Genetics of dyslexia: the evolving landscape

Johannes Schumacher, Per Hoffmann, Christine Schmäl, Gerd Schulte-Körne, Markus M Nöthen


Dyslexia is among the most common neurodevelopmental disorders, with a prevalence of 5–12%. At the phenotypic level, various cognitive components that enable reading and spelling and that are disturbed in affected individuals can be distinguished. Depending on the phenotype dimension investigated, inherited factors are estimated to account for up to 80%. Linkage findings in dyslexia are relatively consistent across studies in comparison to findings for other neuropsychiatric disorders. This is particularly true for chromosome regions 1p34–p36, 6p21–p22, 15q21 and 18q11. Four candidate genes have recently been identified through systematic linkage disequilibrium studies in linkage region 6p21–p22, and through cloning approaches at chromosomal breakpoints. Results indicate that a disturbance in neuronal migration is a pathological correlate of dyslexia at the functional level. This review presents a summary of the latest insights into the genetics of dyslexia and an overview of anticipated future developments.

Familial clustering in dyslexia was recognised a few years after the first description of the disorder by Hinselwood in 1895.3–6 A child with an affected parent has a risk of 40–60% of developing dyslexia. This risk is increased when other family members are also affected.7–11 There is an estimated 3–10-fold increase in the relative risk for a sibling ($\lambda_s$), with an increase in $\lambda_s$ observed when strict criteria are applied.12 Twin studies have confirmed that genetic factors are substantially responsible for the familial clustering of dyslexia.13–15 Whether or not sex has an influence on heritability is controversial. Although the results of a US American twin study (Colorado Twin Study) showed similar heritability between the sexes,16–18 Harlaar et al.19 found a higher heritability for boys in a UK sample (London Twins Early Development Study).

Through molecular genetic linkage studies in families with dyslexia, chromosome regions have been identified in which the presence of dyslexia susceptibility genes is suspected. As with all complex disorders, linkage findings are not completely overlapping between independent studies. However, greater consistency is reported for dyslexia than for most other neuropsychiatric disorders, and the identification of the first candidate genes therefore came as no surprise.

This review presents the current state of molecular genetic research on dyslexia, including discussion of the phenotypic aspects and neuropsychological concepts of dyslexia that have received increasing consideration in genetic research over recent years. Finally, the extent to which our understanding of dyslexia is likely to be increased through the results of current and future molecular genetic research is discussed.

Abbreviations: ADHD, attention-deficit hyperactivity disorder; CNS, central nervous system; DCDC2, doublecortin domain containing protein 2; DX1, dyslexia susceptibility 1; DX9, dyslexia susceptibility 9; DYX1C1, dyslexia susceptibility 1 candidate 1; LD, linkage disequilibrium; QTL, quantitative trait loci; ROBO1, roundabout Drosophila homolog of 1; SSD, speech–sound disorder
impaired sensitivity of cells within the retinocortical magnocellular pathway and in the extrastriate areas in the dorsal stream to which they project. The cerebellar deficit theory suggests that the automatisation of cognitive processes and motor control in the cerebellum are disturbed in individuals with dyslexia. The double deficit hypothesis, which assumes disturbances in phonological processing and the speed of processing, should also be mentioned in this context.

Even though evidence for one or the other of these theories is typically reported in affected individuals, there is no evidence so far for specific subgroups of dyslexia. A reason for this could be that although some of the deficits found in affected individuals are correlated with reading and spelling, they may not be causally associated with dyslexia. Findings from genetic research may have the potential to help delineate which cognitive and neurophysiological processes are causally related.

**LINKAGE FINDINGS IN DYSLEXIA**

To date, linkage analyses in families with dyslexia have identified nine chromosome regions (dyslexia susceptibility 1 (DYX1)–dyslexia susceptibility 9 (DYX9)) listed by the HUGO Gene Nomenclature Committee in which the presence of susceptibility genes is suspected (table 2). There was initially great hope that it would be possible to correlate the respective cognitive components of dyslexia (table 1) with specific linkage regions. Many studies accordingly investigated individual phenotype components as categorical or quantitative (quantitative trait loci (QTL)) subdimensions, and linkages with specific chromosomal regions have been claimed; unfortunately, with little support from independent studies so far.

