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REVIEW

Genetics of developmental dyslexia

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Abstract Developmental dyslexia is a highly heritable disorder with a prevalence of at least 5% in school-aged children. Linkage studies have identified numerous loci throughout the genome that are likely to harbour candidate dyslexia susceptibility genes. Association studies and the refinement of chromosomal translocation break points in individuals with dyslexia have resulted in the discovery of candidate genes at some of these loci. A key function of many of these genes is their involvement in neuronal migration. This complements anatomical abnormalities discovered in dyslexic brains, such as ectopias, that may be the result of irregular neuronal migration.

Keywords Developmental dyslexia · Genetics · Reading · Spelling

Introduction

The ability to use spoken language and to read are unique attributes of *Homo sapiens* that set us aside from other species on the planet. Although it has been argued that language development is an innate ability, reading in contrast is not an innate ability, but is acquired through extensive tuition. Different writing (and hence reading) systems have developed over thousands of years across the globe. The earliest known occurrence of *H. sapiens* ability to read and write dates back over 5,000 years, in a region including the present day middle east [102].

Most individuals can acquire the ability to read and write to a standard of proficient fluency and accuracy, but for at least 5% of school-aged children with the developmental dyslexia (DD; [MIM 127700]) this can be a challenging task that often persists into adulthood. DD is generally referred to as a specific impairment in reading ability that is substantially below the expected reading ability given the person's chronological age, measured intelligence and age-appropriate education. Exclusion criteria are acquired brain trauma or disease and impaired visual and auditory sensory acuity [1, 76, 133, 159, 167, 206, 209].

Recognition of DD

It is reported that the condition of word-blindness, also known as "wortblindheit" or "cétité verbale", was recognised 130 years ago by Kussmaul, and was loosely described as inability to read words, despite being able to see them [82, 99]. About 30 years later, individual cases of word-blindness began to be documented in the English literature. Many of the early reports were by Hinshelwood, who described cases where the ability to read was spontaneously lost or diminished in adulthood. These cases often coincided with secondary conditions, such as a severe headache, stroke, epileptiform seizure, aphasia, hemiplegia or right homonymous hemianopsia, or else a physical strike to the head [82–85, 88]. This condition of acquired word-blindness, or alexia, was attributed to the damage of some parts of the brain. Pathological examinations confirmed this

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by revealing lesions in the left supramarginal and angular gyri of the inferior parietal lobe [82–84]. This is where cross-model integration of auditory and visual information occurs.

At the same time, congenital word-blindness (or DD) began to be recognised [86, 87, 89, 123, 181, 188]. These were cases of children, often described as healthy, bright and intelligent, who had great difficulty in learning to read and write. Given the perceived clinical similarity of DD and acquired word-blindness, it was postulated that individuals with DD would also have abnormalities in their left supramarginal and angular gyri [86].

Neurobiology of DD

Evidence for a neurobiological basis for DD comes from postmortem examinations and brain imaging of individuals with DD. Postmortem examinations of four male and three female brains with DD made two primary observations; an increase in abnormalities of the left hemisphere concentrated around the perisylvian region and near symmetry of the planum temporale [61, 63, 92]. The abnormalities included neuronal ectopias and focal architectonic dysplasias, specifically micropolygyria, of the left planum temporale. The ectopias, consisting of nest of neurones, and occasionally the dysplasias, were often found in layer I of predominantly the left inferior frontal and superior temporal gyri. An important inference from these studies was that the abnormalities, or lesions, occurred at a time of peak neuronal migration during embryonic development [63].

Subsequently, visual processing experiments indicated problems with rapid visual processing in individuals with DD. This led to the postmortem re-examination of the same DD brains as before [61, 63, 92, 108]. This revealed disorganisation of the magnocellular, but not the parvocellular, layers of the lateral geniculate nuclei (LGN). This region of the brain forms part of the primate visual system and so these observations were consistent with the visual processing deficiencies observed in DD [108]. The cell bodies comprising the magnocellular layers of the LGN from the DD brains also appeared smaller than in control brains.

Similarly, the results from auditory processing experiments indicated problems with rapid auditory processing in individuals with DD [147, 185]. This again led to the re-examination of same DD brains. This time the medial geniculate nuclei (MGN) were examined as these are involved in the auditory processing system [61–63, 92]. The DD brains presented greater asymmetry between the left and right MGN than in control brains, and generally the left MGN had more smaller and less larger neurones [62].

Much has been learnt about the processes of reading by functional neuroimaging of brains unaffected with DD. These studies suggest that two posterior pathways exist, namely the dorsal and ventral pathways, along with an anterior component and that generally there is a bias of leftside processing. The dorsal pathway is centred on the left temporoparietal regions. It includes the angular and supramarginal gyri, and also the left posterior end of the superior temporal gyrus [173], and deals with attentionally controlled mapping of graphemes of a visual word onto phonological representation. An underactivation in this pathway is considered as correlate of a phonological deficit. The ventral pathway is centred on the left inferior occipitotemporal region and includes the posterior fusiform gyrus. It may be required for the quick automatic processing of familiar visual words or frequent letter strings within words. The under activation of this pathway in dyslexic subjects was interpreted as correlate of the slow and erroneous word recognition. The anterior component is centred on the left inferior frontal gyrus and mainly correlates with the articulation of speech sounds. An over activation in this brain region was seen as compensatory, although ineffective articulatory-based access to phonological word representations in DD [148].

Many functional neuroimaging studies have demonstrated altered activity of exactly these regions in DD brains [43]. For example, in one study, phonological and lexical tasks resulted in the activation of the left inferior temporal gyrus of most control brains, whereas almost none of the DD brains showed any activation of this region [33]. Several studies have also demonstrated reduced activity of left temporoparietal regions (including the angular and supramarginal gyri) on tasks of word reading, non-word reading and letter rhyming [171, 172, 187], and left occipitoparietal regions on tasks of letter matching [187]. A large study comparing 70 DD brains to 74 control brains similarly revealed reduced left inferior frontal, left superior temporal, left occipitotemporal and left temporoparietal regional activity on several reading-related tasks [166]. In addition, a positive correlation was observed between individual reading skill and activity in left posterior regions, for example, between pseudoword reading and the left occipitotemporal region [166]. A compensatory higher activation pattern in DD subjects was found repeatedly in the left inferior frontal brain area [21, 143, 151, 168]. Imaging studies have also identified greater asymmetry and less grey matter content of the cerebellum in DD brains [19, 45, 103], with one study indicating a smaller right anterior lobe correlates with phonological deficits [103].

Finally, it is often observed that the equivalent homotopic right hemispheres display increased activity in DD brains, perhaps as a compensatory measure. For example, the right temporoparietal regions (including the angular gyrus) displayed greater activation in response to both

word and non-word reading [171, 172], and increased activity in the right relative to the left inferior temporal gyrus during a phonological task [33].

Theories on the basis of DD

Numerous theories and ideas have been put forward to explain the deficits observed in DD individuals, but whilst each may be supported by evidence from a few individuals with DD, not one is able to account for all cases of DD. A brief description of each is given here. The phonological deficit theory is the most widely accepted, and is explained by a problem in representing, storing or retrieving phonemes, resulting in poor or ineffectual reading [17, 177]. The rapid auditory processing theory suggests that DD develops from an auditory deficit that inhibits the perception of short or rapidly varying sounds [185]. The visual deficit theory suggests that an impairment of the visual magnocellular system, and its association with the posterior parietal cortex, is responsible for DD [179]. The cerebellar deficit theory attempts to tie in the motor deficits often associated with DD by recognising that the cerebellum is important in both movement control and the automation of skills [50, 81, 126, 183]. The magnocellular (auditory and visual) theory extends upon both the auditory and visual theories by postulating that a general impairment in magnocellular pathways will affect visual, auditory and tactile sensory modalities [179]. The double-deficit hypothesis proposes that DD arises from deficits in both phonological processes and the rapid naming of simple stimuli such as words [207, 208]. A fundamental argument against each theory is that they can only explain a proportion of individuals with DD, and that some individuals with DD do not have the other peripheral deficiencies often described by these theories [145]. Indeed, it is entirely possible that each theory may account for different sub-sets of dyslexia, brought about by different aetiologies, whether they are genetic or environmental.

