Examining the neuroimaging implications of dyslexia, language impairment, and IQ associated DYX2 markers using MRI data of typically developing children.

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Abstract

The objective of this study was to investigate the neuroimaging implications of DYX2 markers, which showed replicated associations with dyslexia-related, language impairment-related, and IQ measures. We believe neuroimaging phenotypes are likely a mediating step between genetic risk and functional marker in dyslexia, and can inform future functional studies of associated genetic variants.

To accomplish this goal, we used genetic and neuroimaging data collected in the PING study. Specifically, we performed a replication of studies showing several neuroimaging measures, including cognitive thickness, fiber tract volume, and cortical thickness measures in regions of interest previously identified in neuroimaging studies.

The DYX2 RD Risk Locus

Figure 1: Schematic representation of the DYX2 locus on chromosome 6p22. The DYX2 locus on chromosome 6p22 is marked in green. The chromosome has been divided into 6p22.1, 6p22.2, and 6p22.3 regions, and the DYX2 markers are located in the 6p22.2 region. The risk genes (DOCK2, KIAA0319, KIAA0319, and C6orf62) have been identified as risk genes in multiple independent association studies. These genes are associated with cortical thickness and fiber tract volumes, which may reflect changes in neuronal migration. The DYX2 markers showed consistent effects in the brain (volume and white matter integrity) and were reproducible in multiple cohorts.

Table 1: Markers that showed replicated associations with dyslexia (RD), language impairment (LI), and IQ using MRI data of typically developing children.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Trait(s)</th>
<th>LD</th>
<th>rl</th>
<th>rs</th>
<th>p (two-tailed)</th>
<th>p (one-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs9461045</td>
<td>RD, LI, and IQ</td>
<td>0.38</td>
<td>0.00842</td>
<td>0.00601</td>
<td>0.00098</td>
<td>0.00204</td>
</tr>
<tr>
<td>rs9346464</td>
<td>RD, LI, and IQ</td>
<td>0.38</td>
<td>0.03732</td>
<td>0.01892</td>
<td>0.00423</td>
<td>0.00413</td>
</tr>
</tbody>
</table>

rs9461045 in KIAA0319 and Fractional Anisotropy

Figure 2: The PING Imaging Neurogenetics and Genomics (PING) Study

The PING study is a cross-sectional cohort of typically developing children between the ages of 3 and 5 years, recruited to participate by including all families with children attending Utah University. Subjects were genotyped on the Illumina Human660W-Quad BeadChip (San Diego, CA), with markers passing quality control filters (sample call rate > 80%, SNP call rate > 90%, minor allele frequency > 0.05). To prevent possible population stratification, only subjects of European genetic ancestry were included in analyses.

PING Imaging Analysis

Across the 10 slice and 12 scanners, a standardized multi-modal high-resolution structural MRI protocol was implemented, including T1, T2, T1-weighted FLAIR, and T2-weighted FLAIR images. Functional data were collected using a 3T Siemens scanner (Magnetom Prisma, Malvern, PA, USA). fMRI was collected using a task-based paradigm of visual tasks, followed by a resting state scan (200 s). Images were pre-processed and analyzed using the Analysis of Functional NeuroImages (AFNI) software package.

Statistical Analyses

All analyses were performed using linear mixed-effects models, with age, sex, and scanner as fixed effects and subject as a random effect. A Bonferroni correction was applied for multiple comparisons.

Inter-Region Connectivity

To prevent possible population stratification, only subjects of European genetic ancestry were included in analyses. To ensure that this effect of rs9461045 on fractional anisotropy in the corpus callosum but did leave a suggestive association (p=0.066). When average cortical thickness across the entire brain was included as a covariate in the model, the relationship between rs9461045 and fractional anisotropy in the corpus callosum was attenuated by 0.0314 (p=0.151).

Conclusions

1. Markers previously implicated in dyslexia, language impairment, and IQ using MRI data were also associated with neuroimaging phenotypes.
2. Some associations were with specific brain regions (e.g. rs9346464 with fractional anisotropy).
3. rs9461045 and KIAA0319 with cortical thickness, which result from aberrant developmental neuronal migration as seen in animal models of KIAA0319, may reflect improper microstructure connectivity and connectivity, impairing the functional integration of written and verbal language.

References


Acknowledgements

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Figure 3: Association of KIAA0319 with left orbital frontal cortex thickness. All models were adjusted for age, sex, and scanner. The strongest association was with fractional anisotropy throughout fiber tracts of the right orbital frontal cortex (p = 0.005). To ensure that this effect of rs9461045 on fractional anisotropy in the corpus callosum but did leave a suggestive association (p=0.066). When average cortical thickness across the entire brain was included as a covariate in the model, the relationship between rs9461045 and fractional anisotropy in the corpus callosum was attenuated by 0.0314 (p=0.151).