REVIEW

Genetics of dyslexia: the evolving landscape

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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.

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Dyslexia is among the most common neurodevelopmental disorders, with a prevalence of 5–12%.[1 2] The prevalence varies with the use of different diagnostic criteria and, since reading and spelling are normally distributed in the population, is influenced by the cut-off point applied to the psychometric tests. According to the International Classification of Diseases-10, dyslexia is "a disorder manifested by difficulty learning to read despite conventional instruction, adequate intelligence and sociocultural opportunity".[3] Longitudinal studies have shown that the disorder involves an extremely stable developmental disturbance that does not, in contrast to popular opinion, disappear with adolescence.[4] The psychosocial consequences are correspondingly grave. Affected individuals attain a much lower educational level and have substantially higher rates of unemployment and psychosocial stress than would be expected for their level of intelligence.[5–7] In childhood, approximately 20% of those with dyslexia also present with attention-deficit hyperactivity disorder (ADHD),[8–12] whereas in adolescence depressive disorders and disorders of social behaviour are often associated with dyslexia.[13–15] Whether dyslexia is more common among boys than girls has been part of a controversial discussion in the past, although recent epidemiological studies indicate a twofold increase in the risk for boys compared with that in girls.[2 16] The sex ratio may be influenced by severity, IQ and assessed cognitive profiles.[17]

Familial clustering in dyslexia was recognised a few years after the first description of the disorder by Hinshelwood in 1895.[18–20] 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.[19 21–25] There is an estimated 3–10-fold increase in the relative risk for a sibling (λ_S), with an increase in λ_S observed when strict criteria are applied.[25] Twin studies have confirmed that genetic factors are substantially responsible for the familial clustering of dyslexia.[17 26] The proportion of inherited factors involved in the development of dyslexia is between 40% and 80%, the highest estimates being reported for the phenotype dimensions word reading (up to 58%) and spelling (70%).[17 26 27] Twin studies have allowed for the estimation of heritabilities and also the impact of shared and non-shared environmental factors. Although shared environmental effects are low for word reading, they are substantially higher (at about 14%) for reading and spelling correlated traits—for example, phonological awareness.[27]

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,[28 29] Harlaar *et al*[30] 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; DYX1, dyslexia susceptibility 1; DYX9, 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

Table 1 Cognitive components involved in reading and writing

Component	Remark
Visual processing	The magnocellular system responds to moving stimuli and stimuli of low spatial frequency and low contrast. Impaired perception of moving stimuli and the neurophysiological correlates of this have been found repeatedly in individuals with dyslexia. The exact nature of this deficiency and its potential relationship to dyslexia is not yet clear
Phonological awareness	The ability to perceive, segment and manipulate the sounds of spoken words.[31] Phonemes are the smallest meaningfully distinct sounds from which an acoustic speech flow can be constructed. The word dog, for example, consists of three phonemes /d/, /o/, /g/. The capacity for phonological awareness is often tested through a phoneme deletion task
Verbal short-term memory	Various aspects of memory are required for reading. Many known words are no longer dissected into their phonemes, but are recalled directly from memory. Processing of unknown words into their phonemes occurs in short-term memory. Short-term memory is often examined by a digit span task
Phonological coding	The ability to put together the phonemes and then verbally express words which have never been previously read or heard. This ability is tested through reading of pseudowords
Orthographic coding	Orthographic coding refers to the assumed process of recognising a word by its holistic form. Orthographic coding is measured by a pseudohomophone task where an orally presented word has to be compared with a visual presentation of two phonologically indistinguishable words, of which one may be orthographically correct
Rapid naming	Rapid naming is a measure of the speed of processing. The naming of objects, numbers, letters and colours is typically measured