Prevalence of DD

The prevalence of DD, that is the occurrence of DD in the general (unselected) population, has been estimated from epidemiological studies, with large numbers of individuals, typically from Western populations, employing different selection criteria and different test languages. To illustrate this, a study of 5,718 children in a population-based birth cohort in the US has produced prevalence figures of 5.3–11.8% [96]. However, DD is not limited to Western populations. A study of 690 Chinese children from Hong Kong found prevalence rates of 9.7–12.6% [28], and a study of reading disability in 2,878 Egyptian children found a prevalence rate of 1.3% [49]. The prevalence of DD is often observed greater in males than in females, at a ratio of ~2:1 [28, 41, 49, 96], and this is often explained by an ascertainment or referral bias [52, 196]. However, ever increasing sample sizes from unselected populations makes this argument difficult to justify. Four independent epidemiological samples (n = 989, 895, 5,752 and 2,163) from a single study observed prevalences of 18.5–24.6% in boys and 8.3–13% in girls. A huge prospective study in the US of 32,223 children (16,080 boys and 16,143 girls) observed that twice as many boys were affected than girls [56], and a study of reading ability in nearly 200,000 children across 43 different countries found that in every country examined, without exception, girls outperformed boys on reading tests [30].

Genetic studies on dyslexia

Familiarity of DD

Developmental dyslexia does not just occur randomly within the population. In fact, familial clustering of DD was observed well over 100 years ago [89, 181, 188]. It was later observed that an individual's risk of being affected increased, when other family members were already affected [77]. Later, it was observed that 9% of control children had a sibling or parent with some form of reading problem, when compared with 34% of children with DD [152]. Recently, it has been shown that 20–33% of siblings of affected individuals, with unaffected parents, are themselves also affected [67]. This increased to 54–63% if either (but not both) parent was also affected, and to 76–78% if both parents were affected [67]. For spelling disorder, the percentage of affected siblings has been found to be higher (52–62%) than for word reading [156]. The sibling recurrence risk of DD, that is the probability of an individual being affected with DD given a sibling is already affected (regardless of parental affection status), is estimated as 43–60% [197, 213]. With a population prevalence of ~10% and a sibling recurrence risk of ~50%, the sibling relative risk can be estimated as between 4 and 6, and increases with stricter affection status criteria [213].

Heritability of DD

With such a strong familial basis for DD, twin studies have been employed to evaluate the contribution of the environmental and genetic components underlying its aetiology. Typically, such studies utilise large sets of monozygotic (MZ) and same sex dizygotic twins. The concordance rate for DD is then compared between the two sets of twins. A higher concordance rate in the MZ twins

would be suggestive of a genetic aetiology for DD, and fittingly this has been shown consistently; 1.00 versus 0.52 [212], 0.91 versus 0.45 [4] and 0.68 versus 0.38 [41]. Twin studies also enable estimates of the heritability of DD, that is the proportion of phenotypic variation attributable to genetic variation, with figures ranging from 0.30 to 0.70 [27, 42, 64, 182], depending on the diagnostic criteria, age and sample size (see Fig. 1) [38, 79, 106, 136].

Identifying the risk factors behind DD susceptibility

Twin- and family-based studies have shown that DD is highly familial and also heritable and complex, involving multiple risk factors, both genetically and environmentally [53, 58, 76, 133, 155, 159, 206]. Identifying the environmental factors has yielded interesting and controversial results, ranging from the effects of maternal antibodies [195], associations with immune disorders [69, 91, 192], fatty-acid deficiencies [36, 186], imbalances of trace and toxic metals [24, 70] and exposures to high levels of prenatal testosterone [16, 66].

Conversely, the search for genetic risk factors is yielding convincing results, as will be discussed later. However, before we touch on that, there is one more important aspect of DD to be covered is the issue of co-morbidity (see Table 1), particularly with other neurodevelopmental disorders, such as attention deficit/hyperactivity disorder (ADHD [MIM 143465]) [3], developmental dyscalculia (DC) [105], specific language impairment (SLI [MIM 606711) [118] and speech-sound disorder (SSD [MIM 608445]) [13]. ADHD is characterised by inattention, overactivity and impulsiveness and has a population prevalence of ~5% [1]. DC has a population prevalence of about 3.6–6.6% and is generally defined as a specific impairment in arithmetic abilities, despite any deficits in intelligence, socioeconomical background, general motivation, emotional stability, educational opportunity or sensory acuity [1, 75, 105, 164, 165, 209]. SLI is regarded as impairment in the ability to acquire adequate language skills, despite normal intelligence and development and has a population prevalence of approximately 2.3–7.4% between 2 and 5 years old [101, 191]. SSD, or phonological disorder, is characterised by speech–sound production errors associated with deficits in articulation, phonological processing and cognitive linguistic processing, and has an estimated population prevalence of ~15% at 3 years of age, decreasing to 3% by 6 years of age [23, 170]. There is not much evidence of increased co-morbidity between DD and SSD alone, but in conjunction with language impairments there is significant co-morbidity with DD, particularly with deficits in spelling [13, 104].

Co-morbidity with these disorders presents a challenge for researchers studying the genetics of DD. On the one hand, DD individuals recruited for these studies must be carefully vetted with strict exclusion criteria to ensure that a homogenous sample is collected without other underlying neurological disorders. However, on the other hand, from the statistics presented in Table 1, individuals with DD, depending on the diagnostic criteria used to diagnose a comorbid disorder will commonly present with another neurodevelopmental disorder, thus making pure DD individuals rare and not actually representative of the majority of individuals with this disorder. Individuals with DD will display a unique set of symptoms and severity, for both DD and any other neurodevelopmental disorder they possess. Furthermore, whether DD is causative of another neurodevelopmental disorder, or vice versa, or whether both disorders are the results of the same aetiology further

