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Annotation: Genetics of Reading and Spelling Disorder

Gerd Schulte-Körne

Philipps-University Marburg, Germany

Recent advances in understanding the genetics of reading and spelling disorder are reviewed and, based on theoretical models of reading development, different related phenotypes such as phonological and orthographic processing are examined. Family and twin studies show a moderate to high familiality and heritability. Segregation analyses suggest a major gene effect, with reduced penetrance in females, as well as a polygenic model. Linkage analyses and an association study have identified possible loci on chromosomes 6 and 15. These results suggest that reading and spelling disorder should be regarded as a complex disorder, strongly influenced by genetic factors. However, the role of environmental factors should also be considered as the clinical implications of the genetic findings in terms of aetiology and intervention still require far more exploration.

Keywords: Reading and spelling disorder, family studies, twin studies, segregation analyses, linkage, heritability.

Abbreviations: HLA: human leukocyte antigen; QTL: quantitative trait locus.

Introduction

In 1990 an excellent overview on the genetics of dyslexia, by Bruce Pennington, was published in this *Journal*. Since then, major contributions from behaviour and molecular genetics have changed the perception of dyslexia, which is now considered to be a group of related phenotypes rather than a rigidly defined disability. The underlying basic processes of cognition and perception and their neurobiological correlates have been analysed, whilst recent findings of basic auditory (e.g., temporal processing, Schulte-Körne, Deimel, Bartling, & Remschmidt, 1999a) and visual processing deficits of non-linguistic stimuli (e.g., perception of rapid moving stimuli, Eden et al., 1996; Cornelissen, Hansen, Hutton, Evangelinou, & Stein, 1998) in dyslexia have added new dimensions of phenotypic analyses.

Until 1990 (Pennington, 1990), the dyslexia phenotype had been analysed qualitatively, but subsequent molecular genetic studies have demonstrated the advantages of considering dyslexia as a quantitative trait. Furthermore the link between the different dyslexia-related phenotypes and molecular genetics has been analysed.

The main goal of this Annotation is to summarise recent genetic findings from family, twin, and molecular genetic studies. Specifically, it will focus on the progress of the multi-dimensional approach of behaviour-molecular genetic studies. A second goal is to provide the reader with basic knowledge of methodologies used in behaviour and molecular genetic analysis, although the details of these methods will not be covered.

The principal methods of genetic analysis used to study dyslexia are family studies, twin studies, and molecular genetic analyses (see Rutter, Silberg, O'Connor, & Simonoff, 1999). Familiality or increased risk to relatives of probands can be estimated by family studies. Segregation analysis is informative about modes of inheritance and gene frequencies. Twin studies are used to estimate the heritability of the disorder. Molecular genetic analyses attempt to identify the specific allele that may be responsible for the measured familiality and heritability of the phenotype.

Within the Annotation the diagnostic criteria of reading and spelling disorder are first critically reviewed. This is followed by a short overview of cognitive correlates of reading and spelling, namely phonological and orthographic processing. Next, recent findings (largely published since Pennington's 1990 review) of family, twin, and molecular genetic studies are summarised. Finally, perspectives for further research and the clinical implications of genetic research in dyslexia are considered.

Requests for reprints to: Gerd Schulte-Körne, Department of Child and Adolescent Psychiatry, Philipps-University Marburg, Hans-Sachs-Strasse 6, D-30039 Marburg, Germany.

Dyslexia Phenotypes

Reading and Spelling Disorder

Two main topics have influenced genetic research in dyslexia: the diagnostic criteria used for defining reading and spelling disorder and the different so-called "dyslexia-related phenotypes" (Grigorenko et al., 1997). There is continuing controversy concerning the diagnostic criteria for dyslexia (see Stanovich, 1994). Empirical data from the Isle of Wight Study identified two groups of reading disabled children, one in which reading ability was significantly lower than IQ and one in which both reading ability and IQ were low (Rutter & Yule, 1975). This led to an assumption of different aetiologies and the need for different remedial strategies for the two subgroups. However, a number of studies (Rodgers, 1983; Shaywitz, Escobar, Shaywitz, Fletcher, & Makuch, 1992; Van der Wissel & Zeegers, 1985) failed to replicate these

findings and the validity of discrepancy-based definitions of reading disability has been questioned (Fletcher, Francis, Rourke, Shaywitz, & Shaywitz, 1992).

A further problem relates to the terminology used to define dyslexia. Most epidemiological studies of dyslexia are based on reading ability (Lewis, Hitch, & Walker, 1994; Rodgers, 1983; Rutter & Yule, 1975; Shaywitz, Shaywitz, Fletcher, & Escobar, 1990; Van der Wissel & Zeegers, 1985), and the term dyslexia is mainly used for reading disability. In contrast, both ICD-10 (WHO, 1992) and DSM-IV (APA, 1994) distinguish between specific impairments in reading and spelling. Furthermore, ICD-10 differentiates a disorder characterised by a specific impairment in reading plus impairment in spelling, from a specific spelling disorder without specific reading disorder. Although the aetiological validity of this diagnostic differentiation has yet to be demonstrated, it is clearly essential, for both research and clinical practice, to make clear on which definition (reading and/or spelling) the phenotype characterisation is based.

In the present Annotation the term "dyslexia" will be used only if the authors have not clarified whether they mean spelling disorder, reading disorder, or a combined disorder of reading and spelling according to the ICD-10 criteria (World Health Organisation, 1992).

Phonologic and Orthographic Processing

Recent advances in understanding reading and spelling disorder have built upon research based on cognitive processing. Work on the importance of early linguistic abilities for reading and spelling development (Elbro, 1996; Wagner, Torgesen, & Rashotte, 1994) has demonstrated that phonological processing is strongly correlated with reading (Wagner & Torgesen, 1987) and spelling development (Schulte-Körne, 2001). Phonological processing abilities promise to be an important area for genetic research and, in particular, many studies have demonstrated the importance of early sensitivity to the phonological structure of words (Näslund & Schneider, 1996). Phonological awareness (the ability to identify and manipulate phoneme-sized elements of spoken language) is also strongly related to early reading acquisition and is a significant predictor in preschool years of later success in reading and spelling development (Bradley & Bryant, 1978; Cossu, Shankweiler, Liberman, Katz, & Tola, 1988; Lundberg, Frost, & Peterson, 1980; Näslund & Schneider, 1996). Orthographic processing (the knowledge of the specific word structure) (Hultquist, 1997) is a second major area of genetic research. Orthographic knowledge refers to the awareness of the probability of a particular letter following a given letter in any syllable. Some letter combinations are not even possible within a syllable (e.g., fn), whereas other combinations (e.g., th) occur with great frequency (Hultquist, 1997). Skilled readers and writers have implicit knowledge of which letter combinations are orthographically legitimate. In contrast to the phonological deficit hypothesis, there has been very limited research on the role of orthographic knowledge on reading and spelling disability.

Although there is usually a moderate to strong correlation between tasks that measure orthographic and phonological skills in both children (Juel, Griffith, & Gough, 1986) and adults (Stanovich & West, 1989), there is also considerable evidence that phonological and orthographic skills are dissociable in their contribution to word identification. Variation in orthographic skills cannot be entirely explained by variation in phonological skills, and the two make contributions to performance on word reading tasks independent of each other (Barker, Torgesen, & Wagner, 1992). The differential influence of phonological processing and orthographic knowledge on reading and spelling disorder has been integrated in twin research and linkage analyses.

Family Studies

Since the first reports of families with several affected members, a familial aggregation of reading disorder has been described (Pennington, 1990, 1994; Schulte-Körne, Deimel, Müller, Gutenbrunner, & Remschmidt, 1996). The earlier studies suffered from various methodological shortcomings, including problems of diagnosis, failure to use standardised reading and spelling tests, and the selection of families with several affected members, which leads to an overestimation of familial recurrence. However, even keeping these limitations in mind the familial recurrence is about 40–50%.

