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Evidence for the involvement of *ZNF804A* in cognitive processes of relevance to reading and spelling

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Previous studies have shown that individuals with schizophrenia and dyslexia display common neurocognitive abnormalities. The aim of the present study was to determine whether known schizophrenia-risk genes contribute to dyslexia risk or to disease-relevant cognitive functions. For this purpose, we genotyped the schizophrenia-associated risk variants within *zinc-finger protein 804A* (*ZNF804A*), *transcription-factor 4* and *neurogranin* in a large dyslexia case–control sample. We tested all variants for association with dyslexia (927 cases, 1096 controls), and with eight language-relevant cognitive processes (1552 individuals). We observed six significant associations between language-relevant traits and the *ZNF804A*-variant rs1344706. Interestingly, the *ZNF804A* schizophrenia risk variant was associated with a better cognitive performance in our data set. This finding might be consistent with a previously reported *ZNF804A* association in schizophrenia, in which patients carrying the schizophrenia-risk allele at rs1344706 showed a better performance in two memory tests. In conclusion, the present study provides evidence that *ZNF804A* might have a role in cognitive traits of relevance to reading and spelling, and underlines the phenotypic complexity that might be associated with *ZNF804A*.
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Introduction

Several genome-wide association studies have been performed for schizophrenia to date, and *zinc-finger protein 804A* (*ZNF804A*), *transcription-factor 4* (*TCF4*) and *neurogranin* (*NRGN*) were among the first genes to achieve genome-wide significance.[1,2] These findings have since been replicated in independent samples, and these genes are therefore likely to represent true risk factors for schizophrenia.[3]

Given that individuals with dyslexia and schizophrenia have been reported to display certain common neurocognitive abnormalities,[4,5] we were interested in determining whether these genes contribute to dyslexia risk or to disease-relevant cognitive functions. For this purpose, we genotyped the identified schizophrenia risk variants in *ZNF804A* (rs1344706), *TCF4* (rs9960767) and *NRGN* (rs12807809) in five dyslexia case–control samples of Central European descent. Subsequently, we performed association analyses using case–control status (927 cases and 1096 controls) and eight dyslexia-relevant psychometric tests (1552 individuals). The psychometric tests encompass the dyslexia core symptoms of impaired reading and spelling (word reading, word spelling), phonological awareness (phoneme deletion), phonological coding (non-word reading), auditory short-term memory (digit span) and rapid naming (letters, digits, pictures).

Materials and methods

We investigated five dyslexia case–control samples from Salzburg (Austria), Zurich (Switzerland), Marburg (Germany), Munich (Germany) and Maastricht (The Netherlands). The whole sample set was comprised of 927 dyslexia cases and 1096 controls. Besides case–control status, data on eight language-relevant cognitive processes were available for all individuals, with the exception of the Marburg-controls ($N = 1552$, Supplementary Table 1). These eight cognitive processes include word reading, word spelling, phonological awareness (phoneme deletion), phonological coding (non-word reading), auditory short-term memory (digit span) and rapid naming (letters, digits, pictures). Details of the phenotypic measures are provided in Supplementary Table 2.

Genotyping of the variants of interest was carried out on the Sequenom MassArray system (Sequenom, San Diego, CA, USA). Primer sequences and standard assay conditions are available upon request.

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Association analyses were performed using PLINK.[6] Logistic regression was used for case–control analyses, and linear regression was used for quantitative trait analyses. To avoid false-positive results due to possible population stratification in our sample set, we performed an inverse variance weighted fixed effects meta-analysis using the R-library rmeta (http://www.r-project.org/).

Results

In 927 dyslexia cases and 1096 controls, no dyslexia association was found for *TCF4* or *NRGN* (Supplementary Tables 3 and 4). Although the association between rs1344706 in *ZNF804A* and dyslexia was not statistically significant, we observed a similar genetic effect size (odds ratio = 1.12, Table 1) as that reported previously in patients with schizophrenia (odds ratio = 1.09).[1] Notably, the *ZNF804A* schizophrenia-protective allele was more common in dyslexia patients.

In a second step, we combined all cases and controls (1552 individuals) and tested whether the schizophrenia-risk genes were involved in language-relevant cognitive processes. Negative results were obtained for the variants in *TCF4* and *NRGN* (Supplementary Tables 3 and 4). In contrast, rs1344706 in *ZNF804A* showed association with six phenotypes (Table 1). Here, the schizophrenia-protective allele and the schizophrenia-risk allele were consistently associated with a poorer and a better performance in all cognitive tests, respectively. After correction for multiple testing, the associations with word reading, non-word reading and rapid naming of digits remained significant. Forest plots of rs1344706 for the case–control analysis and eight quantitative trait analyses are provided in Supplementary Figure 1. Furthermore, we performed a heterogeneity analysis and observed no differences between the rs1344706 effect sizes for the five subsamples: Salzburg, Zurich, Marburg, Munich and Maastricht ($P > 0.05$, Supplementary Table 5). The estimated effect sizes for the association between rs1344706 and the cognitive phenotypes are shown in Supplementary Table 6. Finally, we tested whether rs1344706 was associated with the intelligence quotient level, and observed no association (Supplementary Table 7).