Nevertheless, the consistency of linkage findings is impressive in comparison to those for other neuropsychiatric disorders. This is particularly true of findings in chromosome regions 1p34–p36, 6p21–p22, 15q21 and 18q11, with support for each of these regions coming from the investigation of at least two large family samples.

The largest family samples reported in the literature are from the USA (Colorado, Seattle and Yale samples), the UK (Cardiff and Oxford samples), Canada (Toronto and Vancouver samples) and Germany (German sample). For the sake of clarity, these samples will be named according to their origin in the following sections. Results from genomewide linkage studies have been reported so far from the Seattle, Oxford and Colorado samples. In addition, genomewide linkage studies of large multiply affected families from Holland, Norway and Finland have been reported. The following section presents results for the individual regions, and discussion is limited to positive findings only.

**DYX1—chromosome 15q21**

DYX1 (MIM 127700) lies in chromosome region 15q21, and a total of four research groups have reported linkage in their family samples (table 2). Evidence for linkage was found for word reading and related phenotype dimensions in three samples (Colorado, Yale and Seattle samples). Six of the four samples showed evidence of linkage for spelling (German sample). Two linkage disequilibrium (LD) studies have been carried out in region DYX1 using short tandem repeat markers and positive evidence for association was obtained for one region of approximately 4 Mb. In both studies, a three-marker haplotype was associated in a total of three independent trios, two samples of British origin (Cardiff sample) and one of Italian origin. Region 15q21 has also shown evidence of linkage to ADHD. A genome scan carried out in 164 Dutch sib pairs with ADHD showed the strongest evidence for linkage in this region. The risk-conferring gene in DYX1 may contribute to the comorbidity reported between the two disorders.
DYX2—chromosome 6p21–p22
The chromosome region 6p21–p22 (DYX2, MIM 600202) is considered to be among the best-replicated regions of linkage for dyslexia (table 2). Evidence of linkage has been reported using a QTL approach in both a US-American (Colorado) and a UK (Oxford) sample.53–56–58–64 Positive evidence for linkage was also reported from a US-American subsample (Yale sample) in which categorical phenotype dimensions had been considered.55 A more precise containment of the phenotype subdimensions associated with DYX2 was not possible. Linkage was found with the phenotypes phonological processing51–54 and orthographic processing.51–52–54 Meanwhile, LD mapping in DYX2 led to the identification of two strong candidate genes (DCDC2 [doublecortin domain containing protein 2] and KIAA0319).71–74 Interestingly, evidence for linkage has also been found in the chromosome region 6p21–p22 for ADHD.55

DYX3—chromosome 2p15–p16
The chromosome region 2p15–p16 (DYX3, MIM 604254) has been identified through linkage analyses in five family samples (including the Oxford, Colorado and Vancouver samples; table 2).53–56–58–77 The linkage peaks of the individual studies lie far apart from each other, however, and so it is not clear whether they indicate the same susceptibility locus. As with DYX2, no phenotype dimension has been found to be specifically linked with this locus, although not all studies have analysed subdimensions.

DYX4—chromosome 6q11–q12
The chromosome region 6q11–q12 (DYX4, MIM 127700) was identified in the context of a chromosome-wide linkage study of a large Canadian family sample (Vancouver sample; table 2).59 The most strongly linked phenotype
were phonological coding and spelling. There has so far been no independent replication of this finding for DYX4.

**DYX5—chromosome 3p12-q13**
The chromosome region 3p12–q13 (DYX5, MIM 606896) showed linkage in a large Finnish family (table 2). ROBO1 (roundabout Drosophila homolog of 1) has been identified as a possible candidate gene in this region. DYX5 also showed a positive evidence for linkage in 77 US-American families with speech–sound disorder (SSD). SSD involves impairments in phonological processing, as with dyslexia.