Recent studies have attempted to overcome such problems by selecting probands from a clinic (Schulte-Körne et al., 1996; Gilger, Hanebuth, Smith, & Pennington, 1996), selecting probands from mainstream and special schools (Gilger et al., 1996; Wolf & Melngailis, 1994), and by psychometric testing of parents and siblings. Nevertheless, diagnostic criteria may still differ between studies (see Table 1), and a further, unsolved problem concerns the definition of reading and spelling disorder in adults. The diagnostic criteria of ICD-10 and DSM-IV are based on empirical research with children, but education and remedial programmes can influence the phenotype in adulthood (Finucci, Guthrie, & Childs, 1986). The reading ability of these "compensated" adults may be in the normal range, hence using the same criteria for adults as for children might lead to an underestimation of affectedness. Some researchers have used a history of difficulties in learning to read as a criterion of affectedness in adults (Wolf & Melngailis, 1994); others (Schulte-Körne et al., 1996) have used the same criteria for adults and children but with the analysis taking account of compensation effects. However, the validity of self-report data for diagnosis of reading and spelling disorder has been questioned (Schulte-Körne, Deimel, & Remschmidt, 1997). Table 1 provides an overview of recent family studies. The analysis only includes studies in which both parents were available, and in which not only the proband but also another child in the family could be classified as having reading and spelling disorder.

All three studies reported a significantly higher rate of affected siblings and parents than expected based on prevalence rates (5–9%; Shaywitz et al., 1992). This estimate of familial risk is similar to that found in previous studies where the phenotype definition was based on history. Although the studies use different diagnostic criteria for probands and first-degree relatives, the pattern of results is very similar in each. However, the relative risk estimates may be artificially inflated due to the response biases among clinically ascertained or referred samples. Estimates of family risk based on epidemiological samples are still required.

Studies by Schulte-Körne et al. (1996) and Gilger et al. (1996) indicated that, despite the use of different

Table 1
Studies of Familial Recurrence in the First-degree Relatives of Reading and/or Spelling Disordered Probands

Study	Probands	Proband diagnostic criteria	Parent diagnostic criteria	% affected siblings	% affected parents
Wolf & Melngailis (1994) Study 1	273	IQ $\geqslant$ 100 RD and SP $\leqslant$ 2 or 3 years below grade level.	Affectedness for all relatives by history.	If father affected: 45% If mother affected: 28% If both parents are affected: 79%	Fathers 40%, mothers 23%, both parents 18%, neither parent affected 19%.
Wolf & Melngailis (1994) Study 2	155	IQ $\geqslant$ 100 RD and SP $\leqslant$ 2 or 3 years below grade level. Siblings < 12 years: Reading and spelling at least 2 grades below grade level. Siblings between 12 and 18 years: Reading and spelling at least 3 grades below grade level.	Relatives above 18 years: Either reading or spelling at least 3 grades below 12th grade ceiling.	If father affected by testing and history: 46% If mother affected by testing and history: 26% If both parents are affected by testing and history: 71%	68% fathers affected by history and testing, 32% mothers affected by history and testing.
Schulte-Körne et al. (1996)	32	1. Discrepancy of 1 *SD* between IQ and expected spelling ability based on IQ. 2. Spelling ability 1 *SD* below expected based on grade level.	The same diagnostic criteria as chosen for children. Compensation: History of reading difficulties, does not meet IQ-discrepancy or achievement criterion	Criterion 1: 61.9% Criterion 2: 52.3%	Criterion 1: 34.0% (54%)[a] Criterion 2: 26.0%
Gilger et al. (1996)	263 (135 from Colorado Family Reading Study, 128 from linkage study)	IQ > 90 (only CFRS) 1. Discrepancy of 1 *SD* between IQ and reading recognition or spelling and reading rec. or spelling < 93 (if not than discrepancy 2 *SD*) or 2. Discriminant score based on weighted average of spelling, reading rec. and reading comprehension + history of school-age difficulties with reading.	The same diagnostic criteria as chosen for children. Compensation: History of reading difficulties, does not meet IQ-discrepancy or discriminant score based underachievement.	Criterion 1: AA = 78%[b] AC = 62% AU = 57% CU = 32% UU = 33%; Criterion 2: AA = 76%[b] AC = 58% AU = 57% CU = 28% UU = 20%	

[a] If those adults who had reported spelling difficulties in school but had an actual spelling within the normal range (compensated adults) were included.
[b] AA = both parents are affected; AC = one affected parent and one compensated parent; AU = one affected parent and one unaffected parent; CU = one compensated parent and one unaffected parent; UU = both parents are unaffected.

diagnostic criteria, and low achievement versus IQ-discrepancy criteria, the rates of affected siblings based on these diagnostic criteria were almost identical. No evidence was found for the hypothesis that the two criteria define different subtypes of reading and spelling disorder. Schulte-Körne et al. (1996) found that nearly all cases identified using the achievement criterion are also rated as affected using the IQ-discrepancy criterion. The IQ-discrepancy criterion defined a slightly larger, but not substantially different, group of individuals. However, as only individuals with an IQ in the normal range (i.e. 85+) were included, the influence of low IQ on familial aggregation of reading disabled children remains to be examined.

The spelling phenotype was also examined in two of the recent family studies (Schulte-Körne et al., 1996; Wolff & Melngailis, 1994). The rates of familial aggregation of spelling and reading disorders were found to be similar, suggesting an equally high genetic load in the families.

It has been found that siblings are at greater risk for reading and spelling deficits when at least one parent is affected (Gilger et al., 1996; Wolff & Melngailis, 1994), although environmental as well as genetic effects might explain these results. Environmental effects could include the kind of teaching used by parents, and the frequency and quality of practising reading and spelling at home. The influence of the parents' affectedness on a child's risk might be explained by a polygenic model because the risk of reading/spelling disorders increases if both parents are affected.

The importance of the parents' phenotype for the children's reading ability is also of clinical relevance in those cases where parents act as remedial tutors (Schulte-Körne, Deimel, & Remschmidt, 1998; Schulte-Körne, Schäfer, Deimel, & Remschmidt, 1997). Of further significance to practitioners and genetic and educational counsellors is the fact that families with two affected parents have a significantly lower socioeconomic status (SES) than families with just an affected father and that these families reported feeling socially isolated and inadequate to compete in an industrial society. Since both genetic and environmental effects may interact, twin studies provide the best means of differentiating environmental from genetic factors.

Twin Studies

Twin studies tend to focus on the heritability of reading, spelling, and correlated cognitive phenotypes (e.g., phonological and orthographic processing), and to differentiate between heritable and environmental factors influencing reading and spelling.

Early twin studies found concordance rates of around 100% in monozygotic twins and about 50% in dizygotic twins, indicating a substantial heritability of reading disability (Bakwin, 1973; Zerbin-Rüdin, 1967). However, several methodological limitations (e.g., lack of psychometric tests and biases in sample selection) reduce the significance of these findings. The two largest twin studies to date are the Colorado Twin Project (Castles, Datta, Gayan, & Olson, 1999; DeFries, Fulker, & LaBuda, 1987; Olson, Gillis, Rack, & Fulker, 1989) and the London twin study (Stevenson, Graham, Fredman, & McLoughlin, 1987). Stevenson et al. ascertained twins from the general population and found a heritability of spelling disability of .53, which increased to .75 when intelligence was controlled for. The high heritability of spelling disorder was also replicated by Olson, Forsberg, and Wise (1994, Table 2). Although no evidence was found in the London study for a significant heritability of word recognition, attempts to explain this unexpected result (e.g., age of probands, too many unusual words in the reading test) remain unconvincing. In all other twin studies a heritability for word reading of around 50% has been found, and thus it seems justified to assume a genetic basis of reading disorder. In summary, it appears that 50 to 60% of reading and spelling disorder variance could be explained by genetic factors.

More recently, researchers have begun to examine the role of phonological and orthographic processing, both of which correlate with reading and spelling abilities. However, it is unclear whether phonological and orthographic processing differentiate dyslexia subtypes (Castles et al., 1999) or are part of an hierarchically structured model of reading and spelling development (Coltheart, 1978; Coltheart, Curtis, Atkins, & Haller, 1993; Schulte-Körne, Deimel, Bartling, & Remschmidt, 1999b). Again, twin studies can be essential in understanding the relationship between these dyslexia-related phenotypes. First, they can examine the genetic basis of

Table 2
Results of Recently Published Twin Studies: Summary of the Values for Heritability of Disability (h_g^2) for Word Recognition, Spelling, Phonological Coding and Awareness, and Orthographic Coding

Study	N_{mz} pairs	N_{dz} pairs	Measure	h_g^2
Stevenson (1991)	10–51	23–62	Word recognition	0.03–0.41[a, b]
	11–48	19–61	Spelling	0.66[b]–0.69*
	15–47	21–47	Phonological coding	0.36[b]–0.82[a]
	6–28	20–50	Orthographic coding	−0.12–−0.68[b]
Olson et al. (1994)	183	126	Word recognition	0.47*
	155	107	Spelling	0.48*
	151	105	Phonological coding	0.59[a]
	132	92	Orthographic coding	0.56*
	93	68	Phonological awareness	0.60[a]

[a] The heritability of group membership using probands at 0.5, 1.0, and 1.5 *SD*s above the mean with IQ controlled.
[b] n.s.
* $p < .05$.

these phenotypes. Second, bivariate[1] analysis developed for twin studies can estimate the degree to which either reading and spelling or their related phenotypes are due to the same genes.

