano S, Hashimoto R, Yamamori H, Okada T, Yasuda Y, Ohi K *et al.* The regulation of gene expression involved in TGF-beta signaling by ZNF804A, a risk gene for schizophrenia. *Schizophr Res* 2013; **146**: 273–278.
108 Schanze D, Ekici AB, Gawlik M, Pfuhlmann B, Reis A, Stober G. Evaluation of risk loci for schizophrenia derived from genome-wide association studies in a German population. *Am J Med Genet B* 2011; **156**: 198–203.
109 Yang Y, Li W, Yang G, Xiao B, Wang X, Ding M *et al.* Evaluation of the relationship between the ZNF804A single nucleotide polymorphism rs1344706 A/C variant and schizophrenia subtype in Han Chinese patients. *Int J Psychiatry Med* 2013; **45**: 269–278.
110 Aberg KA, Liu Y, Bukszar J, McClay JL, Khachane AN, Andreassen OA *et al.* A comprehensive family-based replication study of schizophrenia genes. *JAMA Psychiatry* 2013; **70**: 573–581.
111 Saito T, Kondo K, Iwayama Y, Shimasaki A, Aleksic B, Yamada K *et al.* Replication and cross-phenotype study based upon schizophrenia GWASs data in the Japanese population: support for association of MHC region with psychosis. *Am J Med Genet B* 2014; **165B**: 421–427.
112 Stepanov VA, Bocharova AV, Saduakassova KZ, Marusin AV, Koneva LA, Vagaitseva KV *et al.* Replicative study of susceptibility to childhood-onset schizophrenia in Kazakhs. *Genetika* 2015; **51**: 227–235.
113 Xiao B, Li W, Zhang H, Lv L, Song X, Yang Y *et al.* To the editor: association of ZNF804A polymorphisms with schizophrenia and antipsychotic drug efficacy in a Chinese Han population. *Psychiatry Res* 2011; **190**: 379–381.