PHENOTYPIC ASPECTS AND NEUROPHYSIOLOGICAL THEORIES

In general, the cognitive processes on which reading and spelling are based are complex, and differing cognitive dimensions ease the separate skills of reading and spelling. Such processes include those of short-term memory, phonological awareness, rapid naming, and phonological and orthographic coding (table 1). In recent years, several theories have been developed with the aim of characterising the basic processes underlying dyslexia. These have taken into consideration the increasing body of knowledge obtained from neurophysiological and imaging research (eg, event-related potentials, functional MRI). The phonological deficit theory,[32] which assumes a disturbance in phonological processing, is currently the most salient theory. According to this theory, affected individuals have difficulties in perceiving and segmenting phonemes, leading to difficulties in establishing a connection between phonemes and graphemes. The rapid auditory processing theory is another theory[33] that proposes that phonological deficits are secondary to an auditory deficit in the perception of short or rapidly varying sounds. Many individuals with dyslexia perform poorly on auditory tasks including frequency discrimination[34,35] and temporal order judgement.[36] Abnormal neurophysiological responses to auditory stimuli have also been reported.[36–38] However, individuals with dyslexia also have visual perceptual deficits which these theories cannot adequately explain. The magnocellular theory accounts for disturbances in visual processing.[39–42] The theory proposes that in a proportion of individuals with dyslexia, the perception of visual, rapid moving stimuli and stimuli of low spatial frequency and low contrast is impaired. This deficit is associated at the central nervous system (CNS) level with 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.[43] The double deficit hypothesis,[44] 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.[45]

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,[49,66,67] Oxford and Colorado samples.[53] In addition, genomewide linkage studies of large multiply affected families from Holland,[65] Norway[56] and Finland[58,60] 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).[46–48,49] Evidence for linkage was found for word reading and related phenotype dimensions in three samples (Colorado, Yale and Seattle samples),[46,47,49] and one sample showed evidence of linkage for spelling (German sample).[48] Two linkage disequilibrium (LD) studies have been carried out in region DYX1 using short tandem repeat markers,[68,69] 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 trio-samples, two samples of British origin (Cardiff sample) and one of Italian origin.[68,69] 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.[70] The risk-conferring gene in DYX1 may contribute to the comorbidity reported between the two disorders.

Table 2 Summary of linkage findings in dyslexia

Locus	Number of families (individuals, sib pairs), country	Linkage evidence	Linkage evidence with components of the phenotype	Study design	References
DYX1	9 multiplex families (84 individuals), USA	LOD score 3.20	Reading	Categorical	Smith *et al*[46]
	6 multiplex families (94 individuals), USA	LOD score 3.15	Single-word reading	Categorical	Grigorenko *et al*[47]
	7 multiplex families (67 individuals), Germany	LOD score 1.78	Spelling	Categorical	Schulte-Körne *et al*[48]
	90 families (611 individuals), USA	LOD score 2.34	Single-word reading	Categorical	Chapman *et al*[49]
DYX2	19 multiplex families (358 individuals*, 50 dizygotic twin-pair), USA	p Values between 0.009–0.04	Dyslexia	QTL	Cardon *et al*[50]
	82 families (181 sib pairs), UK	p Values between 0.0004–0.038	Orthographic and phonological processes	QTL	Fisher *et al*[51]
	79 families (126 sib pairs), USA	LOD scores between 2.42 and 3.10	Orthographic and phonological processes	QTL	Gayan *et al*[52]
	89 families (195 sib pairs)†, UK	p Values between 0.00001–0.042	Phonological decoding	QTL	Fisher *et al*[53]
	119 families (180 sib pairs)‡, USA	p Values between 0.002–0.006	Phonological decoding		
	104 families (392 individuals)‡, USA	p Values between 0.0005–0.05	Orthographic and phonological processes	QTL	Kaplan *et al*[54]
	8 multiplex families (176 individuals)§	LOD scores of 1.52 and 2.56	Single-word reading, phoneme awareness	Categorical	Grigorenko *et al*[55]
DYX3	1 multiplex family (36 individuals), Norway	LOD score 4.32	Dyslexia	Categorical	Fagerheim *et al*[56]
	89 families (195 sib pairs), UK	p Value <0.001	Orthographic choice	QTL	Fisher *et al*[53]
	119 families (180 sib pairs), USA	p Value of 0.001	Phonological awareness	QTL	
	96 families (877 individuals), Canada	LOD scores of 1.13 and 3.82	Phonological coding, spelling	QTL and categorical	Petryshen *et al*[57]
	11 multiplex families (97 individuals), Finland	LOD score 3.01	Dyslexia	Categarical	Kaminen *et al*[58]
DYX4	96 families (877 individuals), Canada	LOD scores of 2.08 and 3.34	Phonological coding, spelling	QTL and categorical	Petryshen *et al*[59]
DYX5	1 multiplex family (74 individuals), Finland	LOD score 3.84	Dyslexia	Categorical	Nopola-Hemmi *et al*[60]
DYX6	89 families (195 sib pairs), UK	p Value <0.001	Single-word reading	QTL	Fisher *et al*[53]
	119 families (180 sib pairs), USA	p Value <0.001	Single-word reading	QTL	
	84 families (143 sib pairs), UK	p Value <0.001	Phoneme awareness	QTL	
DYX7	100 families (914 individuals), Canada	p Value <0.001	Dyslexia	Categorical	Hsiung *et al*[61]
DYX8	9 families, USA	LOD score of 1.95 and 2.33	Dyslexia	QTL	Rabin *et al*[62]
	8 multiplex families (165 individuals), USA	LOD scores of 3.00 and 2.30	Single-word reading, phonological decoding	Categorical	Grigorenko *et al*[63]
	100 families (914 individuals), Canada	LOD scores of 4.01 and 1.65	Spelling, phonological coding	QTL and categorical	Tzenova *et al*[64]
DYX9	1 multiplex family (29 individuals), Netherlands	LOD score 3.68	Dyslexia	Categorical	de Kovel *et al*[65]
	89 families (195 sib pairs), UK	p Value of 0.001	Single-word reading	QTL	Fisher *et al* [53]