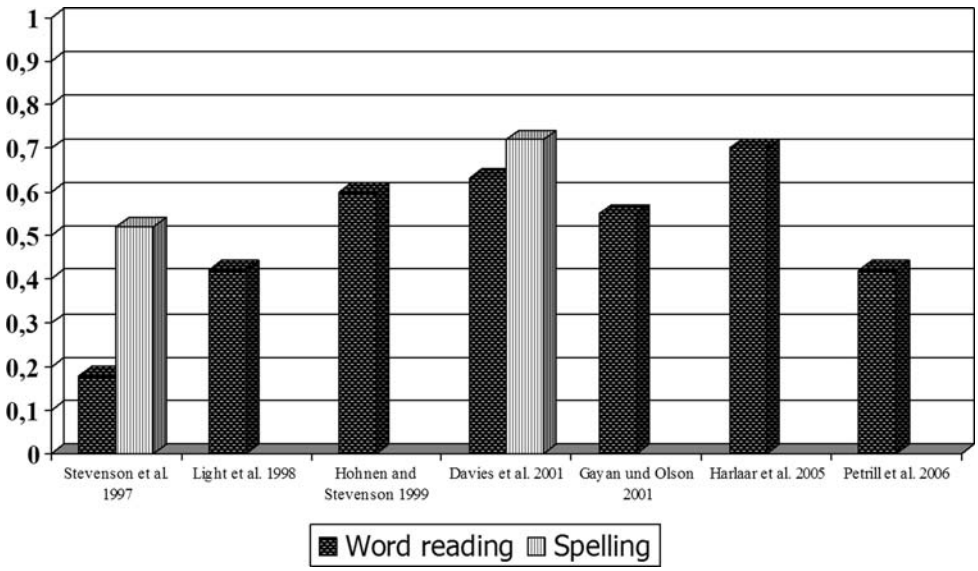

Fig. 1 Heritability estimates of reading and spelling

Table 1 The statistics of disorders co-morbid with developmental dyslexia

Co-morbid disorder (CMD)	Population prevalence of CMD	Group-deficit heritability (h_g^2) of CMD	Co-morbid prevalence with DD	% of DD with CMD	% of CMD with DD	Bivariate group-deficit heritability[a]		Genetic correlation with DD	Phenotypic overlap with DD attributed to common genetic influences
						$h^2_{g(DD/CMD)}$	$h^2_{g(CMD/DD)}$		
ADHD	~5% [1]	0.39–0.9 [68, 169, 205]	–	15–40% [68, 203, 205]	17–45% [3, 162, 202, 205]	0.23–0.55 [106, 204, 205]	~0.3–0.5 [205]	0.37–0.63[205]	64% [204]
DC	3.6–6.6% [75, 105, 164]	0.38 [98]	2.3–2.7% [105, 164]	25–37% [98, 105]	17–70% [75, 98, 105]	0.27 [98]	0.18 [98]	0.53 [98]	40–60% [98]
SLI	2.3–7.4% [101, 191]	0.59–0.88 [14, 15]	–	20–60% [118]	40–80% [118]	–	0.45–0.64 [11]	–	–
SSD	5–15% [23, 170]	0.45–0.97 [12, 190]	–	–	21.6% [178]	–	–	–	–

[a] Deficits in X due to genetic influences also influencing Y (h_g^2(X/Y))

complicates the matter. Indeed, from Table 1, it can be seen that there are shared genetic influences affecting both DD and the co-morbid disorders. Concentrating efforts on homogenous samples affected by DD alone risks delaying the discovery of genes implicated in this disorder. A better strategy might be to record any co-morbid disorders and then treat them as covariates when analysing a sample of DD individuals. Putting this issue aside for now, genetic studies of DD have been successful in the search for candidate susceptibility genes. On the whole, these studies have made stringent attempts to use homogenous samples affected by DD alone.

Molecular genetic studies for DD susceptibility

Not less than 19 independent linkage studies have been performed in the search for DD susceptibility genes (see Table 2). Eight of these were genome-wide linkage screens [39, 46, 47, 54, 93, 94, 117, 127, 129, 146], whilst the remainder generally targeted loci highlighted by the genome-wide screens. Another two genome-wide linkage screens for general reading and spelling ability have also been performed with samples not specifically selected for DD [5, 163].

At least nine DD susceptibility regions have now been mapped and allocated names from *DYX1* to *DYX9* successively (see Table 3). Subsequent association studies focussed at these regions have led the way in identifying the underlying candidate genes at most of these regions, with the exception of *DYX4*, *DYX6* and *DYX9*, where no efforts have yet been reported. A summary now follows the remaining *DYX#* loci where reports exist for the positive identification of candidate DD genes. However, before we begin it should be noted that for the ease of reading, this review does not delve into the different selection criteria or reading-related measures used in each study.

DYX1 on chromosome 15

The first reported linkage to DD susceptibility anywhere in the genome was to the centromere of chromosome 15 [175]. Unfortunately, subsequent studies were unable to replicate this linkage [10, 54, 72, 157]. However, an alternative locus on chromosome 15, from 15q15.1 to 15q21.3, has instead gained support from five independent DD linkage studies (see Fig. 2) [29, 60, 72, 157, 161, 174]. This locus, *DYX1*, was made all the more interesting by the discovery of a Finnish family co-segregating a balanced translocations of 15q21-22, specifically t(2;15)(q11;q21), with reading problems in four members of a two-generation family [128]. The chromosome 15 breakpoint of this translocation disrupts a gene, now known as dyslexia susceptibility 1 candidate 1 (*DYX1C1* [MIM 608706]),

Table 2 A summary of the different linkage studies for developmental dyslexia

Study no.	Sample no.	Sample origin	No. of families	Family type(s)	Loci examined	*DYX#*									References
						1	2	3	4	5	6	7	8	9	
1	1	Finland	1	Extended	Genome screen	×	×	×	×	✔	×	×	×	×	[78, 127]
2	2	Finland	11	Extended	Genome screen	×	×	~	×	×	×	×	×	×	[94, 141]
3	3	Norway	1	Extended	Genome screen	×	×	✔	×	×	×	×	×	?	[46–48]
4	4	Dutch	1	Extended	Genome screen	×	×	×	×	×	×	×	×	✔	[39]
5	5	Dutch	67	ASP males and mothers	Xq27.2-Xq28	.	.	.	.	.	.	.	.	×	[39]
6	6	87% Caucasian	51–52 (+38)	Nuclear + extended	Genome screen	✔	×	×	×	×	×	×	×	?	[29, 93, 146]
7	7	America	9–19	Extended	chr15 + 6p23-q23.1	✔	✔	.	.	.	.	.	×	.	[25, 60, 174–176]
8	8	America	9	Multiplex	Various regions	×	.	.	.	.	.	.	✔	.	[144]
9	9	America	50 → 46	Nuclear twins	6p23-q23.1	.	✔	.	.	.	.	.	.	.	[25, 26]
10	10	America	79	Nuclear twins	6p22.3-6p21.2	.	✔	.	.	.	.	.	.	.	[65]
11	9+10	US	119 (104)	Nuclear twins	Genome screen	×	✔	✔	×	✔	✔	×	×	×	[54, 57, 95])
12	11	UK	82–89	Nuclear	Genome screen	×	✔	✔	×	~	✔	~	×	~	[54, 55, 117]
13	12	UK	84	Nuclear	18p11.31-18q12.2	.	.	.	.	.	✔	.	.	.	[54, 117]
14	13	German	7	Multiplex	chr6 and chr15	✔	×	.	.	.	.	.	.	.	[130, 157]
15	14	German	82	Nuclear	18p11.21-18q12.3; 15q13.3-15q22.2	✔	.	.	.	.	×	.	.	.	[160, 161]
16	15	Norway	1	Extended	Genome screen	×	×	×	×	×	×	×	×	×	[129]
17	16	Canadian	79–100	46–51 nuclear + 30–50 extended	1p34-p36; 2p16.3-2p16.1; 6p25.1-p21.2; 6p12.1-6q16.1; 11p15.5-11p15.4	.	~	✔	✔	.	.	✔	✔	.	[51, 90, 137, 139, 140, 194]
18	17	America	6–8	Extended	1p36-1q23; 6p23-p21.3; chr15; chr16	✔	✔	.	.	.	.	.	✔	.	[71–74]
19	18	Danish	5	Backcross families	chr15	×	.	.	.	.	.	.	.	.	[10]
20	19	?	1	Extended	Various regions	×	×	.	.	.	.	.	×	.	[153]