**DYX6—chromosome 18p11**
DYX6 (MIM 606616), which lies in chromosome region 18p11, was identified in two independent family samples (Oxford and Colorado samples) through a genome scan applying a QTL approach (table 2). The strongest evidence for linkage was found for word reading. This finding was replicated in a third family sample (expanded Oxford sample), the strongest evidence for linkage being found for the phenotype subdimension phoneme awareness. The results of a subsequent multivariate analysis in the two Oxford samples indicate that a QTL in DYX6 influences multiple aspects of reading ability and is not correlated with specific phenotype subdimensions.

**DYX7—chromosome 11p15**
Linkage with markers in the region of DYX7 (MIM 127700), which lies in chromosome region 11p15, has been described only in one family sample to date (Vancouver sample; table 2). The authors selected DYX7 as a candidate region on the basis that the gene for the dopamine D4 receptor (DRD4) is localised there. DRD4 is a possible risk gene for ADHD.

**DYX8—chromosome 1p34-1p36**
Three research groups in total have reported linkage between DYX8 (MIM 608995) in chromosome region 1p34–p36 and dyslexia (including the Yale and Vancouver samples; table 2). Even though individual studies have shown linkage to differing phenotype subdimensions of dyslexia, linkage evidence from two studies was particularly strong when focus was placed on the phonological aspects of dyslexia.

**DYX9—chromosome Xq26-q27**
Evidence for linkage was found in chromosome region Xq27 (DYX9, MIM 300509) in a Dutch multiplex family with dyslexia (table 2). The same research group failed to replicate their result in 67 affected sib pairs. However, positive evidence for linkage was found in region DYX9 in one of the UK samples (Oxford sample; table 2).

**Additional linkage regions in dyslexia**
In addition to the HGNC-listed DYX1–DYX9 regions, linkage with dyslexia has also been reported for other regions, although without replication in independent samples. This includes evidence for linkage on chromosome 13q12 for word reading, and on chromosome 2q22 for phonological decoding efficiency. Two further studies have been conducted which aimed to identify chromosomal loci with pleiotropic effects on dyslexia and ADHD. In the Colorado sample, families with dyslexia having ADHD problems showed evidence for linkage in chromosome regions 14q32, 13q32 and 2q11. In families with ADHD, evidence for linkage is shown for reading ability in regions 10q11, 16p12 and 17q22.

**CANDIDATE GENE FINDINGS IN DYSLEXIA**
Of the newly identified candidate genes, DCDC2 and KIAA0319 seem to be of most significance for dyslexia. Both were identified through systematic investigation of LD (LD mapping) within DYX2 on chromosome 6p22. Initial findings for both genes have been replicated in independent samples, with the strongest findings being reported among severely affected individuals. By contrast, the genes DYXIC1 (dyslexia susceptibility 1 candidate 1) and ROBO1, which were identified through breakpoint mapping in Finnish patients, seem to be less involved in the development of dyslexia across different populations. Their contribution may be limited to a few families in the Finnish population.

**DCDC2 (doublecortin domain containing protein 2)**
Initial evidence for the involvement of DCDC2 (MIM 605755) and dyslexia was obtained through gene-based LD mapping in a gene-dense 680 kb section of linkage region 6p22 (DYX2; table 3). The sample was drawn from 114 US-American nuclear families of predominantly European origin (Colorado sample). Positive evidence for association was found in two genome loci, in which a total of six genes were localised: VMP1/DCDC2/KIAAG1 and KIAA0319/TTTRAP/Them2. In a subsequently expanded Colorado sample (153 nuclear families), the strongest evidence for association was found in DCDC2 (table 3). Additionally, a deletion of 2.4 kb in intron 2 of DCDC2, which encodes tandem repeats of putative brain-associated transcription factor binding sites, was identified, which had an allele frequency of 8.5% in the parents. The tandem repeats in the deleted region demonstrate several alleles. For the purposes of the association study, the authors combined the deletion and the rare repeat alleles into one allele, for which they reported a strong association with reading performance.

Findings from two trio-samples also indicate the involvement of DCDC2 in the development of dyslexia (German sample; table 3). Strong evidence for association was shown in both samples at the single-marker and haplotype level. This effect seemed to be particularly substantial in severely affected individuals. In the pooled sample, severely affected individuals showed a genotypic relative risk of 4.88 on the basis of the homozygous presence of the identified risk haplotype.