Discussion

The present findings provide evidence that *ZNF804A* might be involved in cognitive functions of relevance to reading and spelling. This hypothesis might be supported by the 2q31.2-2q32.3-deletion syndrome phenotype, which includes severe speech impairment.[7] *ZNF804A* is one of the few genes present within the deleted region, and previous authors have speculated that the deletion in *ZNF804A* may influence the speech phenotype in 2q31.2-2q32.3-syndrome patients.[7] Furthermore, our data provide evidence that the allele at *ZNF804A*-rs1344706 that influences the risk for schizophrenia might be associated with a better performance in language-relevant processes. In contrast, the schizophrenia-protective allele at rs1344706 appeared to be associated with a poorer performance in cognitive processes of relevance to reading and spelling. A similar effect was observed in a

Table 1 Dyslexia case–control association analysis (above) and quantitative trait analysis in cases and controls (below) using rs1344706 in *ZNF804A*

Tests		*All, 927 cases/1096 controls*[a]		*Salzburg, 185 cases/203 controls*		*Zurich, 30 cases/43 controls*		*Marburg, 400 cases/471 controls*		*Munich, 171 cases/210 controls*		*Maastricht, 141 cases/169 controls*	
Case–control analysis	***Allele***[b]	***OR***	***P-value***	***OR***	***P-value***	***OR***	***P-value***	***OR***	***P-value***	***OR***	***P-value***	***OR***	***P-value***
	G	1.12	0.0843	1.36	**0.0389**	0.62	0.2244	1.00	0.9992	1.26	0.1230	1.18	0.3349
Quantitative trait analysis	*Allele*[b]	*All, 1552 individuals*[a]		*Salzburg, 388 individuals*		*Zurich, 73 individuals*		*Marburg, 400 individuals*		*Munich, 381 individuals*		*Maastricht, 310 individuals*	
		β	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
Word reading	G	−0.1416	**0.0011**[c]	−0.1585	**0.0479**	0.1110	0.6589	−0.1010	0.1500	−0.2211	0.0234	−0.1672	0.2428
Word spelling	G	−0.1040	**0.0196**	−0.0642	0.4683	0.1406	0.6595	−0.0681	0.3316	−0.2874	**0.0047**	−0.0564	0.6515
Digit span	G	−0.0314	0.4003	0.0228	0.7702	0.1661	0.4384	−0.0320	0.6475	−0.0632	0.3748	−0.0844	0.3381
Non-word reading	G	−0.1673	**0.0005**[c]	−0.1724	0.1197	0.1068	0.7012	−0.1441	**0.0396**	−0.3210	**0.0044**	−0.0911	0.4933
RN: letters	G	−0.1194	**0.0048**	−0.0566	0.5033	−0.1348	0.5094	−0.1752	**0.0123**	−0.2079	**0.0291**	0.0498	0.6643
RN: digits	G	−0.1406	**0.0007**[c]	−0.1063	0.1884	0.0312	0.8721	−0.1558	**0.0257**	−0.2123	**0.0221**	−0.1176	0.3185
RN: pictures	G	−0.0527	0.1991	−0.0746	0.3550	−0.1028	0.6412	−0.0895	0.2017	−0.1236	0.1738	0.1669	0.1073
Phoneme deletion	G	−0.0942	**0.0263**	−0.1769	**0.0325**	−0.4051	**0.0462**	0.0467	0.5059	−0.1444	0.1281	−0.1387	0.2501

Abbreviations: OR, odds ratio; RN, rapid naming.
[a]*P*-values for the combined sample were calculated on the basis of a fixed effects meta-analysis. [b]Reference allele, whereby 'G' represents the protective allele in the schizophrenia association study performed by O'Donovan *et al.*[1] [c]After a correction by a factor of 27 (3 variants × 9 tests), the associations for word reading ($P = 0.0297$), non-word reading ($P = 0.0135$) and rapid naming of digits ($P = 0.0189$) remained significant. The results for the analysis of each of the five subsamples and analyses across all subsamples are shown. Nominal *P*-values < 0.05 are depicted in bold. β represents the regression coefficient.

previous study, which analyzed cognitive profile in two schizophrenia samples.[8] In that study, patients carrying the *ZNF804A* schizophrenia-risk allele also showed a significantly better performance in two memory tests compared with patients carrying the protective allele. However, it is difficult to assess the extent to which these two studies and their findings can be compared, as different cognitive tests were applied. Another interesting aspect of the present study is that impairments in *ZNF804A*-associated cognitive functions (word reading, word spelling, non-word reading, rapid naming: letters and digits, and phoneme deletion) constitute the characteristic pattern of dyslexia.[9] Therefore, additional studies of larger samples are required to determine the precise role of *ZNF804A* in dyslexia *per se*.

In summary, the same rs1344706 allele in *ZNF804A* was associated with a better performance in language-related cognitive functions in the present cohort, and was associated with schizophrenia in previous independent studies. If our findings are true, it remains unknown whether these two phenotypes are mediated by the same or different neurobiological pathways, and whether previously reported *ZNF804A*-imaging findings in healthy individuals[10] reflect schizophrenia- and/or language-related cognitive processes.

The present findings underline the phenotypic complexity that might be associated with *ZNF804A,* and illustrate the benefit of testing neurocognitive phenotypes in studies of dyslexia.

Conflict of interest

The authors declare no conflict of interest.

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