Table 3 A summary of the *DYX#* loci

DYX#	Chromosome region	MIM	No. of positive studies[a]	References of positive studies[a]	No. of negative studies	References of negative studies	Candidate DD susceptibility genes
DYX1	15q21	127700	6	[29, 60, 72, 116, 124, 130, 157, 161, 174]	10	[10, 39, 47, 54, 94, 117, 127, 129, 144, 153]	*DYX1C1*
DYX2	6p22.3-p21.3	600202	7	[25, 26, 54, 55, 65, 71–73, 95, 117, 174, 193]	9	[29, 39, 46–48, 51, 93, 94, 127, 129, 130, 140, 146, 153, 157]	*DCDC2* and *KIAA0319*
DYX3	2p16-p15	604254	4 (+1)	[46–48, 54, 57, 117, 139] (+[94, 141])	4	[29, 39, 93, 127, 129, 146]	*MRPL19* and *C2ORF3*
DYX4	6q11.2-q12	[#127700]	1	[137]	8	[39, 47, 54, 93, 94, 117, 127, 129, 146]	–
DYX5	3p12-q13	606896	2 (+1)	[54, 78, 127] (+ [54, 117])	5	[39, 47, 93, 94, 129, 146]	*ROBO1*
DYX6	18p11.2	606616	3	[54, 117]	7	[29, 39, 47, 93, 94, 127, 129, 146, 160]	–
DYX7	11p15.5	[#127700]	1 (+1)	[90] (+ [54, 117])	7	[39, 47, 54, 93, 94, 127, 129, 146]	–
DYX8	1p36-p34	608995	3	[74, 144, 194]	9	[39, 46–48, 54, 93, 94, 117, 127, 129, 146, 153]	*KIAA0319L*
DYX9	Xq27.2-q28	300509	1 (+1)	[39] (+ [54])	5	[39, 54, 94, 127, 129]	–

[a] Positive studies, and their references, in brackets indicate linkages close to the DYX# loci

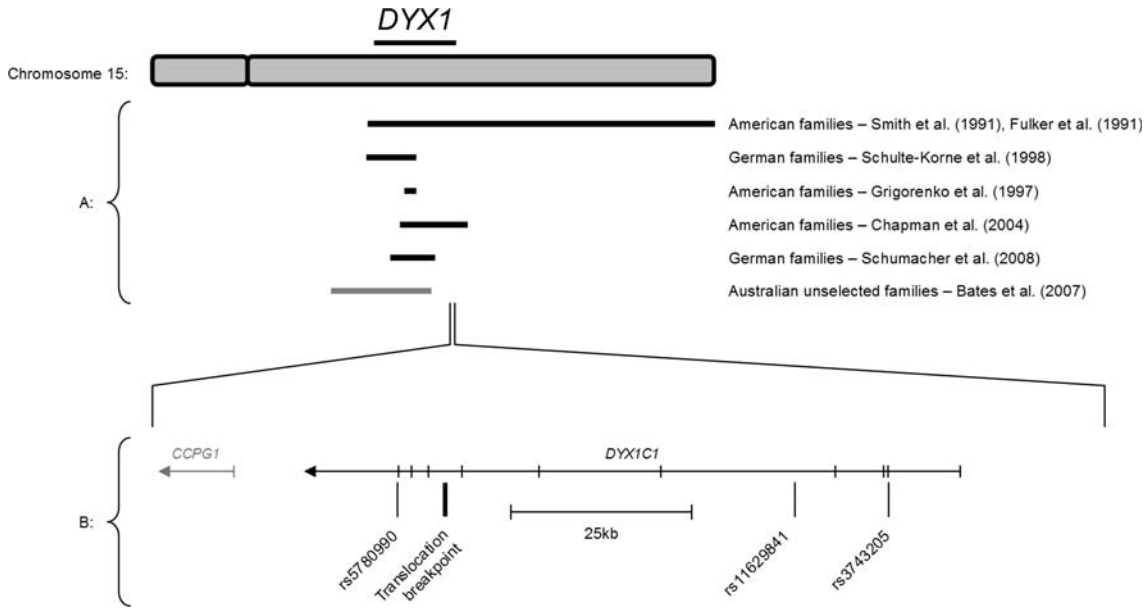

Fig. 2 The *DYX1* locus on chromosome 15. **a** *Black horizontal lines* are linkage reports for DD from independent samples. *Box with diagonal lines* indicates a translocation. **b** Genes that have been tested for association. Interesting SNPs, deletions or translocation breakpoints are *highlighted*

between exons 8 and 9 [184]. A subsequent association study of *DYX1C1* performed with a Finnish sample revealed an increased frequency of two alleles in DD individuals; −3A from the SNP rs3743205 (−3G>A) and 1249T from rs57809907 (1249G>T) [184]. A haplotype of these two alleles, −3A:1249T, also associated with DD. A separate sample of Finnish cases and controls again revealed a significant association with these same alleles [184]. The allele −3A disrupts a putative promoter-binding site and 1249T is a nonsense mutation resulting in the loss of ten amino acids from the N-terminus of the full-length protein. Hence, both SNPs made attractive functional mutations with regard to DD.

Efforts to replicate these associations have produced mixed results and interpretations (see Table 4). Ten independent studies have tested rs3743205, rs57809907 and numerous other SNPs within *DYX1C1* for association with DD or reading-related measures [6, 7, 18, 32, 37, 113, 114, 122, 154, 184, 200]. Four of these studies provide no support for either rs3743205 or rs57809907 [6, 7, 32, 122], whilst the others produce conflicting results [18, 37, 113, 154, 184, 200]. Specifically, two studies lend support to −3A and 1249T, and four studies to −3G and 1249G. The associations from the studies are mostly nominally significant and may result from multiple testing of numerous phenotypes. Four of these studies also report associations with other *DYX1C1* variants, but none are replicated as yet. Two further studies have tested autism and ADHD samples for association with rs3743205 and rs57809907, but only yield limited support for −3G:1249G and ADHD [201, 202, 210].

Therefore, it is unlikely, but not impossible, that rs3743205 and rs57809907 are causative for DD. An alternative explanation is that they are in linkage disequilibrium with a causative genetic variant. This idea is supported by the fact that the four DD samples yielding association between the alleles −3G and 1249G are of central European descent, whilst the others supporting −3A and 1249T are of Finnish and Italian descent. Hence, the causative genetic variant could be present on one haplotypic background of central European descent, and on a different haplotypic background in other populations. Alternatively, different causative mutations might exist between different populations.

DYX2 on chromosome 6

A DD susceptibility locus on the short arm of chromosome 6, known as *DYX2*, has been reported by at least five independent studies (see Fig. 3) [25, 54, 55, 65, 71–73, 95, 174]. *DYX2* is located at 6p22.3-p21.3 and spans over 15 Mb. It was the first locus to be positively replicated for DD susceptibility. Possibly for this reason, *DYX2* became a focal point for subsequent association studies employing extensive high-throughput genotyping methods (Table 5). Many genetic variants have been tested, including microsatellites and SNPs, and lots of sporadic associations have been observed to a range of genes. However, from all these studies of *DYX2*, there are two genes that stand out: *KIAA0319* and *DCDC2*. These genes are just 150 kb from one another on 6p22.2.

Table 4 Reported associations of *DYX1C1* at *DYX1*

Study	Study and reference	Proband's disorder	Study population	Sample	Reported associations with *DYX1C1*			
					rs3743205 [−3G>A]	rs57809907 [1249G>T]	Haplotype: rs3743205:rs57809907	Other (s)
1	Taipale et al. [184]	Dyslexic	Finnish	109 Cases and 195 controls	−3A	1249T	−3A:1249T	None
2	Scerri et al. [154]	Dyslexic	British	264 Families	n/s	1249G	−3G:1249G	None
3	Wigg et al. [200]	Dyslexic	Canadian	148 Families	−3G	n/s	−3G:1249G	rs11629841(G), Two 2-marker haplotypes[e]
4	Cope et al. [32]	Dyslexic	British	247 Trios	n/s	n/s	n/s	None
5	Marino et al. [113, 114]	Dyslexic	Italian	~212 Families	n/s	n/s	−3A:1249T	None
6	Meng et al. [122]	Dyslexic	American	150 Families	n/s	n/s	n/s	None
7	Bellini et al. [7]	Dyslexic	Italian	57 Cases and 96 controls	n/s	n/s	n/s	−2A[f]
8	Brkanac et al. [18]	Dyslexic	American	191 Trios, and 191 cases and 192 controls[b]	n/s	1249G[b]	n/s	None
9	Dahdouh et al. [37]	Dyslexic	German	366 Trios	[−3G][c]	n/s	n/s	3-Marker haplotype[c]
10	Ylisaukko-Oja et al. [210]	Autistic	Finnish	100 Families	n/s	n/s	n/s	None
11	Wigg et al. [201, 202]	ADHD	Canadian	253 Families	n/s	n/s	[−3G:1249G][d]	6-Marker haplotype[d]
12	Bates et al. [6]	Unselected[a]	Australian	789 Families	n/s	n/s	n/s	Other not specified

n/s not significant

[a] Unselected population tested for reading

[b] Over-transmission of 1249G observed with the trios, but no associations were observed with the case:control analysis; the cases are derived from the trios