A number of different tasks have been used to measure phonological and orthographic processing in twin studies. Phonological coding was measured by nonword reading (Olson et al., 1989, 1994; Stevenson, 1991). Nonwords can only be read by a nonlexical strategy, i.e., by using the grapheme-phoneme correspondence. More recently, phoneme awareness assessed by phoneme segmentation and phoneme deletion tasks has also been examined (Castles et al., 1999; Olson et al., 1994).

Olson, Kliegel, Davidson, and Foltz (1985) measured orthographic processing by means of a pseudohomophone task, requiring the ability to recognise the correct orthographic pattern for a word as quickly as possible out of two simultaneously presented choices (e.g., "rane" and "rain"). However, Stevenson (1991) assessed orthographic processing by two different tests: reading of irregular or exceptional words that could only be read by a lexical strategy, and by a homophone recognition task (determing whether or not two words, e.g., "higher" and "hire", sounded the same).

High and significant heritability was found for phonological coding in the Colorado and London studies and for phonological awareness in the Colorado study (Table 2). In the London sample, one of the orthographic coding tasks (reading irregular and exception words) failed to show significant heritability values, but results for the homophone recognition task were significant. The London finding was treated as evidence for the hypothesis that phonological processing is under high genetic influence whereas orthographic processing (i.e., lexical information processing) is less influenced by genetic effects. This result was replicated in the earlier study of Olson et al. (1989) and Olson, Wise, Conners, and Rack (1990). However, more recently high and significant heritability of orthographic coding was found in the Colorado study (Table 2), possibly because of the increase in sample size and the change in the probands' selection criteria (see Olson et al., 1994).

Nevertheless, finding high heritability of orthographic and phonological coding does not necessarily mean that this is due to the same genes. Based on new statistics (see Olson et al., 1994; Stevenson, Pennington, Gilger, DeFries, & Gillis, 1993), which allow examination of the extent to which the genes affecting one condition (e.g., phonological coding) also influence another condition, Olson et al. (1994) found a significant bivariate heritability between phonological coding and orthographic coding of .43, between phonological coding and phonological awareness of .51, and between orthographic coding and phonological awareness of .44. Thus, within twin pairs, genetic mechanisms appear to be the same for the deficits in phonological and orthographic coding. Furthermore, the bivariate heritability between word recognition and phonological coding, between word recognition and orthographic coding, and between word recognition and phonological awareness were also high, signifying that the correlation between the variables is due to heritable influences.

Although a high proportion of the variance of reading, spelling, and phonological and orthographic coding can be explained by genetic factors, there is a considerable amount of variance that can be explained by environmental factors. Olson et al. (1994) found a significant influence of shared family environment for all group deficits except phonological awareness. These factors could relate to the differing quality of reading instructions or differences to print exposure (Cunningham & Stanovich, 1993; Olson & Wise, 1992).

Mode of Inheritance

Ever since the first description of single extended family pedigrees with reading disabilities, pedigree analysis has revealed a transmission of reading disability over three generations and provides evidence for an autosomal-dominant transmission with sex-dependent penetrance[2] (J. H. Fisher, 1905; Hallgren, 1950; Hinshelwood, 1907; Stephenson, 1907). However, different genetic models of reading and spelling disorder have been postulated and there is evidence for both polygenic and monogenic inheritance. For example, the finding that the rate of affectedness in siblings is mainly influenced by whether one or both parents are affected (Gilger et al., 1996; Hallgren, 1950; Wolff & Melngailis, 1994) can best be explained by a polygenic model. Further evidence for this model came from the finding that siblings in families with two affected parents were more severely impaired than siblings in families with one affected parent (Wolff & Melngailis, 1994).

The finding that the rate of affected first-degree relatives is higher in families of female than male probands is again best explained by a polygenic model (sex-influenced polygenic threshold model, see Schulte-Körne et al., 1996). However, the similar recurrence rate in parents and siblings of around 50% (see Table 1), and the fact that the gender ratio of affected relatives is close to unity (although males slightly outnumber females; DeFries, 1989; Pennington et al., 1991; Wolff & Melngailis, 1994) are consistent with an additive or autosomal major locus effect. The most appropriate method to examine the mode of inheritance is complex segregation analysis. Unfortunately, only three formal segregation analyses of reading disorder have been conducted (Hallgren, 1950; Lewitter, DeFries, & Elston, 1980; Pennington et al., 1991). Hallgren, in a study of 112 families, found that in 90 the data best fitted with an autosomal dominant transmission, but because the diagnosis in siblings and parents was made on the basis of past history data, the reliability of the diagnosis is questionable. Lewitter et al. used a continuous phenotype (psychometric tests) measure based on discriminant analysis. In this study no evidence was found for a single major locus (autosomal dominant, autosomal recessive, or codominant transmission). However, the rate of affectedness in adults in this study may have been underestimated due to the practice of counting adults with a history of reading disability as unaffected because

[1] This bivariate analysis is based on the univariate multiple regression procedure developed by DeFries and Fulker (1985). In the bivariate extension, the proband is selected for a deficit on one variable and co-twin regression to the population mean is assessed for the second variable (see Olson et al., 1994).

[2] Penetrance is a statistical concept that refers to the probability of phenotypic expression of a given gene carrier.

they did not fulfil the diagnostic criteria for reading disorder (see Table 1[3]).

More recently, complex segregation analyses were applied to four samples, involving a total of 204 families and 1698 individuals (Pennington et al., 1991). The analyses were performed using the computer program Pointer, which considers a so-called "mixed model" consisting of a major gene effect and a polygenic background. In contrast to Lewitter et al. (1980), parental compensation was considered as a phenotype in two samples (Colorado). The analyses were run with different prevalence rates (1.5%, 7.5%, 10%) and male-to-female ratios for reading and spelling disorder of 1.8:1 and 3.5:1. Samples were recruited from four different studies: two were part of the Colorado Family Reading Study, and one each came from Washington and Iowa. However, it should be noted that the diagnostic criteria in the four samples were different, and a subsample of families was included that was selected because of their high rate of affectedness (which might indicate autosomal dominant transmission).

In three samples (Colorado, Washington) sex-influenced autosomal or additive transmission best fitted the data, and both polygenic and recessive transmission could be rejected. Further, the gene penetrance in females was clearly reduced in all samples. The estimated gene frequency of this major locus was between 3% and 5% across samples. In contrast, the findings of the Iowa study were not consistent with a major locus transmission and best fitted a polygenic model. The broader phenotype definition for relatives in the Iowa sample and the lack of test data on these individuals might explain this discrepancy. Thus it is possible that individuals with a range of academic difficulties were all diagnosed as reading disabled, which would increase the number of false positive cases within family pedigrees.

In summary, the few segregation studies published to date all suffer from methodological constraints (sample selection criteria, diagnostic criteria for probands and relatives, different computer programs used for segregation analyses). Two studies support a dominant transmission of reading and spelling disorder, which might provide an explanation for the rates of familial aggregation found. However, the data suggesting a polygenic model of reading and spelling disorder could be explained by different traits for subgroups of reading and spelling disorder.

Molecular Genetic Findings

Several approaches to gene localisation and identification of reading and spelling disorder have been undertaken since 1983, when Smith, Kimberling, Pennington, and Lubs first reported linkage of dyslexia to chromosome 15 markers. Parametric linkage[4] analyses are powerful methods for identifying linkage even in one single, large family if a number of parameters (e.g., penetrance, allele frequency, mode of inheritance) can be reliably specified. However, linkage strategies also require a dichotomised classification of affected/not affected for reading and/or spelling disorder. This means that information is lost because reading and spelling show a continuous distribution. Moreover, the reliability of diagnosis of reading and spelling disorder across generations and ages is often unknown, and misclassification of individuals directly influences the results of parametric linkage analysis.

Nonparametric methods[5] are generally thought to be more powerful if the parameters are unknown. These methods do not require knowledge about the mode of inheritance and penetrance and can be applied to detect genes susceptible to different reading and spelling related phenotypes. Thus far, four chromosomal regions (1, 2, 6, 15; see Table 3) have been examined by parametric and nonparametric methods for linkage. Reports of a full genome scan are not yet available.