By contrast, investigation of the DCDC2 locus in the two UK samples (Oxford and Cardiff) had inconsistent results. In the Oxford sample, evidence of association between DCDC2 variants and various phenotype components of dyslexia were found, albeit with a weak level of significance. This association disappeared, however, when only severely affected cases were included in the analysis. Interestingly, the 2.4 kb deletion in intron 2 of DCDC2 was more common than by chance in severely affected patients. There was no association between dyslexia and DCDC2 in the Cardiff sample. Joint analysis of the two samples, however, produced evidence of a possible interaction between DCDC2 and KIAA0319.

In summary, these results suggest that DCDC2 is involved in the development of dyslexia. It is unlikely that KAAAG1 is the susceptibility gene at this locus. KAAAG1 overlaps at the genomic level with exon 1 of DCDC2, although KAAAG1 does not seem to be expressed in the CNS. By contrast, DCDC2 is widely expressed in the CNS, including areas of the brain in which lower activation patterns have been observed in individuals with dyslexia, such as the inferior temporal and medial temporal cortices.

Functionally, DCDC2 is involved in processes of cortical neuronal migration during brain development and contains a double cortin homology domain which is typical of this. RNA interference studies of in utero rats have shown that downregulation of DCDC2 leads to a significant reduction in neuronal migration. Determining whether the intron 2 deletion is one of the responsible variants will require further investigation in larger samples. There is no real rationale for combining the deletion with rare alleles of the STR polymorphism. Functional studies of the possible effect of the different
alleles on expression or splicing are required to justify the combining of alleles.

**KIAA0319**

Besides evidence for association in the region of DCDC2, positive association with variants in the region of the KIAA0319/TTRAP/THEM2 gene cluster (MIM 609269) was reported in the Colorado sample. Association for the same gene cluster was reported by Francks et al in two independent samples (Oxford samples), which was particularly notable in severely affected individuals (table 3). Association in this region was replicated in a third UK sample (Cardiff sample; table 3). There was an