[c] The 3-marker haplotype is rs3743205[G]:rs3743204[G]:rs600753[G], and hence includes −3G

[d] The 6-marker haplotype is rs2007494[A]:rs3743205[G]:rs3743204[C]:rs11629841[T]:rs692691[C]:rs57809907[G], and hence includes −3G:1249G

[e] The 2-markers haplotypes are rs11629841[G]:rs692691[T] and rs3743204[C]:rs11629841[G]

[f] The allele −2A is for a SNP without an official name, but it is immediately adjacent to rs3743205

Association with *KIAA0319* was first identified in a study of *DXY2* using samples from the Colorado Learning Disabilities Research Center (CLDRC) [95]. In this study, association was observed to a microsatellite marker known as JA04 that resides within the first exon of *KIAA0319*. Although association with JA04 has never been replicated, four of the five independent DD studies to have tested *KIAA0319* do find association with other markers [18, 31, 40, 44, 59, 80, 95, 121, 158]. Although these associated markers are distributed across the entire 102 kb length of *KIAA0319*, there is a tendency for the most significant associations to cluster around the first intron and predicted promoter region of this gene. Four markers, namely rs4504469, rs6935076, rs2038137 and rs2143340 (actually located in the adjacent gene called "TRAF and TNF receptor associated protein" (*TTRAP* [MIM 605764])), have each been robustly associated in at least two independent samples. Furthermore, a specific risk-haplotype composed of rs4504469, rs2038137 and rs2143340 has been shown to associate with DD in three independent samples. This risk-haplotype has also been tested and associated with a range of reading-related measures in two large unselected samples; approximately 6,000 children from the Avon Longitudinal Study of Parents and Children (ALSPAC) [134] and a sample of 440 twins collected from Queensland, Australia [110]. Disconcertingly, the haplotype within *KIAA0319* was actually associated with better reading scores in the Australian twin sample. The two likely explanations for this are a type I error or a consequence of the sample being ethnically heterogeneous—only ~82% of the sample was reportedly of Anglo-Celtic origin [110]. Nevertheless, functional studies have been performed with this risk-haplotype, and an elegant experiment has associated it with a reduction in the expression of

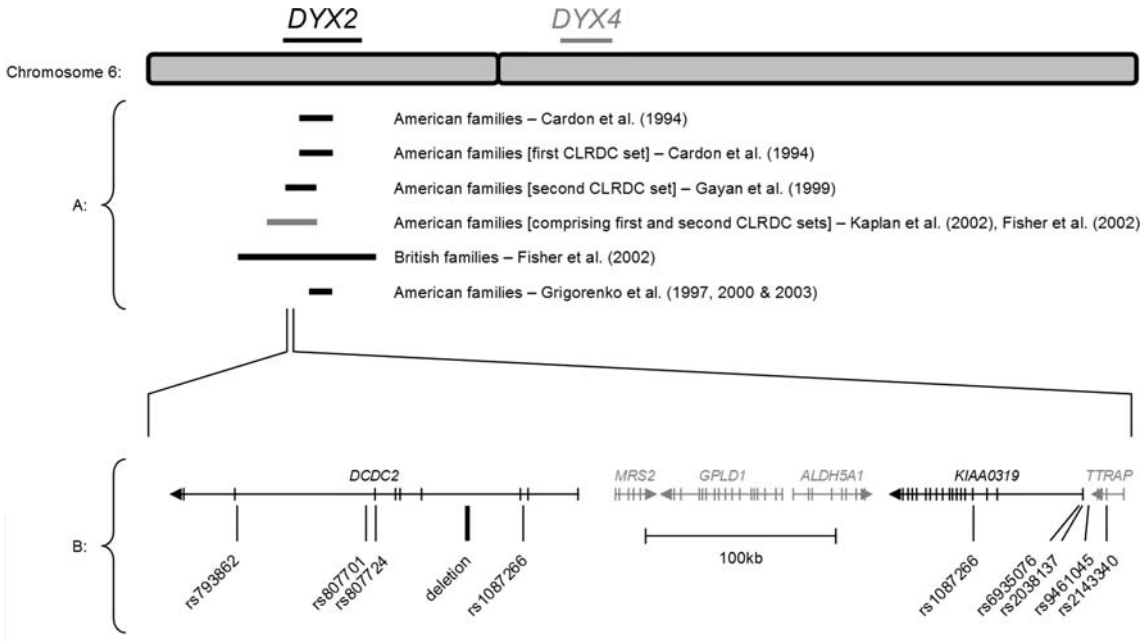

Fig. 3 The *DYX2* locus on chromosome 6. **a** *Black horizontal lines* are linkage reports for DD from independent samples. *Box with diagonal lines* indicates a translocation. **b** Genes that have been tested for association. Interesting SNPs, deletions or translocation breakpoints are *highlighted*

KIAA0319 [135]. Subsequent characterisation of the risk-haplotype sequence has revealed an allele of the SNP rs9461045 that occurs rarely on other (non-risk) haplotypic backgrounds [44]. The association analysis of rs9461045 proves to be highly significant with respect to DD [44]. Furthermore, a series of functional experiments that tested the regulatory properties of numerous sequence variants in the promoter region of KIAA0319 found that the risk allele of rs9461045 specifically reduced gene expression.

Association with *DCDC2* was also first observed in samples from the CLDRC [40]. In all, five of the six independent DD studies that have been tested recently, association has been found between *DCDC2* and a variety of markers across the 212 kb length of this gene [18, 31, 40, 59, 80, 95, 112, 121, 158]. Several noteworthy genetic variants have been identified in *DCDC2* which have produced mixed results when tested in independent samples. A polymorphic deletion has been associated in three of six studies [18, 80, 112, 121], and the SNP rs793862 in four of the six independent DD studies [18, 40, 80, 121, 158]. A haplotype of rs793862 and another SNP, rs807701, has also proved significant association in two of five DD studies [158]. Both rs793862 and rs807701, and their haplotype, have also been tested in a sample of families with ADHD probands and also tested for reading measures, and revealed association with attentional phenotypes, but not the reading phenotypes. Although the association of rs793862 to DD or ADHD in four of the five studies appears to be with the minor allele [35, 40, 121, 158], in the remaining British sample, it is with the major allele [80]. However, the association observed in this British sample is modest (*P* values from 0.02 to 0.04), suggesting it may be a type I error. Lastly, an independent study has examined the effect of the *DCDC2* deletion on the brain morphology of healthy samples (not selected for DD). A significant increase in grey matter in regions of the brain involved in reading was observed in individuals heterozygous for the deletion (individuals homozygous for the deletions were too infrequent and so not tested) [120].

For both *KIAA0319* and *DCDC2*, independent studies have observed that the significance of the associations within these genes increase on selecting a sub-set of samples containing the more severe cases of DD [59, 80, 158]. On the other hand, it is interesting to note that markers within these genes have also been associated with general reading ability within two unselected populations [6, 110, 134]. One possible interpretation is that variants within both genes can influence the development of reading ability, but that there are also specific functional variants within these genes that can cause DD.