LOD, logarithm of the odds; QTL, quantitative trait loci.
*Including 18 families with linkage evidence at DYX2 previously reported by Smith *et al.*[46]
†Including 82 families with linkage evidence at DYX2 previously reported by Fisher *et al.*[51]
‡Including 39 families with linkage evidence at DYX2 previously reported by Cardon *et al*[50] and 70 families with linkage evidence at DYX2 previously reported by Gayan *et al.*[52]
§Including 8 families with linkage evidence at DYX2 previously reported by Grigorenko *et al.*[47 55]

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 50–52 54] 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 processing [51–54] and orthographic processing.[51 52 54 55] Meanwhile, LD mapping in DYX2 led to the identification of two strong candidate genes (*DCDC2* (doublecortin domain containing protein 2) and *K1AA0319*).[71–75] Interestingly, evidence for linkage has also been found in the chromosome region 6p21–p22 for ADHD.[76]

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 dimensions 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 606 896) showed linkage in a large Finnish family (table 2).[60] *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).[78] 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).[53] 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.[53] 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.[79]

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).[61] 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.[80]

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).[62–64] 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.[63 64]

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).[65] 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).[53]

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,[66] and on chromosome 2q22 for phonological decoding efficiency.[67] 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 20q11.[81] In families with ADHD, evidence for linkage is shown for reading ability in regions 10q11, 16p12 and 17q22.[82]

CANDIDATE GENE FINDINGS IN DYSLEXIA

Of the newly identified candidate genes, *DCDC2* and *K1AA0319* 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 *DYX1C1* (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 (DXY2; table 3).[72] 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: *VMP/DCDC2/KAAG1* and *K1AA0319/TTRAP/THEM2.* In a subsequently expanded Colorado sample (153 nuclear families), the strongest evidence for association was found in *DCDC2* (table 3).[74] 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.[74] 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).[75] 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 *K1AA0319*.[90]

In summary, these results suggest that *DCDC2* is involved in the development of dyslexia. It is unlikely that *KAAG1* is the susceptibility gene at this locus. *KAAG1* overlaps at the genomic level with exon 1 of *DCDC2*, although *KAAG1* does not seem to be expressed in the CNS.[74] 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.[74 75 91–93]

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.[74] 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