Chromosome 1. Suggestive linkage of dyslexia to chromosome 1p34-p36 has been reported by Rabin et al. (1993). They found a maximum lod score of 2.33, but this is too low to confirm linkage (Lander & Kruglyak, 1995; Thomson, 1994), and their result could not be replicated by others (Fagerheim et al., 1999; Schulte-Körne, Nöthen, et al., 1998; Smith, Kelly, & Brower, 1998).

A second possible locus on chromosome 1 is at 1p22. Froster, Schulte-Körne, Hebebrand, and Remschmidt (1993) found a cosegregation of a balanced translocation[6] (1p22;2q31) and a spelling and reading disorder associated with an expressive speech disorder. The two regions on chromosome 1 have been subject to linkage analysis and the relevance for reading and spelling disorder has yet to be shown. It is possible that these chromosomal regions are good candidate gene regions for a dyslexia subtype, characterised by severe reading and spelling problems associated with severe speech disorder.

Chromosome 2. Recently, Fagerheim et al. (1999) studied an extended pedigree with 36 members of a Norwegian family in which the reading problems were inherited in an autosomal dominant fashion. The phenotype was based on phonological decoding (nonword reading), phonological awareness (sound blending), single word reading with and without time constraint, and spelling. Because no single reliable diagnostic test was available, an individual was considered affected when scores on tests of phonological decoding and one of the other measures used were below a cutoff score (for percentage correct answers and reaction time in the tests)

[3] The compensation rate (difference between the rate of affectedness based on psychometric tests and on history only) in two studies (Pennington et al., 1991; Schulte-Körne et al., 1996) is about 20–22%.

[4] Linkage analyses: The transmission of marker alleles through at least two generations of a family is compared with the transmission of the trait phenotype. If there is free recombination of parental haplotypes the marker and the trait locus assort independently. If they show decreased recombination this indicates that the marker and trait locus are close together on the same chromosome. Maximum likelihood methods are used to compute the likelihood of linkage at a given level of recombination. The statistical term for the likelihood of linkage compared with likelihood of free recombination is the lod score (the log of the odds of linkage). A lod score over 3 is generally accepted as showing evidence of linkage, while a lod score less than −2 rejects linkage (Morton, 1950).

[5] The proportion of marker alleles identical by descent (i.e., the same allele inherited from the same parent) in sets of relatives (e.g., pairs of siblings) is compared with the phenotypic similarity between relatives. Methods are (e.g.) sib pair analysis or affected pedigree members analysis.

[6] Balanced translocation means that broken parts of the chromosomes are joined with other chromosomes. These translocations do not necessarily entail loss of material. *In this family the dyslexics were also carriers of the balanced translocation.*

Table 3
Linkage Studies of Dyslexia

Study	Materials and methods	Phenotype	Chromosomal regions	Results
Smith et al. (1983)	8 multiplex families, tests and history, LOD-score analysis	Reading disability	15	Evidence for linkage to 15cen
Smith et al. (1991)	18 multiplex families tests, LOD-score analysis, sib pair analysis (QTL)	Reading disability	6p21, 15cen-15qter	Evidence for linkage to 6p21.3, 15cen and 15q15-qter; evid. for heterogeneity
Rabin et al. (1993)	9 three-generation families, LOD-score	Reading disability	1p34-p38	Suggestive linkage to 1p34-p38
Cardon et al. (1994)	19 multiplex families (including the sample from Smith et al. 1991) and a twin sample, tests, sib pair analysis (QTL)	Composite discriminant score (reading comprehension, reading recognition, spelling)	6p21	Evidence for linkage to 6p21.3
Grigorenko et al. (1997)	6 multiplex families, tests, LOD-score and nonparametric analysis	5 different phenotypes: phonological awareness, phonological decoding, rapid automized naming, single word reading, discrepancy of the composite reading cluster from vocabulary	6p23-p21.3, 15, and 16	Evidence for linkage of phonological awareness to 6p22-p21.3 and for linkage of word reading to 15q21
Schulte-Körne et al. (1998)	7 multiplex families, tests, LOD-score and nonparametric analysis	Spelling disability	6, 15	Evidence for linkage to 15q21
Field and Kaplan (1998)	79 families (including 30 multiplex families), tests and history, LOD-score and nonparametric analysis	Phenotype definition was based on the results of different tests measuring phonological awareness, reading and spelling. For adults anamnestic data were used additionally for phenotype definition	6	No evidence for linkage
Fisher et al. (1999)	82 families, 181 sib pairs, tests, sib-pair analyses (QTL)	4 different phenotypes: word reading, IQ-reading discrepancy, orthographic coding, nonword reading	6p25-21.3	Evidence for a QTL in 6p21.3 (reading of irregular words and nonwords)
Gayán et al. (1999)	79 families, 126 sib pairs, tests, sib-pair analyses (QTL)	4 different phenotypes: word reading, orthographic coding, nonword reading, phonological awareness	6p22.3-p21.1	Evidence for linkage of phonological and orthographic skills to 6p22.3-p21.3
Fagerheim et al. (1999)	1 multiple family with 36 members, history and tests, LOD-score and nonparametric analysis	Test results in 2 of 6 tests of a test battery: word reading with and without time constraint, phonological awareness, (phonol. blending with words and nonwords), phonological decoding, spelling	2p16-p15	Evidence for linkage to 2p16-p15
Grigorenko et al. (2000)	8 multiplex families, tests, LOD-score and nonparametric analysis	6 different phenotypes: phonemic awareness, phonological decoding, rapid automized naming (RAN), single word reading, vocabulary, spelling	6p22.3-6p21.3	Evidence for linkage of single word reading, vocabulary and spelling to 6p21.3
Morris et al. (2000)	178 parent-proband trios, association study	Reading disorder	15q15-q21	Highly significant association in 2 independent samples with a 3-marker haplotype
Petryshen et al. (2000)	79 families, tests, sib-pair analyses (QTL), variance-components analyses	4 different phenotypes: phonological awareness, spelling, RAN, nonword reading	6p25-p21.3	No evidence for linkage

generated by the unaffected subjects of the family. This unusual method of defining affectedness may have resulted in high levels of unreliability of the examined phenotypes.

Linkage analysis was performed assuming an autosomal dominant inheritance with sex-dependent penetrance. Three different models were used; in Model 1 affectedness was assumed if probands scored positive on history and test scores. Subjects with either a positive test result or positive history, but not both, were given a diagnostic weight of 75% of the clear dyslexic cases (Fagerheim et al., 1999). Model 2 included only cases with both a positive history and positive test scores. In Model 3 the same subjects as in Model 1 were used, but individuals below the age of 20 were excluded from the analysis as the number of unaffected family members of that age group was too low to guarantee a reliable classification. Parametric linkage analysis revealed maximum lod scores of 3.52 (Model 1), 2.92 (Model 2), and 4.32 (Model 3) for DNA markers in region 2p16-p15. The nonparametric analyses revealed significant p values for all three models. The most likely position of the dyslexia gene is in a 4-cM interval between D2S2352 and D2S1337. Although genes have been identified in this region, to date none of these seems to be a candidate gene for dyslexia.

Chromosome 6. The influential work of Geschwind and Galaburda (Behan & Geschwind, 1985; Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985) on the neuroanatomical correlates of reading disorder suggests an association of immune disorders with reading disorder. Based on the assumption that both reading and immune disorder might have a common aetiology, the human leukocyte antigen (HLA)[7] region on chromosome 6 is an interesting candidate gene region for reading and spelling disorder. Although the hypothesis of a common genetic aetiology of immune disorder and reading disorder has not been supported in several family studies (Gilger, Pennington, & DeFries, 1992; Gilger et al., 1998), some linkage studies with DNA markers in the HLA region (6p21.3) were conducted. Smith, Kimberling, and Pennington (1991) found a significant linkage of two markers in the suggested region on chromosome 6. Cardon et al. (1994) confirmed this linkage result in a study of 19 families with an autosomal dominant inheritance by use of more informative DNA markers, and in a matched sample of monozygotic (MZ) and dizygotic (DZ) twins in which one member of each pair had a history of reading disorder. Sibling pair analysis of reading and spelling disorder indicated a QTL[8] in the HLA region. This result was replicated in the twin sample. Combining the family and twin samples and selecting only individuals with extreme deficits (i.e., those having discriminant scores of 2 *SD* or more below the mean, for reading/spelling; see Table 1) yielded stronger evidence for a QTL.