### Table 3 Summary of association findings in dyslexia

<table>
<thead>
<tr>
<th>Gene</th>
<th>Study design</th>
<th>Sample characteristics, country</th>
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<th>References</th>
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<td>DYX1C1</td>
<td>Case-control</td>
<td>55 cases vs 113 controls, Finland</td>
<td>8 SNPs</td>
<td>Significance at the single-marker and haplotype level</td>
<td>Taipale et al</td>
</tr>
<tr>
<td></td>
<td>Case-control</td>
<td>54 cases vs 82 controls, Finland</td>
<td>8 SNPs†</td>
<td>Significant association at the single-marker level</td>
<td></td>
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<tr>
<td></td>
<td>Family based</td>
<td>148 nuclear families, Canada</td>
<td>6 SNPs†</td>
<td>Significant association at the single-marker and haplotype level, association in the opposite direction compared to Taipale et al</td>
<td>Wigg et al</td>
</tr>
<tr>
<td></td>
<td>Family based</td>
<td>264 nuclear families, UK</td>
<td>8 SNPs†</td>
<td>Significant association at the single-marker and haplotype level</td>
<td>Scerri et al</td>
</tr>
<tr>
<td></td>
<td>Family based</td>
<td>150 nuclear families, USA</td>
<td>2 SNPs†</td>
<td>No association</td>
<td>Meng et al</td>
</tr>
<tr>
<td></td>
<td>Family based</td>
<td>158 nuclear families, Italy</td>
<td>3 SNPs†</td>
<td>No association</td>
<td>Marino et al</td>
</tr>
<tr>
<td></td>
<td>Family based</td>
<td>247 nuclear families, UK</td>
<td>3 SNPs†</td>
<td>No association</td>
<td>Cope et al</td>
</tr>
<tr>
<td>DCDC2</td>
<td>Family based</td>
<td>114 nuclear families, USA</td>
<td>31 SNPs within 680 kb (including VMP, DCDC2, KIAA0319, TTRAP and THEM2)</td>
<td>Strongest association at the single-marker and haplotype level within the VMP/DCDC2/KAAg1 locus</td>
<td>Deffenbacher et al</td>
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<tr>
<td></td>
<td>Family based</td>
<td>153 nuclear families, USA</td>
<td>147 SNPs within 1.5 Mb (including VMP, DCDC2, KIAA0319, TTRAP and THEM2)</td>
<td>Strongest association at the single-marker and haplotype level within DCDC2</td>
<td>Meng et al</td>
</tr>
<tr>
<td></td>
<td>Case-control</td>
<td>240 cases vs 312 controls, UK‡</td>
<td>137 SNPs within VMP, DCDC2, KAAg1, KIAA0319, TTRAP and THEM2</td>
<td>No association within the VMP/DCDC2/KAAg1 locus</td>
<td>Cope et al</td>
</tr>
<tr>
<td></td>
<td>Family based</td>
<td>137 triads, Germany</td>
<td>18 SNPs and 4 STRs within the VMP/DCDC2/KAAg1 locus</td>
<td>Strongest association at the single-marker and haplotype level within DCDC2</td>
<td>Schumacher et al</td>
</tr>
<tr>
<td></td>
<td>Family based</td>
<td>239 triads, Germany</td>
<td>2 SNPs, 1 STR within DCDC2</td>
<td>Strongest association at the single-marker and haplotype level</td>
<td>Schumacher et al</td>
</tr>
<tr>
<td>KIAA0319</td>
<td>Family based</td>
<td>114 nuclear families, USA</td>
<td>31 SNPs within 680 kb (including VMP, DCDC2, KIAA0319, TTRAP and THEM2)</td>
<td>Significant association at the single-marker and haplotype level within the KIAA0319/TTRAP/ THEM2 locus</td>
<td>Deffenbacher et al</td>
</tr>
<tr>
<td></td>
<td>Family based</td>
<td>42 nuclear families, UK‡</td>
<td>31 SNPs within 680 kb (including the KIAA0319/TTRAP/ THEM2 locus)</td>
<td>Strongest association at the single-marker and haplotype level within KIAA0319 and TTRAP</td>
<td>Franks et al</td>
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<tr>
<td></td>
<td>Family based</td>
<td>84 nuclear families, UK‡</td>
<td>20 SNPs within KIAA0319 and TTRAP</td>
<td>Significant association at the single-marker and haplotype level within KIAA0319 and TTRAP</td>
<td>Cope et al</td>
</tr>
<tr>
<td></td>
<td>Family based</td>
<td>124 nuclear families, USA‡</td>
<td>21 SNPs within KIAA0319 and TTRAP</td>
<td>Significant association at the single-marker and haplotype level within KIAA0319 and TTRAP</td>
<td>Cope et al</td>
</tr>
<tr>
<td></td>
<td>Case-control</td>
<td>240 cases vs 312 controls, UK‡</td>
<td>137 SNPs within VMP, DCDC2, KAAg1, KIAA0319, TTRAP and THEM2</td>
<td>Strongest association at the single-marker and haplotype level within KIAA0319</td>
<td>Franks et al</td>
</tr>
<tr>
<td></td>
<td>Family based</td>
<td>223 cases vs 273 controls, UK‡</td>
<td>10 SNPs within the KIAA0319/TTRAP/ THEM2 locus</td>
<td>Strongest association at the single-marker and haplotype level within KIAA0319</td>
<td>Schumacher et al</td>
</tr>
<tr>
<td></td>
<td>Family based</td>
<td>376 triads, Germany</td>
<td>10 SNPs within the KIAA0319/TTRAP/ THEM2 locus</td>
<td>Nominal significant association at the single-marker level for 1 variant within KIAA0319 in the most severely affected subsample</td>
<td>Harold et al</td>
</tr>
<tr>
<td></td>
<td>Family based</td>
<td>126 nuclear families, UK‡</td>
<td>16 SNPs within DCDC2, KIAA0319 and flanking region</td>
<td>Strongest association at the single-marker level within 20 kb in intron1 of KIAA0319</td>
<td>Deffenbacher et al</td>
</tr>
<tr>
<td></td>
<td>Case-control</td>
<td>320 cases vs 312 controls, UK‡</td>
<td>28 SNPs and 1 STR within DCDC2, KAA0319 and flanking regions</td>
<td>Evidence for gene-gene interaction between KIAA0319 and DCDC2</td>
<td>Deffenbacher et al</td>
</tr>
<tr>
<td></td>
<td>Family based</td>
<td>419 cases vs 273 controls, UK‡</td>
<td>4 SNPs and 1 STR within DCDC2 and 5 SNPs within KIAA0319</td>
<td>Strongest association at the single-marker and haplotype level within KIAA0319</td>
<td>Schumacher et al</td>
</tr>
</tbody>
</table>