Finally, two independent analysis have tested for an interaction been the markers of *DCDC2* and *KIAA0319* [80, 111]. Both studies find an interaction with a single SNP (rs761100) within *KIAA0319* and either rs793862 alone [80], or the haplotype it forms with rs807701 [111], within *DCDC2*. Further work is required to determine

Table 5 Reported associations of *DCDC2* and *KIAA0319* at *DYX2*

Study	Study and reference	Proband's disorder	Study population	Sample	Reported significant associations														
					DCDC2 markers							*KIAA0319* markers							Other(s) around *DYX2*
					rs793862	rs807701	Risk haplotype[h]	rs807724	deletion	rs1087266	others	rs4504469	rs6935076	rs2038137	rs9461045	rs2143340	Risk haplotype[i]	others	
1[a]	Kaplan et al. [95] and Meng et al. [121]	Dyslexic	American (CLDRC)	104 and 153 Families	y	n	–	y	y	y	y	n	–	–	–	–	–	y	y
	Deffenbacher et al. [40]			349 Families	y	–	–	n	–	y	y	–	–	y	–	–	–	y	y
	Francks et al. [59]			124 Families	–	–	–	–	–	–	–	n	–	n	–	y	y	y	y
2[b]	Francks et al. [59]; Harold et al. [80] andDennis et al. [44]	Dyslexic	British	126^{S} and 264^{A} Families[b]	y^{A}	n	n	y^{A}	y^{S}	y^{A}	n	y	n	y	y	y	y	y	y
3[c]	Cope et al. [31] and Harold et al. [80]	Dyslexic	British	143 Trios, and 350 cases and 273 controls[c]	n	n	n	n	n	n	n	y	y	y	–[e]	n	y	y	y
4[d]	Schumacher [158]	Dyslexic	German	137^{A} and 47^{S} Trios[d]	$y^{A/S}$	y^{S}	y	–	n	–	y	n	n	n	–	n	–	y^{S}	n
5[d]	Ludwig [112]	Dyslexic	German	239^{A} and 64^{S} Trios[d]	y^{S}	y^{S}	y	–		–	–								–
6	Brkanac et al. [18]	Dyslexic	American	191 trios	n	n	n	n	y	n	–	n	n	–	–	–	–	–	–
7[e]	Luciano et al. [110] and Bates et al. [6]	Unselected[e]	Australian	440 and 789 Families[e]	–	–	–	–	–	–	y	n	y	n	–	y	y	n	n
8[f]	Paracchini et al. [134]	Unselected[f]	British	~6,000 Children[f]	–	–	–	–	–	–	–	y	y	y	–	y	y	–	–
9[g]	Couto et al. [35]	ADHD[g]	Canadian	264 Families	y	y	y	–	–	–	–	n	n	n	–	n	n	y[g]	y

n no (not significant), *y* yes (significant), – not tested

[a] Different studies using overlapping sub-sets of samples from the Colorado Learning Disabilities Research Center (CLDRC)

[b] The 126 families (S) are a severe sub-set of all the 264 families (A)

[c] Trios, and case and controls samples not independent; the proxy SNP rs7766230 in LD ($r^2 = 1$) with rs9461045 is not associated

[d] Two independent samples; all 376 trios used for *KIAA0319* and *DCDC2* deletion analyses, as well as a severe sub-set of these 376 trios (S)

[e] Tested for reading and spelling; *KIAA0319* markers tested with 440 families and *DCDC2* markers tested with the extended set of 789 families

[f] Tested for reading and spelling; sample ranges from 5,254 to 7,090 children depending on phenotype measured

[g] Also tested for reading measures, but yielded only a single nominally significant results with the SNP rs12194307

[h] Risk haplotype within *DCDC2* composed of rs793862 and rs807701

[i] Risk haplotype within *KIAA0319* composed of rs4504469, rs2038137 and rs2143340

whether the interactions are between the same alleles in these two studies.

DYX3 on chromosome 2

A locus for DD susceptibility on chromosome 2 was first observed in one of the earliest genome-wide linkage scans for this disorder, using a large pedigree of Norwegian descent [47]. *DYX2* is located on the short arm of chromosome 2, at 2p15-16. Linkage to DD has since been observed to *DYX2* in at least three independent studies of British, American and Canadian families (see Fig. 4) [54, 139]. A further study has identified a locus close to *DYX2*, at 2p11, reportedly linked to DD in a sample of Finnish families [94]. From the few early association studies to investigate this region, negative findings were reported for a very small number of SNPs in the gene tachykinin receptor 1 (*TACR1* [MIM 162323]) within the Finnish families [141], and also the two genes "sema domain, immunoglobulin domain, transmembrane domain and short cytoplasmic domain, (semaphorin) 4F″ (*SEMA4F* [MIM 603706]) and orthodenticle homeobox 1 (*OTX1* [MIM 600036]) in the American families [57].

Subsequently, the Finnish locus has been re-investigated in a high-density SNP association study covering ~5 Mb of genomic sequence [2]. On this occasion, association was observed in an overlapping region in two independent samples of Finnish and German descent. In both samples, a range of haplotypes were found associated with DD. Common to several of these risk-haplotypes were the two SNPs rs917235 and rs714939, and importantly in both the Finnish and German samples an allele G at both rs917235 and rs714939 was over-transmitted to the DD samples. Flanking these two SNPs are three genes; "family with sequence similarity 176, member A" (*FAM176A*), mitochondrial ribosomal protein L19 (*MRPL19* [MIM 611832]) and chromosome 2 open reading frame 3 (*C2ORF3* [MIM 189901]). A reduction in the expression of both *MRPL19* and *C2ORF3* was subsequently observed from chromosomes carrying derivates of the risk-haplotype; specifically, from chromosomes carrying both rs917235[G] and rs714939[G] [2].

DYX5 on chromosome 3

Linkage to the peri-centromeric region of chromosome 3 has been observed for DD susceptibility in three independent genome-wide screens (see Fig. 5). First, linkage was reported in a Finnish family spanning the centromere of chromosome 3 from 3p12 to q13 [127]. Within this four generation family, it was deduced that 19 out of 21 affected individuals carried a common haplotype identical-by-descent that was about 35 Mb in length. Linkage to DD was subsequently reported at 3p13 in a British sample and 3q13 in an American sample [54]. In addition, linkage for reading ability at this peri-centromeric region was also observed in a sample of American families ascertained for SSD [178]. Specifically, linkage for the reading measures was observed at 3p12 and from 3p12 to q12 for other language-related measures also tested [178].

The first DD association study to examine this region produced negative results in a sample of Italian families for the gene dopamine receptor D3 (*DRD3* [MIM 126451]) located at 3q13 [115].

Subsequently, the gene "roundabout, axon guidance receptor, homolog 1 (*Drosophila*)" (*ROBO1* [MIM