Grigorenko et al. (1997) replicated the findings of Smith et al. (1991) and Cardon et al. (1994). Various measures of phonological processing (phonological decoding, phonological awareness) as well as single word reading, rapid automised naming, and an IQ-reading discrepancy were used as different phenotypes in this study. Highly significant linkage of the phonological awareness phenotype (phoneme segmentation) to five markers in the region 6p22-p21 was found. The linkage of the other phenotypes with the markers was less significant, the lowest significance level being obtained with single word reading. Recently Grigorenko, Wood, Meyer, and Pauls (2000) added two families to their sample, and examined two more phenotypes (spelling and vocabulary). They found significant linkage with seven phenotypes (word reading, phonological awareness, phonological decoding, rapid naming, vocabulary, spelling, and lifelong diagnosis) to 6p22-p21. In contrast to the previously published study, word reading was linked to the 6p region.

S. E. Fisher et al. (1999) used a sample of 181 sib pairs from 82 families to evaluate linkage to the 6p25-21.3 region. Families were selected if one or more of the proband's siblings were reading disabled, either according to parents' report or school history. Several quantitative measures of reading and reading-related phenotypes were examined: word recognition, irregular word reading, nonword reading, and an IQ-reading discrepancy score. The analyses suggested a QTL in 6p21.3 which is linked to irregular word reading ($p = .0016$) and nonword reading ($p = .0024$). This locus affects phonological and orthographic coding whereas the finding of a nonsignificant linkage of this QTL with word reading suggests a lower significance of this locus for word reading. This is the third independent study to provide evidence for a locus on chromosome 6 for reading-disorder-related-phenotypes.

Gayán et al. (1999) analysed 126 sib pairs (siblings and twins) from 79 families that were completely independent of the sample analysed by Cardon et al. (1994). Twin pairs in which at least one member had a positive history of reading problems were selected for this study. In addition to word reading several dyslexia-related phenotypes (e.g., orthographic coding, phonological decoding, and phonological awareness) were studied. For each phenotype, individuals scoring lower than 2 *SD*s below the mean of the normal population were considered to be affected. However, because not all subjects exhibited low scores on all measures, this procedure resulted in different sample sizes (28–76 sib pairs). The highest lod scores were obtained for orthographic choice (3.10), phonological decoding (2.42), and phonological awareness (1.46), confirming previous findings. Further analyses indicated a region between markers D6S276 and D6S105, which is close to the location found by Fisher et al. (1999) and Cardon et al. (1994). The lod score for word reading of 0.09 suggested that this QTL is of minor relevance for word reading. Interestingly, the effect size of this QTL on chromosome 6 for the trait is high, explaining 20% of the variance for phonological decoding and phoneme deletion and 60% of the variance for orthographic coding.

Three studies have failed to prove linkage of dyslexia-related phenotypes with a locus on chromosome 6. Schulte-Körne, Grimm, et al. (1998) investigated seven families with spelling disorder. They found no convincing evidence for linkage of spelling disability to markers on chromosome 6. A maximum multipoint lod score of -0.64 was observed between D6S1570 and D6S434 on the long arm of chromosome 6. Nonparametric analysis also failed to reveal significant results for linkage. With regard to the previous positive findings on chromosome 6p21.3, this sample may have been too small to detect a significant effect although it may also be that the gene on

[7] The HLA region contains many genes that influence immune functions.

[8] Reading and spelling are phenotypes with a normal distribution. A gene that contributes in part to the overall variation of the trait is termed a quantitative trait locus (QTL).

chromosome 6 is of only minor influence for the spelling disability component of dyslexia.

Field and Kaplan (1998) and Petryshen, Kaplan, Liu, and Field (2000) examined 79 families with at least two affected siblings using parametric and nonparametric methods. In contrast to the other studies described above, the definition of affectedness was based on a phonological coding deficit (Field & Kaplan, 1998). Eight DNA markers spanning a 43-cM region on chromosome 6p25-p21.3 were genotyped, including D6S105, which was found to be linked to reading disorder by Cardon et al. (1994), S. E. Fisher et al. (1999), and Gayán et al. (1999). Four different dyslexia-related phenotypes were examined: phonological awareness, phonological coding, spelling, and rapid automised naming. QTL-analyses did not detect significant evidence for a locus influencing the four phenotype dimensions in the 6p23-p21.3 region. One reason for this could be the sample selection criteria. Whereas Cardon et al. (1994), S. E. Fisher et al. (1999), Gayán et al. (1999), and Grigorenko et al. (1997) selected probands according to reading underachievement, in the Field and Kaplan (1998) and Petryshen et al. (2000) studies a subtype characterised by a deficit in nonword reading was selected. Although the correlated phenotypes are very similar between Petryshen et al. and the other reported studies, the different ascertainment criteria may have resulted in the selection, thereby leading to different linkage results.

In summary, there are now four independent linkage studies that find significant evidence for a locus on chromosome 6 relevant for reading-, spelling-, and reading-related phenotypes. All these studies located the QTL in 10-cM region on chromosome 6p. However, it is unclear how this locus influences the different cognitive process and what the relative contributions of this locus for reading and for spelling disorder are.

Chromosome 15. In 1983, Smith and co-workers found a linkage of reading and spelling disorder to chromosome 15. They examined nine extended pedigrees that were consistent with an autosomal dominant inheritance through at least three generations. This sample was gradually increased to 19 families, on whom data were analysed by parametric and nonparametric methods (Smith et al. 1991). With a locus distal to the region initially identified on chromosome 15, significant linkage with a qualitative (reading and spelling disorder) and quantitative (discriminant score based discriminant analysis of the reading and spelling test data, see Table 1) phenotype was found. The significance level was further increased if the analyses were restricted to sib pairs in which at least one sib was severely affected.

Two recent studies confirm the locus on the long arm of chromosome 15. Grigorenko et al. (1997) reported linkage for five different dyslexia-related components (phonological awareness, phonological decoding, rapid automised naming, single word reading, discrepancy of the composite reading cluster from vocabulary; see Table 3). A significant lod score of 3.15 under an autosomal dominant inheritance model was obtained with the single word reading and the DNA marker D15S143 on chromosome 15q21. For the other dyslexia-related phenotypes the lod scores were negative and nonparametric analyses revealed nonsignificant results. With parametric and nonparametric methods Schulte-Körne, Grimm, et al. (1998) confirmed the locus on chromosome 15q with spelling disorder phenotype. A multipoint lod score of 1.79 corresponding to a p value of .0042 was found with the DNA marker D15S143. This result meets the criteria for confirmation of linkage (Lander & Kruglyak, 1995).

Recently Morris et al. (2000) used family-based association mapping[9] with two independent samples of 178 parent-proband trios. Diagnosis was based on an achievement criterion (reading ability at least 2.5 years behind chronological age). They found a highly significant association between reading disorder and a three-marker haplotype (D15S146/D15S214/D15S994), suggesting one or more genes contributing to reading disorder within 1 cM of the region between D15S994 and D15S146.

More recently, two families with a balanced translocation involving the region 15q21-22 have been found (Nopola-Hemmi et al., 2000). In one family, reading and spelling disorder of the father and two children cosegregated with a balanced translocation (2q11, 15q21). In the second family only one of three children had a translocation (2p13, 15q22) and reading and spelling disorder. The breakpoints on chromosome 15 were located in a region between D15S143 and D15S1029, where Grigorenko et al. (1997) and Schulte-Körne, Grimm, et al. (1998) have also found significant linkage with reading.

In summary, given that three independent studies have shown linkage of reading (single word reading) and spelling to the same chromosomal region on 15q, this locus might be considered as established for dyslexia. It could be confirmed by an association study and the finding of balanced translocation (2;15) (Nopola-Hemmi et al., 2000) that cosegregates with reading and spelling disorder.

Perspectives

Reading and spelling disorder is a complex condition that aggregates in families and for which moderate to high heritability has been found. Since Pennington's Annotation in 1990 consistent positive linkage results have been published. Using different linkage analysis methods and, more recently, association analysis, two regions on chromosome 6 and 15 have been identified as promising candidate gene regions. In contrast to other complex psychiatric disorders (McGuffin & Martin, 1999), both these loci for reading and spelling disorder have been replicated by several independent studies. Although the results of a genome scan of reading and spelling disorder have not yet been published, the discovery in the future of even more genes related to reading/spelling disorder seems very likely. However, the variance that a single gene can provide may be small and it might be the *interaction* of several genes that is more relevant for our understanding of such a complex phenotype. Based on linkage studies, small regions of chromosome 6 and 15 have been identified but these regions will contain many genes, all of which may contain

[9] Association analysis is an additional way of detecting relevant disease locus. Association is based on the observation that there is nonrandom co-occurrence of specific alleles. For example, the association of one HLA allele with reading disorder is significantly more frequent in individuals with reading disorders than in the general population. Finding an association can mean a linkage disequilibrium (co-occurrence of specific alleles) between marker allele and a susceptibility locus; the marker allele is directly related to the phenotype; or an artefact (e.g., due to stratification effects).

the relevant mutation. Thus, the chromosomal region of interest has to be further narrowed by different molecular genetic methodologies. Of particular help in this research is to have candidate genes that might be involved in the pathogenesis of the trait. However, candidate genes for reading and spelling disorder which, for example, affect the neural migration in early brain development, have not been found in these linked chromosomal regions.