DCDC2, doublecortin domain containing protein 2 gene; SNP, single-nucleotide polymorphism. *Some cases were extracted from the same families and are related. †Including the two significantly associated SNPs reported by Taipale et al. ‡Samples represent subsamples selected for severity of the phenotype. *Individual genotyping of markers that were associated in the pooled samples (most of the cases and controls are identical).
association with SNPs in the region of KIAA0319 through the use of a DNA pooling screening step and subsequent replication through individual genotyping.

Meanwhile, further analyses of the two samples (Oxford and Cardiff) have shown that the responsible gene variant(s) is (are) probably localised near exon 1 of KIAA0319. Investigation of both UK samples has resulted in evidence of a gene–gene interaction between KIAA0319 and DCDC2.96 One sample (German sample), which had reported strong association with DCDC2, has so far produced no convincing evidence for association with the KIAA0319/ITTRAP/THEM2 gene cluster.97 There was no further evidence of association at the KIAA0319 locus from the extended Colorado sample (153 related families), although the genomic segment that had shown the strongest association findings in the two UK samples was insufficiently analysed.

The evidence of association for KIAA0319 obtained from independent samples is convincing. As with DCDC2, involvement of the KIAA0319 locus seems to be particularly marked in severely affected cases. Association findings, which were strongest around KIAA0319, and results from gene expression and functional studies suggest that KIAA0319 is the most likely susceptibility gene for dyslexia in this gene cluster. Allele-specific expression analyses in lymphoblastoid cells have shown that carriers of the risk-associated haplotype have a 40% reduction in the expression of KIAA0319, whereas the expression of other genes in this region remains unaffected.94 The expression of KIAA0319 is particularly strong in the cerebral neocortex of developing mouse and human brain tissue, and, similar to DCDC2, reduced expression of KIAA0319 through RNA interference leads to disturbed neuronal migration in rats in utero.94

**DYX1C1**

DYX1C1 (MIM 608706) was cloned in a two-generation Finnish family with a translocation t(2;15)(q11;q21).95 DYX1C1, which lies in chromosome region 15q21, is interrupted through the translocation breakpoint. All four family members in whom the translocation was detected showed reading-associated dyslexia.96–98 The evidence of association for KIAA0319 obtained from independent samples is convincing. As with DCDC2, involvement of the KIAA0319 locus seems to be particularly marked in severely affected cases. Association findings, which were strongest around KIAA0319, and results from gene expression and functional studies suggest that KIAA0319 is the most likely susceptibility gene for dyslexia in this gene cluster. Allele-specific expression analyses in lymphoblastoid cells have shown that carriers of the risk-associated haplotype have a 40% reduction in the expression of KIAA0319, whereas the expression of other genes in this region remains unaffected. The expression of KIAA0319 is particularly strong in the cerebral neocortex of developing mouse and human brain tissue, and, similar to DCDC2, reduced expression of KIAA0319 through RNA interference leads to disturbed neuronal migration in rats in utero.94

**ROBO1**

As with DYX1C1, the identification of ROBO1 (MIM 602430) was achieved through breakpoint mapping of a translocation. A translocation, which had probably occurred de novo, was diagnosed in an affected individual from Finland t(3;8)(p12;q11). Positive association findings, which were insufficiently analysed.