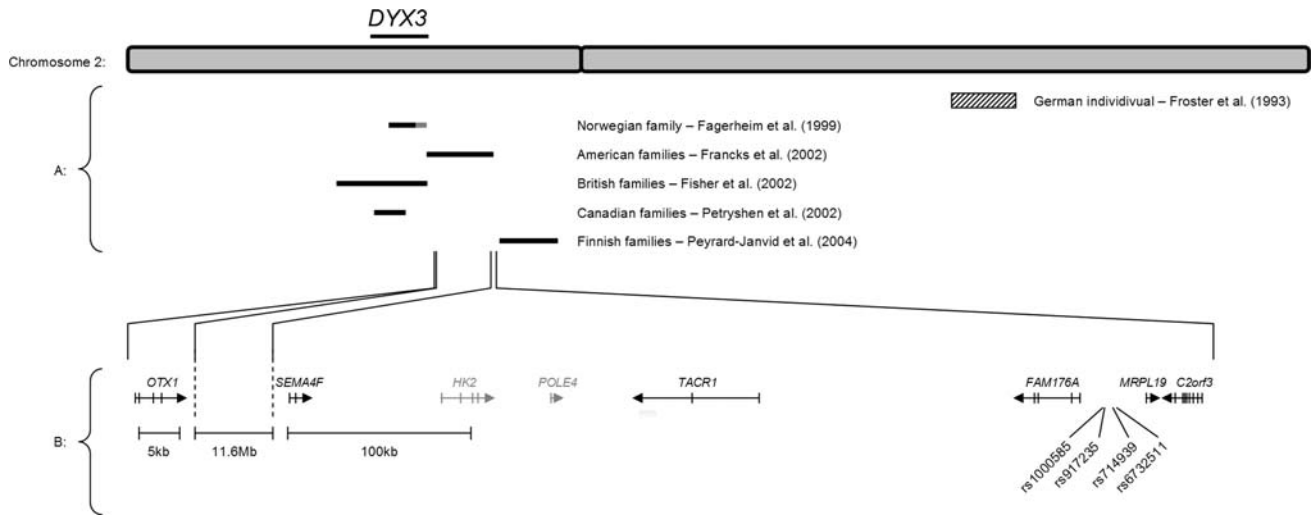

Fig. 4 The DYX3 locus on chromosome 2. **a** *Black horizontal lines* are linkage reports for DD from independent samples. *Box with diagonal lines* indicates a translocation. **b** Genes that have been tested for association. Interesting SNPs, deletions or translocation breakpoints are *highlighted*

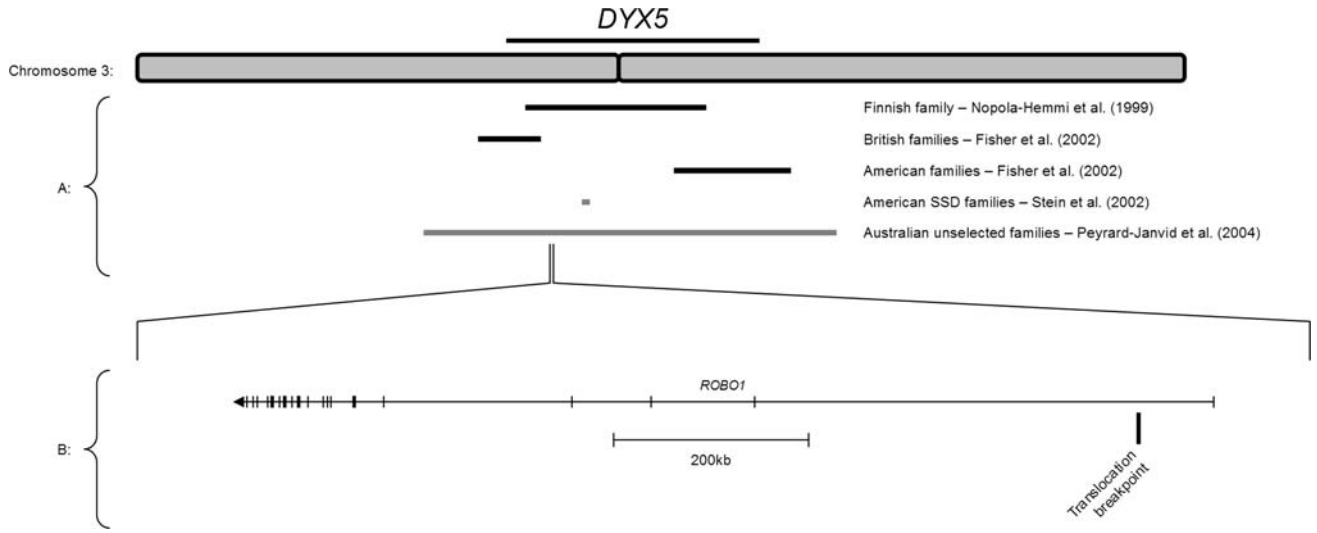

Fig. 5 The DYX5 locus on chromosome 3. **a** *Black horizontal lines* are linkage reports for DD from independent samples. *Box with diagonal lines* indicates a translocation. **b** Genes that have been tested for association. Interesting SNPs, deletions or translocation breakpoints are *highlighted*

602430]) has been identified as a likely candidate gene for DD susceptibility. The primary evidence comes from an individual carrying a translocation involving *DYX5*, specifically t(3;8)(p12;q11), and who is also affected with DD [78]. The chromosome 3 breakpoint of this translocation was identified between exons 1 and 2 of *ROBO1*. The 35-Mb haplotype co-segregating with DD in the large Finnish family includes *ROBO1*, and expression of *ROBO1* from this specific haplotype was shown to be significantly reduced, either partially or completely [78]. *ROBO1* is nearly 1 Mb in length and contains thousands of SNPs. A limited assessment of some of these SNPs in independent samples could not yield evidence for an association with DD [78], which may be explained by a different diagnostic criteria in the replication sample.

DYX7 on chromosome 11

Just two studies report the linkage of a DD susceptibility locus to chromosome 11. Both studies report linkage at 11p15; specifically at 11p15.4 in a British sample [54] and 11p15.5 in a Canadian sample [90]. The linkage observed in the latter study appears to peak in a region containing the gene dopamine receptor D4 (*DRD4* [MIM 126452]). However, analysis of *DRD4* in the Canadian sample and also in an independent sample of Italian families has found no evidence of an association with DD [90, 115].

DYX8 on chromosome 1

Linkage to DD susceptibility has been reported at chromosome 1 in three independent studies (see Fig. 6) [74, 144, 194]. Up-to-date genetic maps reveal a consensus region of linkage at 1p36 in all three studies [74, 144, 194], but there is also evidence for linkage at 1p34-35 from two of these studies as well [74, 194]. Located at 1p34.3 is the gene KIAA0319-like (*KIAA0319L*) which has a high-protein sequence identity to *KIAA0319*. *KIAA0319L* is therefore a natural target for association studies given its proximity to *DYX8* and homology to *KIAA0319*. However, just a single study has reported an investigation of *KIAA0319L* in a sample of Canadian families [34]. Of the handful of SNPs to have been tested, modest association with DD was observed in just one SNP and a haplotype derived from that SNP [34].

Other candidate DD gene studies

Other loci have received attention from DD linkage and association studies, despite limited evidence from linkage studies. For example, dopamine receptor D1 (*DRD1* [MIM 126449]) at 5q35, dopamine receptor D2 (*DRD2* [MIM 126450]) at 11q23, dopamine receptor D5 (*DRD5* [MIM 126453]) at 4p16 and "solute carrier family 6 (neurotransmitter transporter, dopamine), member 3" (SLC6A3 [MIM 1406597]) at 5p15 have all been investigated, but show modest or no linkage or association with DD susceptibility [109, 115, 138].