The detection of genes for reading and spelling disorder is mainly influenced by the phenotypes used for the analyses. Several phenotypes have been found to be correlated with reading and spelling, but the aetiological link between these related phenotypes has yet to be established. If one of these levels of visual (orthographic processing) or auditory (phonological processing) information processing is closer to the function of a gene than a more global measure of reading and spelling then this should provide a more informative phenotype for linkage analysis. Up to now the phenotypes included have been cognitive ones, such as phonological and orthographic processing. The constraints of these phenotypes are that they are confounded with other cognitive processes, such as attention, working memory, and IQ, all of which might interact with reading and spelling (Hari, Valta, & Uutela, 1999; Wadsworth, Olson, Pennington, & DeFries, 2000; Wijsman et al., 2000). Furthermore, a basic visual phenotype, as defined by functions of the magnocellular system (Cornelissen et al., 1998; Eden et al., 1996) is easier to relate to gene function than orthographic processing. This is because animal models of these basic functions are available and suited to find neurobiological correlates (e.g., neuroanatomical) of these functions (Preuss, Qi, & Kaas, 1999). Another example for a good candidate phenotype is the preattentive perception for speech, which differentiates reading and spelling disorder in children and adults from controls (Schulte-Körne, Deimel, et al., 1998; Schulte-Körne, Deimel, Bartling, & Remschmidt, 2001). Again, the physiology of this phenotype has been examined in an animal model, which helps to localise the brain areas principally involved in the generation of this basic ability (Kraus, McGee, Littman, Nicol, & King, 1994; Kraus, McGee, Carrell, et al., 1994). Thus a challenge for the genetic research of reading and spelling disorder is to bridge the divide between neuroscience and molecular neuroscience.

High familiality and heritability does not of course mean that reading and spelling disorder is under complete genetic control, any more than any other psychiatric disorder. Twin data strengthen the evidence for the role of shared environment factors, which should be regarded as being as important as genetic factors. The role of nongenetic factors is further supported by the segregation analyses that found evidence for a major gene effect as well as for a multifactorial model. Thus, it can be assumed that with complex traits such as reading and spelling disorder, several different genes operate together; these do not cause the disorder directly but increase the likelihood of an individual's being affected (Plomin & Rutter, 1998).

The implications of the high familiality and heritability of reading and spelling disorder are that parents should be aware that a child is at risk of becoming affected if a sibling or a parent has reading and/or spelling disorder. Results from longitudinal studies suggest that the early precursors of reading and spelling disorder are present even at 3 or 4 years of age. Speech perception (McBride-Chang, 1996) and phonological awareness in the preschool years (Näslund & Schneider, 1996) are significant predictors of reading and spelling. Furthermore, the high genetic correlation between word recognition and phonological processing provides evidence for the role of phonological processing as a genetically based cognitive process influencing reading and spelling ability.

Finally, what are the perspectives for the future? If dyslexia genes can be located, a molecular test of reading and spelling disorder would allow earlier diagnosis of children at risk. This in turn would offer the opportunity for very early intervention, at a time when the language areas are at an earlier, more plastic stage of development. Another benefit from identifying the genes contributing to reading and spelling disorder will be a better understanding of the basic neurobiology. This too should lead to fundamental advances in intervention.

References

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington DC: Author.

Bakwin, H. (1973). Reading disability in twins. *Developmental Medicine and Child Neurology, 15*, 184–187.

Barker, T. A., Torgesen, J. K., & Wagner, R. K. (1992). The role of orthographic processing skills on five different reading tasks. *Reading Research Quarterly, 27*, 334–345.

Behan, P., & Geschwind, N. (1985). Dyslexia, congenital anomalies, and immune disorders: The role of the foetal environment. *Annals of the New York Academy of Science, 457*, 13–18.

Bradley, L., & Bryant, P. E. (1978). Difficulties in auditory organization as a possible cause of reading backwardness. *Nature, 271*, 746–747.

Bradley, L., & Bryant, P. E. (1985). *Rhyme and reason in reading and spelling*. Ann Arbor, MI: University of Michigan Press, International Academy for Research in Learning Disabilities, No 1.

Cardon, L. R., Smith, S. D., Fulker, D. W., Kimberling, W. J., Pennington, B. F., & DeFries, J. C. (1994). Quantitative trait locus for reading disability on chromosome 6. *Science, 266*, 276–279.

Castles, A., & Coltheart, M. (1993). Varieties of developmental dyslexia. *Cognition, 47*, 149–180.

Castles, A., Datta, H., Gayan, J., & Olson, R. K. (1999). Varieties of developmental reading disorder: Genetic and environmental influences. *Journal of Experimental Child Psychology, 72*, 73–94.

Coltheart, M. (1978). Lexical access in simple reading tasks. In G. Unterwood (Ed.), *Strategies in information processing*. London: Academic Press.

Coltheart, M., Curtis, B., Atkins, P., & Haller, M. (1993). Models of reading aloud: Dual route and parallel-distributed-processing approaches. *Psychological Review, 1000*, 589–608.

Cornelissen, P. L., Hansen, P. C., Hutton, J. L., Evangelinou, V., & Stein, J. F. (1998). Magnocellular visual function and children's single word reading. *Vision Research, 38*, 471–482.

Cossu, G., Shankweiler, D., Liberman, I. Y., Katz, L., & Tola, G. (1988). Awareness of phonological segments and reading ability in Italian children. *Applied Psycholinguistics, 9*, 1–16.

Cunningham, A. E., & Stanovich, K. E. (1991). Tracking the unique effects of print exposure in children: Associations with vocabulary, general knowledge, and spelling. *Journal of Educational Psychology, 83*, 264–274.

Cunningham, A. E., & Stanovich, K. E. (1993). Children's literacy environments and early word recognition subskills. *Reading and Writing: An Interdisciplinary Journal, 5*, 193–204.

DeFries, J. C. (1989). Gender ratios in reading disabled children and their affected relatives. *Journal of Learning Disabilities, 22*, 544–545.

DeFries, J. C., & Fulker, D. W. (1985). Multiple regression analysis of twin data. *Behavior Genetics, 15*, 467–473.

DeFries, J. C., Fulker, D. W., & LaBuda, M. C. (1987). Evidence for a genetic aetiology in reading disability of twins. *Nature, 329*, 537–539.

Eden, G. F., VanMeter, J. W., Rumsey, J. M., Maisog, J. M., Woods, R. P., & Zeffiro, T. A. (1996). Abnormal processing of visual motion in dyslexia revealed by functional brain imaging. *Nature, 382*, 66–69.

Elbro, C. (1996). Early linguistic abilities and reading development: A review and a hypothesis. *Reading and Writing: An Interdisciplinary Journal, 8*, 453–485.

Fagerheim, T., Raeymaekers, P., Tonnessen, F. E., Pedersen, M., Tranebjaerg, L., & Lubs, H. (1999). A new gene (DYX3) for dyslexia is located on chromosome 2. *Journal of Medical Genetics, 36*, 664–669.

Field, L. L., & Kaplan, B. J. (1998). Absence of linkage of phonological coding dyslexia to chromosome 6p23-p21.3 in a large family data set. *American Journal of Human Genetics, 63*, 1448–1156.

Finucci, J. M., Guthrie, J. T., & Childs, A. L. (1986). A follow-up study of dyslexic boys. *Annals of Dyslexia, 35*, 117–136.

Finucci, J. M., Guthrie, J. T., Childs, A. L., Abbey, H., & Childs, B. (1976). The genetics of specific reading disability. *Annual Review of Human Genetics, 40*, 1–23.

Fisher, J. H. (1905). Case of congenital word-blindness (inability to learn to read). *Ophthalmologic Review, 24*, 315.

Fisher, S. E., Marlow, A. J., Lamb, J., Maestrini, E., Williams, D. F., Richardson, A. J., Weeks, D. E., Stein, J. F., & Monaco, A. P. (1999). A genome-wide search strategy for identifying quantitative trait loci involved in reading and spelling disability (developmental dyslexia). *American Journal of Human Genetics, 64*, 146–156.

