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Investigation of interaction between *DCDC2* and *KIAA0319* in a large German dyslexia sample

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Abstract The dyslexia susceptibility locus DYX2 (chr. 6p21-p22) harbours two candidate genes, *DCDC2* and *KIAA0319*. In 2006, Harold et al. reported evidence for interaction between both genes. Having previously identified a risk haplotype for dyslexia in *DCDC2*, but not *KIAA0319,* in German families, we also tested for interaction between this risk haplotype and *KIAA0319*. We found a nominally significant association for the quantitative dimension "word reading", the core phenotype in the study of Harold et al., which may be considered as supportive evidence.

Keywords DYX2 · Doublecortin domain · Interaction · Reading · Spelling

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Dyslexia is amongst the most common neurodevelopmental disorders with a prevalence of 5–12% depending on the applied diagnostic criteria (Schumacher et al. 2007). According to ICD-10, dyslexia is "a disorder manifested by difficulty learning to read despite conventional instruction, adequate intelligence and sociocultural opportunity" (WHO 1993). Longitudinal studies have shown that it involves an extremely stable developmental disturbance which does not, in contrast to popular opinion, disappear with adolescence (Shaywitz et al. 1999).

In order to identify regions that confer susceptibility for dyslexia, results from several independent linkage studies have pointed towards a susceptibility locus on chromosome 6p21–p22 (DYX2) (for review Schumacher et al. 2007). This region harbours two independent gene clusters in close proximity to one another, namely *VMP/DCDC2/KAAG1* and *KIAA0319/TTRAP/THEM2*. Both regions have received support from different independent samples (Cope et al. 2005; Deffenbacher et al. 2004; Francks et al. 2004; Meng et al. 2005; Schumacher et al. 2006) and it has been concluded that of the candidate genes discussed to date, the evidence for *DCDC2* and *KIAA0319* is the most convincing (Fisher Francks 2006; McGrath et al. 2006; Schumacher et al. 2007; Williams O'Donovan 2006). Their involvement in the development of dyslexia has been further strengthened by functional analyses which showed that inhibition of each of the two genes, *DCDC2* and *KIAA0319*, leads to

poorer neuronal migration in the neocortex of fetal rats through RNA interference methods (Meng et al. 2005; Paracchini et al. 2006). However, as a limiting fact it should be noted that despite favourable findings, negative associations have been reported for both genes (Cope et al. 2005; Deffenbacher et al. 2004; Francks et al. 2004; Meng et al. 2005; Schumacher et al. 2006). Importantly, only a single study to date has sufficiently covered both genes at the same time, which is necessary to understand the relative contribution of both genes and to identify possible interactions between them. Harold et al. (2006) reported a combined analysis of the *KIAA0319* and *DCDC2* genes in two large samples from the UK (Cardiff and Oxford sample). While the results of this study strongly supported their previously observed association with *KIAA0319*, no support was obtained for *DCDC2*. Interestingly, weak evidence was obtained for an interaction between the two loci when analysing a combined case-control set from both samples.

We have previously reported strong association of the *DCDC2* gene with dyslexia in severely affected German individuals (Schumacher et al. 2006). In the same study we did not obtain any evidence for a contribution of the *KIAA0319* gene, however, we did not include the markers that Harold et al. (2006) reported as the most strongly associated markers in their recent study. Consequently, we expanded our study to include those markers in order to obtain a comprehensive picture of the contribution of *KIAA0319* to the development of dyslexia in the German population. Our sample consisted of 244 German families with a severely affected child showing a discrepancy of at least 2 SD between expected and observed spelling score. The inclusion criteria and phenotypic measures have been previously described (Schulte-Körne et al. 2007). Genotyping was performed using the iPlex-assay by Sequenom^{TM}, and analytes were measured with a MALDI-TOF (matrix-assisted-laser desorption/ionisation time-of-flight) mass spectrometry system (Bruker Daltonics). Data were analysed using the SpectroTyper v3.1 software provided by Sequenom. Cluster positions were manually checked by two different members of the lab. In ambiguous situations, data points were excluded. Additionally, we included four duplicate samples to ensure data quality. They did not show any inconsistencies.

None of the six markers in *KIAA0319* showed significant association with dyslexia or one of the subdimensions, neither for the entire data set nor when restricting the analysis to the most severely affected patients (SD $\geq$ 2.5; $n = 114$; Table 1). When testing for interactions applying the multiplicative (allelic) model using UNPHASED 3.0.6 between markers in *KIAA0319* and our previously identified risk haplotype in *DCDC2* [rs793862-rs807701 (A–C)] (Schumacher et al. 2006) we focussed the analysis on *KIAA0319*-SNPs rs4504469 and rs761100, as these SNPs had yielded significant evidence for interaction in Harold et al. (2006). As shown in Table 1, we obtained no significant interaction for dyslexia itself, but could identify a nominally significant result for the subdimension word reading (rs761100; $P = 0.0351$). This may be seen as evidence for interaction between *KIAA0319* and *DCDC2*. However, an effect of *KIAA0319* alone, as reported for the UK samples, is not found in the German population.

Currently, it is not easy to interpret these discrepant findings. It is rather unlikely that different genetic factors would exist in closely related populations such as those found in the UK and in Germany, especially when considering that the results suggest the involvement of common genetic variants. The dyslexia core phenotype, however, might differ between languages. On the cognitive level, for example, various processes such as phonological

Table 1 Results of transmission disequilibrium test (TDT) and interaction analysis

Marker in *KIAA0319*	Single marker TDT analysis*		Interaction analysis[a],*			
	TDT results by criterion		*DCDC2* risk haplotype [rs793862-rs807701 (A–C)]			
	SD $\geq$ 2 ($n = 244$)	SD $\geq$ 2.5 ($n = 114$)	Dyslexia	Spelling	Word reading	Phonological decoding
rs2179515	0.543	0.9156	–	–	–	–
rs761100	0.3055	0.4859	0.3567	0.0912	**0.0351**	0.3437
rs7766230	0.4828	0.8997	–	–	–	–
rs17491230	0.0579	0.3757	–	–	–	–
rs1555090	0.6346	1.0	–	–	–	–
rs3212236	0.4794	1.0	–	–	–	–
rs4504469[b]	–	–	0.0553	0.2334	0.2382	0.6269

[a] All trios (SD $\geq$ 2) included

[b] Previously included in Schumacher et al.

* P values, bold if significant ($P \leq 0.05$)

decoding, phoneme awareness or orthographic processing are involved in the dyslexia core phenotype (Ramus et al. 2003; Schulte-Körne et al. 2007). Languages of different transparencies, such as German and English, differently apply at least some of these distinct processes. For instance, it has been shown that grapheme-phoneme recording skills require more time to develop in less transparent orthographies (Seymour et al. 2003). Thus, it seems more plausible that language-specific effects together with different ascertainment strategies may be the basis of the observed inconsistencies across the studies. This hypothesis receives some support in this present study, since a nominally significant interaction between *DCDC2* and *KIAA0319* is observed for the dyslexia subdimension "word reading", which is the core phenotype of the UK studies.

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