Investigation of interaction between \textit{DCDC2} and \textit{KIAA0319} in a large German dyslexia sample

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Abstract:

The dyslexia susceptibility locus DYX2 (chr. 6p21-p22) harbours two candidate genes, \textit{DCDC2} and \textit{KIAA0319}. In 2006, Harold et al. reported evidence for interaction between both genes. Having previously identified a risk haplotype for dyslexia in \textit{DCDC2}, but not \textit{KIAA0319}, in German families, we also tested for interaction between this risk haplotype and \textit{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
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 M 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. (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™, 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 ≥ 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. (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 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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Ethical standards:

The study was approved by the ethical committees of the Universities of Marburg and Würzburg. Informed consent was given by all participants or their parents if aged 14 or younger.
References:


Table 1: Results of transmission disequilibrium test TDT (1) and interaction analysis (2)

<table>
<thead>
<tr>
<th>Marker in KIAA0319</th>
<th>(1) Single Marker TDT Analysis</th>
<th>(2) Interaction Analysis&lt;sup&gt;a&lt;/sup&gt;</th>
<th>DCDC2 risk haplotype (rs793862-rs807701 (A-C))</th>
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<tbody>
<tr>
<td></td>
<td>TDT results by criterion</td>
<td></td>
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<tr>
<td></td>
<td>SD ≥ 2 (n = 244)</td>
<td>SD ≥ 2.5 (n = 114)</td>
<td>dyslexia</td>
</tr>
<tr>
<td>rs2179515</td>
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<td>rs761100</td>
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</tr>
<tr>
<td>rs4504469&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>0.0553</td>
</tr>
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<sup>a</sup> All trios (SD ≥ 2) included

<sup>b</sup> Previously included in Schumacher et al.

* P-values, bold if significant (p ≤ 0.05)