Fletcher, J. M., Francis, D. J., Rourke, P., Shaywitz, S. E., & Shaywitz, B. (1992). The validity of discrepancy definitions of reading disabilities. *Journal of Learning Disabilities, 25*, 555–561.

Froster, U., Schulte-Körne, G., Hebebrand, J., & Remschmidt, H. (1993). Cosegregation of balanced translocation (1;2) with retarded speech development and dyslexia. *Lancet, 342*, 178–179.

Galaburda, A. M., Sherman, G. F., Rosen, G. D., Aboitiz, F., & Geschwind, N. (1985). Developmental dyslexia: Four consecutive patients with cortical anomalies. *Annals of Neurology, 18*, 222–233.

Gayán, J., Smith, S. D., Cherny, S. S., Cardon, L. R., Fulker, D. W., Brower, A. M., Olson, R. K., Pennington, B. F., & DeFries, J. C. (1999). Quantitative-trait locus for specific language and reading deficits on chromosome 6p. *American Journal of Human Genetics, 64*, 157–164.

Gilger, J. W., Borecki, I. B., DeFries, J. C., & Pennington, B. F. (1994). Comingling and segregation analysis of reading performance in families of normal reading probands. *Behavior Genetics, 24*, 345–355.

Gilger, J. W., Hanebuth, E., Smith, S. S., & Pennington, B. (1996). Differential risk for developmental reading disorders in the offspring of compensated versus noncompensated parents. *Reading and Writing: An Interdisciplinary Journal, 8*, 407–417.

Gilger, J. W., Pennington, B. F., & DeFries, J. C. (1992). A twin study of the etiology of comorbidity: Attention-deficit hyperactivity disorder and dyslexia. *Journal of the American Academy of Child and Adolescent Psychiatry, 31*, 343–348.

Gilger, J. W., Pennington, B. F., Harbeck, R. J., DeFries, J. C., Kotzin, B., Green, P., & Smith, S. (1998). A twin and family study of the association between immune system dysfunction and dyslexia using blood serum immunoassay and survey data. *Brain and Cognition, 36*, 310–333.

Gilger, J. W., Pennington, B. F., Green, P., Harbeck, R. J., Smith, S. A., & Smith, S. (1994). Dyslexia, immune disorders, and left-handedness: Twin and family studies of their relations. *Neuropsychologia, 30*, 209–227.

Grigorenko, E. L., Wood, F. B., Meyer, M. S., Hart, L. A., Speed, W. C., Shuster, A., & Pauls, D. L. (1997). Susceptibility loci for distinct components of developmental dyslexia on chromosomes 6 and 15. *American Journal of Human Genetics, 60*, 27–39.

Grigorenko, E. L., Wood, F. B., Meyer, M. S., & Pauls, D. L. (2000). Chromosome 6p influences on different dyslexia-related cognitive processes: Further confirmation. *American Journal of Human Genetics, 66*, 715–723.

Hallgren, B. (1950). Specific dyslexia (congenital word-blindness): A clinical and genetic study. *Acta Psychiatrica et Neurologica* (Suppl.), *65*, 1–287.

Hari, R., Valta, M., & Uutela, K. (1999). Prolonged attentional dwell time in dyslexic adults. *Neuroscience Letters, 27*, 202–204.

Hinshelwood, J. (1907). Four cases of congenital word-blindness occurring in the same family. *British Medical Journal, 2*, 1229–1232.

Hultquist, A. M. (1997). Orthographic processing abilities of adolescents with dyslexia. *Annals of Dyslexia, 47*, 89–114.

Juel, C., Griffith, P., & Gough, P. (1986). Acquisition of literacy: A longitudinal study in first and second grade. *Journal of Educational Psychology, 78*, 234–255.

Kraus, N., McGee, T., Carrell, T., King, C., Littman, T., & Nicol, T. (1994). Discrimination of speech-like contrasts in the auditory thalamus and cortex. *Journal of the Acoustical Society of America, 96*, 2758–2768.

Kraus, N., McGee, T., Littman, T., Nicol, T., & King, C. (1994). Nonprimary auditory thalamic representation of acoustic change. *Journal of Neurophysiology, 72*, 1270–1277.

Kruglyak, L., & Lander, E. S. (1995). High-resolution genetic mapping of complex traits. *American Journal of Human Genetics, 56*, 1212–1223.

Lander, E., & Kruglyak, L. (1995). Genetic dissection of complex traits: Guidelines for interpreting and reporting linkage results. *Nature Genetics, 11*, 241–247.

Lewis, C., Hitch, G. J., & Waker, P. (1994). The prevalence of specific arithmetic difficulties and specific reading difficulties in 9- to 10-year-old boys and girls. *Journal of Child Psychology and Psychiatry, 35*, 283–292.

Lewitter, F. I., DeFries, J. C., & Elston, R. C. (1980). Genetic model of reading disability. *Behavior Genetics, 10*, 9–30.

Lundberg, I., Frost, J., & Peterson, O. (1988). Effects of an extensive programme for stimulating phonological awareness in pre-school children. *Reading Research Quarterly, 23*, 263–284.

Lundberg, I., Wall, S., & Olofsson, A. (1980). Reading and spelling skills in the first school years predicted from phonemic awareness skills in kindergarten. *Scandinavian Journal of Psychology, 21*, 159–173.

McBride-Chang, C. (1996). Models of speech perception and phonological processing in reading. *Child Development, 67*, 1836–1856.

McGuffin, P., & Martin, N. S. (1999). Science, medicine, and the future. Behaviour and genes. *British Medical Journal, 319*, 37–40.

Morris, D. W., Robinson, L., Turic, D., Duke, M., Webb, V., Milham, C., Hopkin, E., Pound, K., Fernando, S., Easton, M., Hamshere, M., Williams, N., McGuffin, P., Stevenson, J., Krawczak, M., Owen, M. J., O'Donovan, M. C., & Williams, J. (2000). Family-based association mapping provides evidence for a gene for reading disability on chromosome 15q. *Human Molecular Genetics, 22*, 843–848.

Morton, N. E. (1950). Sequential tests for the detection of linkage. *American Journal of Human Genetics, 7*, 277–318.

Näslund, J. C., & Schneider, W. (1996). Kindergarten letter knowledge, phonological skills, and memory processes: Relative effects on early literacy. *Journal of Experimental Child Psychology, 62*, 30–59.

Nopola-Hemmi, J., Taipale, M., Haltia, T., Lehesjoki, A. E., Voutilainen, A., & Kere, J. (2000). Two translocations of chromosome 15q associated with dyslexia. *Journal of Medical Genetics, 37*, 71–75.

Olson, R. K., Forsberg, H., & Wise, B. (1994). Genes, environment, and development of orthographic skills. In V. W. Berninger (Ed.), *The varieties of orthographic knowledge I: Theoretical and developmental issues* (pp. 27–71). Dordrecht, The Netherlands: Kluwer.

Olson, R. K., Gillis, J. J., Rack, J. P., & Fulker, D. W. (1989). Specific deficits in component reading and language skills: Genetic and environmental influences. *Journal of Learning Disabilities, 22*, 339–348.

Olson, R. K., Kliegel, R., Davidson, B. J., & Foltz, G. (1985). Individual and developmental differences in reading disability. In G. E. MacKinnon & T. G. Waller (Eds.), *Reading research: Advances in theory and practice, Vol. 4* (pp. 1–64). New York: Academic Press.

Olson, R. K., & Wise, B. W. (1992). Reading on the computer with orthographic and speech feedback: An overview of the Colorado Remedial Reading Project. *Reading and Writing: An Interdisciplinary Journal, 4*, 107–144.

Olson, R. K., Wise, B. W., Conners, F., & Rack, J. (1990). Organisation, heritability, and remediation of component word recognition and language skills in disabled readers. In T. H. Carr & B. A. Levy (Eds.), *Reading and its development: Component skills approach* (pp. 261–322). New York: Academic Press.

Pennington, B. F. (1990). Annotation: The genetics of dyslexia. *Journal of Child Psychology and Psychiatry, 2*, 193–201.

Pennington, B. F. (1994). Genetics of learning disabilities. *Journal of Child Neurology* (Suppl), *10*, S69–S76.

Pennington, B. F., Gilger, J., Pauls, D., Smith, S. S. A., Smith, S. D., & DeFries, J. C. (1991). Evidence for a major gene transmission of developmental dyslexia. *Journal of the American Medical Association, 18*, 1527–1534.