Table 3 Summary of association findings in dyslexia

Gene	Study design	Sample characteristics, country	Genotyped variants	Results	References
DYX1C1	Case–control	55 cases* vs 113 controls, Finland	8 SNPs	Significant association at the single-marker and haplotype level	Taipale *et al*[83]
	Case–control	54 cases* vs 82 controls, Finland	8 SNPs†	Significant association at the single-marker level	
	Family based	148 nuclear families, Canada	6 SNPs†	Significant association at the single-marker and haplotype level, association in the opposite direction compared to Taipale *et al*[83]	Wigg *et al*[84]
	Family based	264 nuclear families, UK	8 SNPs†	Significant association at the single-marker level, association in the opposite direction compared to Taipale *et al*[83]	Scerri *et al*[85]
	Family based	150 nuclear families, USA	2 SNPs†	No association	Meng *et al*[86]
	Family based	158 nuclear families, Italy	3 SNPs†	No association	Marino *et al*[87]
	Case–control	57 cases vs 96 controls, Italy	3 SNPs†	No association	Bellini *et al*[88]
	Family based	247 nuclear families, UK	3 SNPs†	No association	Cope *et al*[89]
DCDC2	Family based	114 nuclear families, USA	31 SNPs within 680 kb (including *VMP*, *DCDC2*, *KAAG1*, *KIAA0319*, *TTRAP* and *THEM2*)	Strongest association at the single-marker and haplotype level within the *VMP/DCDC2/KAAG1* locus	Deffenbacher *et al*[72]
	Family based	153 nuclear families, USA	147 SNPs within 1.5 Mb (including *VMP*, *DCDC2*, *KAAG1*, *KIAA0319*, *TTRAP* and *THEM2*)	Strongest association at the single-marker and haplotype level within *DCDC2*	Meng *et al*[74]
	Case–control	240 cases vs 312 controls, UK‡	137 SNPs within VMP, DCDC2, KAAG1, KIAA0319, TTRAP and THEM2	No association within the *VMP/DCDC2/KAAG1* locus	Cope *et al*[71]
	Family based	137 triads, Germany	18 SNPs and 4 STRs within the *VMP/DCDC2/KAAG1*-locus	Strongest association at the single-marker and haplotype level within *DCDC2*, strongest results with severity selection	Schumacher *et al*[75]
	Family based	239 triads, Germany	2 SNPs, 1 STR within *DCDC2*	Significant association at the haplotype level, strongest results with severity selection	
KIAA0319	Family based	114 nuclear families, USA	31 SNPs within 680 kb (including *VMP*, *DCDC2*, *KAAG1*, *KIAA0319*, *TTRAP* and *THEM2*)	Significant association at the single-marker and haplotype level within the *KIAA0319/TTRAP/THEM2* locus	Deffenbacher *et al*[72]
	Family based	42 nuclear families, UK§	31 SNPs within 680 kb (including the *KIAA0319/TTRAP/THEM2* locus)	Strongest association at the single-marker and haplotype level within *KIAA0319* and *TTRAP*	Francks *et al*[73]
	Family based	84 nuclear families, UK§	20 SNPs within *KIAA0319* and *TTRAP*	Significant association at the single-marker and haplotype level	
	Family based	124 nuclear families, USA§	21 SNPs within *KIAA0319* and *TTRAP*	Significant association at the single-marker and haplotype level	Cope *et al*[71]
	Case– control	240 cases vs 312 controls, UK‡¶	137 SNPs within VMP, DCDC2, KAAG1, KIAA0319, TTRAP and THEM2	Strongest association at the single-marker and haplotype level within *KIAA0319*	
	Case–control	223 cases vs 273 controls, UK‡¶	10 SNPs within the *KIAA0319/TTRAP/THEM2*-locus	Strongest association at the single-marker and haplotype level within *KIAA0319*	Schumacher *et al*[75]
	Family based	376 triads, Germany	10 SNPs within the *KIAA0319/TTRAP/THEM2* locus	Nominal significant association at the single-marker level for 1 variant within KIAA0319 in the most severely affected subsample	Harold *et al*[90]
	Family based	126 nuclear families, UK§	16 SNPs within *DCDC2*, *KIAA0319* and flanking region	Strongest association at the single-marker level within 20 kB in intron1 of *KIAA0319*	
	Case–control	350 cases vs 273 controls, UK	28 SNPs and 1 STR within *DCDC2*, *KIAA0319* and flanking regions	Evidence for gene–gene interaction between *KIAA0319* and *DCDC2*	
	Case–control	419 cases vs 273 controls, UK	4 SNPs and 1 STR within *DCDC2* and 5 SNPS within *KIAA0319*		

DCDC2, doublecortin domain containing protein 2gene; 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.*[83]
‡Cases and controls were analysed using a DNA pooling approach.
§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).