**CONCLUSIONS**

Of the candidate genes discussed to date, the evidence for DCDC2 and KIAA0319 is the most convincing. Their identification represents an important step in our understanding of the molecular processes that lead to dyslexia. However, many outstanding questions will need to be addressed by future studies. It is necessary to clarify whether population-specific genetic heterogeneity and/or phenotypic differences between samples have led to differing findings for the respective loci. Identifying which of the genetic changes in these candidate genes are causal is also important. The lack of associated variants in the coding regions suggests that it is variants influencing generegulation and expression which are responsible.

The nature of the genes identified to date suggests that a disturbance in cortical neuron migration and reduced activity in left-hemispheric brain regions are pathophysiological correlates of dyslexia. With DCDC2, as with KIAA0319, inhibition leads to poorer neuronal migration in the neocortex of fetal rats through specific small interfering RNAs. This concept of disturbed neuronal migration is also supported by the few results available from postmortem brain studies of affected individuals, which report cortical malformations in the region of the perisylvian cortex. The concept of disturbed neuronal migration in dyslexia is intriguing and will stimulate further research in this area. In view of the fact that DCDC2 and KIAA0319 only contribute a limited part to the development of dyslexia and that most susceptibility genes are still unknown, it may be possible in the future to identify completely new pathophysiological mechanisms.

To date, no specific cognitive processes are known to be influenced by the proposed susceptibility genes. Some studies have already started to include neurophysiological (eg, event-related potential) and imaging (eg, functional MRI) procedures in their phenotype characterisation of patients. Such samples are an important prerequisite for the identification of those genes.
processes that are most proximal to the effects of particular genes and their associated biological pathways.

Through the availability of detailed clinical data, it should be possible to associate special phenotype dimensions of dyslexia with specific risk genes (genotype–phenotype association). Phenotype subdimensions are, of course, correlated with each other, and the effects will not affect isolated subdimensions. Nor is it to be expected that specific genes will affect the whole spectrum of phenotype dimensions equally. Studies have not yet managed to establish genotype–phenotype relations convincingly, although samples may have been too small to demonstrate these effects. However, proof of genotype-phenotype associations could be facilitated through the joint analysis of larger samples and the identification of causative variants.

The molecular genetic studies conducted so far have not considered sex-specific genetic effects. Differing prevalence rates between males and females could be suggestive of a sex-specific gene effect. A sufficient power to detect such effects can be provided only when sex is taken into account during the analysis of results, and this should be a feature of future studies.

Identification of susceptibility genes will allow research into the molecular background of clinically observed comorbidity. Eight loci have already been proposed as having pleiotropic effects on dyslexia and ADHD at a linkage level.14–25 The identification of susceptibility genes also allows examination of the extent to which dyslexia-associated disorders, such as SSD and language impairment, are influenced by the same susceptibility genes. For SSD, overlapping linkage evidence in DYS3 already provides the first concrete evidence of such common effects.26–28

The identification of susceptibility genes will enable the analysis of gene–gene interactions, through which epistatic effects can be discovered. A first example of this might be the proposed interaction between DCD2 and KIAA0319.19 A further aim of future research will be to establish a better understanding of gene–environment interactions in order to identify relevant exogenous risk factors. It has long been recognised that environmental factors are of great relevance to the development of dyslexia, but only some of these factors have been identified so far.29–30 If such factors can be modulated, future dyslexia prevention and individual genetic risk profiling could be envisaged.

The genes that accompany the development of dyslexia are naturally of great interest from an evolutionary perspective.32 Through the identification of the gene at the DNA level, comparison with species that are closely related to us but that do not have the same speech capacity could be carried out, as well as examination of sequence variability between humans. Speech-associated genes may have been under a selection pressure, which proved advantageous for the development of modern man.

As is generally the case with research on complex genetic disorders, it can be assumed that the speed by which susceptibility genes are identified will be increased through increasing knowledge and huge technological advances (eg, genomewide association studies). Future research efforts will be of a collaborative nature, drawing on complementary expertise from various scientific disciplines and involving the combining of large samples, an approach exemplified by the large multidisciplinary European research consortium (www.neurodys.com) which integrates the work of research groups from nine countries.

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