Pennington, B. F., Van Orden, G. C., Smith, S. D., Green, P. A., & Haith, M. M. (1990). Phonological processing skills and deficits in adult dyslexics. *Child Development, 61*, 1753–1778.

Petryshen, T. L., Kaplan, B. J., Liu, M. F., & Field, L. L. (2000). Absence of significant linkage between phonological coding dyslexia and chromosome 6p23-21.3, as determined by use of quantitative-trait methods: Confirmation of qualitative analyses. *American Journal of Human Genetics, 66*, 708–714.

Plomin, R., & Rutter, M. (1998). Child development, molecular genetics, and what to do with genes once they are found. *Child Development, 69*, 1223–1242.

Preuss, T. M., Qi, H., & Kaas, J. H. (1999). Distinctive compartmental organization human primary visual cortex. *Proceedings of the National Academy of Science, 96*, 11601–11606.

Rabin, M., Wen, L., Hepburn, M., Lubs, H. A., Feldman, E., & Duara, R. (1993). Suggestive linkage of developmental dyslexia to chromosome lp34-p36. *Lancet, 342*, 178.

Rodgers, B. (1983). The identification and prevalence of specific reading retardation. *British Journal of Educational Psychology, 53*, 369–373.

Rutter, M., Silberg, J., O'Connor, T., & Simonoff, E. (1999). Genetics and child psychiatry: I Advances in quantitative and molecular genetics. *Journal of Child Psychology and Psychiatry, 40*, 3–18.

Rutter, M., & Yule, W. (1975). The concept of specific-reading retardation. *Journal of Child Psychology and Psychiatry, 16*, 181–197.

Schneider, W., Küspert, P., Roth, E., & Visé, M. (1997). Short- and long-term effects of training phonological awareness in kindergarten: Evidence from two German studies. *Journal of Experimental Child Psychology, 66*, 311–340.

Schulte-Körne, G. (2001). *Dyslexia and speech perception [Legasthenie und Sprachwahrnehmung]*. Münster, Germany: Waxmann Verlag.

Schulte-Körne, G., Deimel, W., Bartling, J., & Remschmidt, H. (1998). Auditory processing and dyslexia: Evidence for a specific speech deficit. *NeuroReport, 9*, 337–340.

Schulte-Körne, G., Deimel, W., Bartling, J., & Remschmidt, H. (1999a). Pre-attentive processing of auditory patterns in dyslexic human subjects. *Neuroscience Letters, 276*, 41–44.

Schulte-Körne, G., Deimel, W., Bartling, J., & Remschmidt, H. (1999b). The role of phonological awareness, speech perception, and auditory temporal processing for dyslexia. *European Child and Adolescent Psychiatry*, (Suppl) *8*, 28–34.

Schulte-Körne, G., Deimel, W., Bartling, J., & Remschmidt, H. (2001). Speech perception deficit in dyslexic adults as measured by mismatch negativity (MMN). *International Journal of Psychophysiology, 40*, 77–87.

Schulte-Körne, G., Deimel, W., Müller, K., Gutenbrunner, C., & Remschmidt, H. (1996). Familial aggregation of spelling disorder. *Journal of Child Psychology and Psychiatry, 37*, 817–822.

Schulte-Körne, G., Deimel, W., & Remschmidt, H. (1997). Can self-report data on deficits in reading and spelling predict spelling disability as defined by psychometric tests? *Reading and Writing, 9*, 55–63.

Schulte-Körne, G., Deimel, W., & Remschmidt, H. (1998). The Marburger Parent-Child Spelling Training. Follow-up after two years of intervention [Das Marburger Eltern-Kind-Rechtschreibtraining- Verlaufsuntersuchungen nach zwei Jahren]. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie, 25*, 151–159.

Schulte-Körne, G., Grimm, T., Nöthen, M. M., Müller-Myhsok, B., Cichon, S., Vogt, I. R., Propping, P., & Remschmidt, H. (1998). Evidence for linkage of spelling disability to chromosome 15. *American Journal of Human Genetics, 63*, 279–282.

Schulte-Körne, G., Nöthen, M. M., Cichon, S., Grimm, T., Müller-Myhsok, B., & Propping, P. (1998). A linkage study of spelling disorder on chromosomes 1, 6 and 15. 6th World Congress on Psychiatric Genetics. *American Journal of Medical Genetics, 81*, 459.

Schulte-Körne, G., Schäfer, J., Deimel, W., & Remschmidt, H. (1997). The Marburger Parent-Child Spelling Training. First results [Das Marburger Eltern-Kind-Rechtschreibtraining-Erste Befunde]. *Zeitschrift für Kinder- und Jugendpsychiatrie, 25*, 151–159.

Shaywitz, S. E., Escobar, M. D., Shaywitz, B. A., Fletcher, J. M., & Makuch, R. (1992). Evidence that dyslexia may represent the lower tail of a normal distribution of reading ability. *New England Journal of Medicine, 326*, 145–150.

Shaywitz, S. E., Shaywitz, B. A., Fletcher, J. M., & Escobar, M. D. (1990). Prevalence of reading disability in boys and girls. *The Journal of the American Medical Association, 264*, 998–1002.

Smith, S. D., Kelly, P. M., & Brower, A. M. (1998). Molecular approaches to the genetic analysis of specific reading disability. *Human Biology, 70*, 239–256.

Smith, S. D., Kimberling, W. J., & Pennington, B. F. (1991). Screening for multiple genes influencing dyslexia. *Reading and Writing: An Interdisciplinary Journal, 3*, 285–298.

Smith, S. D., Kimberling, W. J., Pennington, B. F., & Lubs, H. A. (1983). Specific reading disability: Identification of an inherited form through linkage analysis. *Science, 219*, 1345–1347.

Stanovich, K. (1994). Annotation: Does dyslexia exist? *Journal of Child Psychology and Psychiatry, 35*, 579–595.

Stanovich, K., & West, R. F. (1989). Exposure to print and orthographic processing. *Reading Research Quarterly, 24*, 402–433.

Stephenson, S. (1907). Six cases of congenital word-blindness affecting three generations in one family. *Ophthalmoscope, 5*, 482–484.

Stevenson, J. (1991). Which aspects of processing text mediate genetic effects? *Reading and Writing: An Interdisciplinary Journal, 3*, 249–269.

Stevenson, J., Graham, P., Fredman, G., & McLoughlin, V. (1987). A twin study of genetic influences on reading and spelling ability and disability. *Journal of Child Psychology and Psychiatry, 28*, 229–247.

Stevenson, J., Pennington, B. F., Gilger, J. W., DeFries, J. C., & Gillis, J. J. (1993). Hyperactivity and spelling disability: Testing for shared genetic aetiology. *Journal of Child Psychology and Psychiatry, 34*, 1137–1152.

Thomson, G. (1994). Identifying complex disease genes: Progress and paradigms. *Nature Genetics, 8*, 108–110.

Van der Wissel, A., & Zeegers, F. E. (1985). Reading retardation revisited. *British Journal of Developmental Psychology, 3*, 3–9.

Vogler, G. P., DeFries, J. C., & Decker, S. N. (1985). Family history as an indicator of risk for reading disability. *Journal of Learning Disability, 18*, 419–421.

Wadsworth, S. J., Olson, R. K., Pennington, B. F., & DeFries, J. (2000). Differential etiology of reading disability as a function of IQ. *Journal of Learning Disabilities, 33*, 192–199.

Wagner, R. K., & Torgesen, J. K. (1987). The nature of phonological processing and its causal role in the acquisition of reading skills. *Psychological Bulletin, 101*, 192–212.

Wagner, R. K., Torgesen, J. K., & Rashotte, C. A. (1994). Development of reading-related phonological processing abilities: New evidence of bi-directional causality from a latent variable longitudinal study. *Developmental Psychology, 30*, 73–87.

Wijsman, E. M., Peterson, D., Leutenegger, A. L., Thomson, J. B., Goddard, K. A., Hsu, L., Berninger, V. W., & Raskind, W. H. (2000). Segregation analysis of phenotypic components of learning disabilities. I. Nonword memory and digit span. *American Journal of Human Genetics, 67*, 631–646.

Wolff, P. H., & Melngailis, I. (1994). Family patterns of developmental dyslexia: Clinical findings. *American Journal of Medical Genetics, 54*, 122–131.

World Health Organisation. (1992). *The ICD-10 classification of mental and behavioral disorders: Clinical descriptions and diagnostic guidelines*. Geneva: Author.

Zerbin-Rüdin, E. (1967). Congenital word-blindness. *Bulletin of the Orton Society, 17*, 47–54.

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