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 *K1AA0319/TTRAP/THEM2* gene cluster (MIM 609269) was reported in the Colorado sample.[72] 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).[73] Association in this region was replicated in a third UK sample (Cardiff sample; table 3).[71] There was an 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 *K1AA0319*. Investigation of both UK samples has resulted in evidence of a gene–gene interaction between *K1AA0319* and *DCDC2*.[90]

One sample (German sample), which had reported strong association with *DCDC2*, has so far produced no convincing evidence for association with the *KIAA0319*/*TTRAP*/*THEM2* gene cluster.[75] There was no further evidence of association at the *K1AA0319* locus from the extended Colorado sample (153 nuclear families),[74] although the genomic segment that had shown the strongest association findings in the two UK samples was insufficiently analysed.

The evidence of association for *K1AA0319* 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).[83] *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 problems.[95] To determine whether *DYX1C1* is of significance for affected cases outside of this family, a polymorphism discovery approach was used in 20 Finnish individuals with dyslexia. A total of eight SNPs were identified, which were then investigated in affected individuals and controls of Finnish origin. In an initial sample, two SNPs were found to be associated in the single-marker and haplotype analysis. Replication was then achieved for one of the two variants in a second sample (table 3). However, the sample sizes were limited, and a proportion of the affected individuals in the initial sample were related to each other.[83]

DYX1C1 is expressed in many tissues, including those of the CNS, where it is found in cortical neurones and white matter glial cells.[83] Interestingly, it has recently been shown that DYX1C1, similar to KIAA0319 and DCDC2, functions in neuronal migration in rodent neocortex.[96]

Six other association analyses using independent samples of predominantly European origin have been carried out to date (including the Oxford, Cardiff, Colorado and Toronto samples).[84–89] Overall, the results must be viewed as being negative, since the initial findings have not been replicated. Positive findings have been reported from two of these studies, although the association was with the opposite two-marker haplotype (Oxford and Toronto samples; table 3).[84 85] Given this failure to replicate, it is unlikely that *DYX1C1* makes a significant contribution to the development of dyslexia in non-Finnish European populations.

It is highly probable that the linkage findings in chromosome region 15q21 (DYX1) cannot be traced back to *DYX1C1*, since *DYX1C1* lies outside of the linkage peaks. Whether or not *DYX1C1* contributes to dyslexia in the Finnish population requires clarification through larger association studies.

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).[97] *ROBO1* was interrupted through the translocation breakpoint, localised in linkage region 3p12 (DYX5). A rare *ROBO1* haplotype was identified in the Finnish family, in which the original linkage finding for DYX5 had been found, and cosegregation of this haplotype with dyslexia was reported. Lymphocyte investigation of four affected family members showed that expression of the risk haploytpe was reduced.[97] Investigation of the orthologous gene in Drosophila (robo) and mice (Robo1) suggests that *ROBO1* functions as a neuronal axon guidance gene involved in brain development.[98–100]

Whether or not *ROBO1* actually contributes to the development of dyslexia is currently not clear. A critical point is that the connection between the translocation and dyslexia in the original translocation patient was not imperative: A sibling of the translocation carrier also had dyslexia without carrying the translocation. Should the dyslexia of the Finnish multiplex family be based on a rare and highly penetrant mutation, the causal variant will not be easy to identify, given its size (990 kb of genomic DNA) and the difficulties involved in separating the effects of individual variants from the background variation characterising the haplotype.

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 neurone 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.[74 94] 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.[101–103] 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 *K1AA0319* 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 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 geneeffect. A satisfactory power to detect such effects can be provided only when sex is taken into account during the analysis of results, [66] 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.[46–54 70 76 81 82] 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 DYX5 already provides the first concrete evidence of such common gene effects.[60 78]

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 *DCDC2* and *KIAA0319*.[90] 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.[104] 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.[105] 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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