A single family co-segregating dyslexia and a telomeric deletion of at least 176 kb from the q-arm of chromosome 21 in four out of nine family members has also been reported [142]. This region contains four genes that may be variably affected by the deletion; pericentrin (*PCNT* [MIM 605925]), DIP2 disco-interacting protein 2 homolog A (*Drosophila*) (*DIP2A* [MIM 607711]), S100 calcium-binding protein B (*S100B* [MIM 176990]), and protein

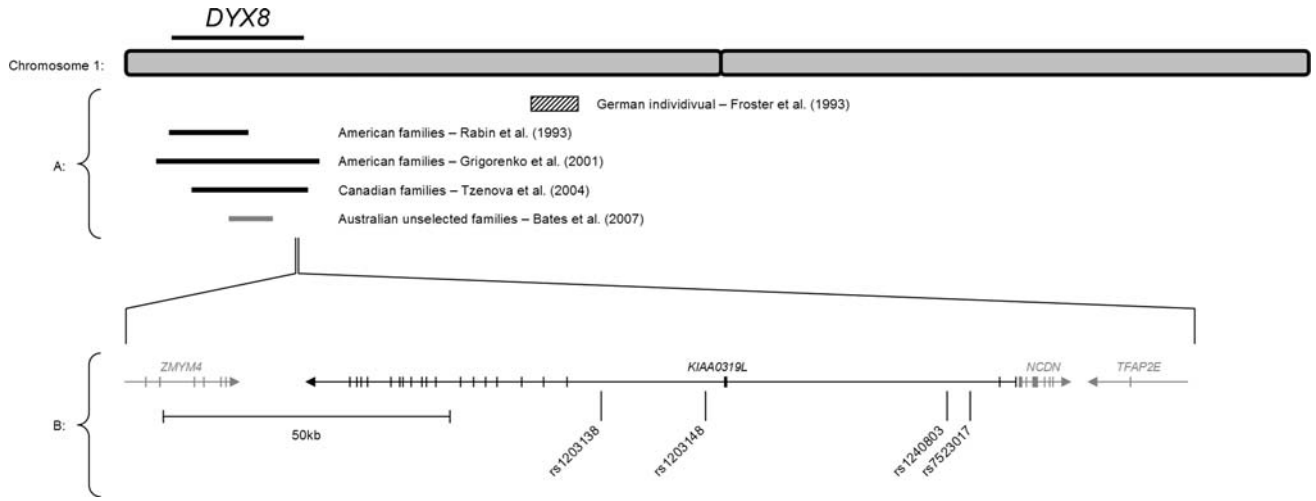

Fig. 6 The DYX8 locus on chromosome 1. **a** *Black horizontal lines* are linkage reports for DD from independent samples. *Box with diagonal lines* indicates a translocation. **b** Genes that have been tested for association. Interesting SNPs, deletions or translocation breakpoints are *highlighted*

arginine methyltransferase 2 (*PRMT2* [MIM 601961]). The authors suggest *DIP2A* as the most likely candidate DD susceptibility gene of the four because of its function in the regulation of neuronal connectivity [142]. However, this inference of *DIP2A*s function is incorrect as the authors have inadvertently identified *DIP2A* as "DLX interacting protein 2 (DIP2)" which is an alternatively spliced form of glutamate receptor interacting protein 1 (*GRIP1* [MIM 604597]) [211], rather than "DIP2 disco-interacting protein 2 homolog A (*Drosophila*)". *DIP2A* may still be involved in neuronal connectivity although as shown by mutation experiments of the disconnected gene (disco) in *Drosophila* [125, 180]. *S100B* is also an attractive candidate for DD susceptibility as SNPs within this gene have been associated with low cognitive ability in the elderly [100], schizophrenia [107] and bipolar disorder [149]. However, it is impossible to assess the influence of any of the four genes with respect to DD without evidence from linkage or association studies from independent samples.

Characterisation of the DD susceptibility genes

As described, seven candidate DD genes have been identified with supporting evidence from two or more independent DD studies; *DYX1C1* at *DYX1*, *KIAA0319* and *DCDC2* at *DYX2*, *MRPL19* and *C2orf3* at *DYX3*, *ROBO1* at *DYX5* and *KIAA0319L* at *DYX8*. Some evidence for other genes has been identified from a single family co-segregating DD and a deletion on chromosome 21; *PCNT*, *DIP2A*, *S100B* and *PRMT2*.

Functional characterisation of these genes has revealed that many of them have important roles in the brain, often during embryonic development. In particular, *DYX1C1*, *DCDC2*, *KIAA0319*, *S100B* and *ROBO1* have all been implicated in neuronal migration [20, 121, 135, 150, 189, 198, 199]. *ROBO1* and *DIP2A* may also be involved in axon guidance and neural development [97, 125, 180]. This adds further weight to their involvement in DD because disruptions of these genes could result in the abnormalities observed from the postmortem examinations of DD brains, such as the focal architectonic dysplasias and neuronal ectopias which result from disruptions in neuronal migration [61, 63, 92]. Indeed, disruption of *Dyx1c1* activity in adult rodent brains revealed hippocampal dysplasias and molecular layer ectopias similar in appearance to those reportedly seen in the postmortem DD brains [150]. Behavioural studies of rodents with disruptions of *Dyx1c1* activity revealed deficits in discerning auditory stimuli and spatial learning, particularly in the rodents displaying hippocampal heterotopias [189]; auditory detection deficits are good behavioural markers for SLI and DD [8, 185], and the hippocampus is important in spatial and working memory [9, 22, 132]. However, only a sub-set of DD individuals actually presents deficits in these phenotypes, and these deficits are not part of the definition of DD. Hence, it is possible that the effect of disrupting *DYX1C1* activity is to produce a general or wide-ranging cognitive deficit that would not be restricted to just reading ability in humans.

Nevertheless, disrupting the activity of these candidate genes in rodents has shown that they may produce anatomical phenotypes similar to those observed in human DD brains. However, it should be noted that only a small number of human DD brains have actually been examined anatomically. Furthermore, the specificity of the anatomical effects observed in rodents may not correlate precisely

with regions affected by autopsies or functional imaging studies of DD brains. Indeed, the disruption of *Dyx1c1* produced quite general effects, including regions of the brain not implicated in DD.

Whole-genome association studies

Although there have been no published whole-genome-wide association screens for DD specifically, there have been two other studies of reading ability. The first has used several thousand samples from the Twins Early Development Study (TEDS) [131], and compared genotypes from pooled samples of high and low reading ability individuals [119]. The second involved 705 stroke- and dementia-free individuals from the Framingham study tested for a range of cognitive measures [163]. Both studies genotyped their samples on the 100 K Affymetrix microarrays. Neither study found associations within any of the candidate DD genes discussed in this review, although both studies did find a variety of signals in the broader linkage regions of the DYX# loci. Lastly, we are part of a large consortium known as NeuroDys (http://www.neurodys.com) that is in the latter stages of a whole-genome-wide association screen for DD. We have individually genotyped 600 samples with DD on either the 350 or 550 K Illumina microarrays, and several hundreds more on the 1 M Illumina chip with a pooled sample approach. Integrating individual data from intensive neuropsychogical testing, brain imaging and electrophysiological studies, the significance of different endophenotypes will be investigated. The overall goal of this project is to understand the biological basis of dyslexia through investigating the correlations between candidate genes and brain functions that are found to be relevant for learning to read and to spell like speech perception and grapheme–phoneme association.

Summary and outlook

Numerous candidate DD susceptibility genes have now been identified at a variety of loci; *DYX1C1* at *DYX1* [184], *KIAA0319* and *DCDC2* at *DYX2* [31, 59, 80, 121, 135, 158], *MRPL19* and *C2ORF3* close to *DYX3* [2], *ROBO1* at *DYX5* [78] and *KIAA0319L* at *DYX8* [34]. The evidence for each of these genes has been acquired from cytogenetic, linkage, association and biological studies.

Upon discovering genes for DD susceptibility and their underlying causal variants, it is envisaged that 1-day young people may be screened for their potential risk in developing DD. Appropriate action may then be taken to reduce this risk by providing tailored tuition governed by their underlying genetic makeup. There may even be the potential for the design of drugs to be prescribed in the most extreme of cases. Finally, the discovery of these genes will allow us to learn more about human cognition and our unique abilities to communicate with one another.

To achieve these aims, the subsequent steps of molecular genetic work are genome-wide association studies based on the samples of several thousand of dyslexic individuals. This goal can be reached by joint research initiatives such as the EU project NeuroDys that currently has access to the DNA from two thousand dyslexic children from eight EU member states. Essential for this research strategy is that the dyslexic individuals are phenotypically well characterised. Based on the gene–gene interaction studies, the contribution of a single susceptibility genes will be better understood. Moreover, the investigation of copy number variants in dyslexic samples might help in detecting clinically relevant variations that contribute to the development of dyslexia.

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