doi: 10.1111/j.1469-1809.2006.00312.x

Interrelationship and Familiality of Dyslexia Related Quantitative Measures

G. Schulte-Körne[1,*], A. Ziegler[2], W. Deimel[1], J. Schumacher[4], E. Plume[3], C. Bachmann[1], A. Kleensang[2], P. Propping[4], M. M. Nöthen[5], A. Warnke[3], H. Remschmidt[1] and I. R. König[2]

[1]*Department of Child and Adolescent Psychiatry and Psychotherapy, University of Marburg, Marburg, Germany*
[2]*Institute of Medical Biometry and Statistics, University Hospital Schleswig-Holstein - Campus Lübeck, Lübeck, Germany*
[3]*Department of Child and Adolescent Psychiatry and Psychotherapy, University of Würzburg, Würzburg, Germany*
[4]*Institute of Human Genetics, University of Bonn, Bonn, Germany*
[5]*Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany*

Summary

Dyslexia is a complex gene-environment disorder with poorly understood etiology that affects about 5% of school-age children. Dyslexia occurs in all languages and is associated with a high level of social and psychological morbidity for the individual and their family; approximately 40-50% have persistent disability into adulthood. The core symptoms are word reading and spelling deficits, but several other cognitive components influence the core phenotype.

A broad spectrum of dyslexia related phenotypes, including phonological decoding, phoneme awareness, orthographic processing, short-term memory, rapid naming and basic mathematical abilities, were investigated in large sample of 287 German dyslexia families. We explored the interrelationship between the component phenotypes using correlation and principal component analyses (PCA). In addition, we estimated familiality for phenotypes as well as for the factors suggested by PCA.

The correlation between the component phenotypes varied between -0.1 and 0.7. The PCA resulted in three factors: a general dyslexia factor, a speed of processing factor and a mathematical abilities factor. The familiality estimates of single components and factors ranged between 0.25 and 0.63.

Instead of analyzing single dyslexia-related components, multivariate analyses including factor analytic approaches may help in the identification of susceptibility genes.

Keywords: dyslexia, familiality, genetics, heritability, principal component analysis, linkage, chromosome 18.

Introduction

Dyslexia[†] is a specific disorder of learning to read and spell, which is not the direct result of other disorders such as mental retardation or lesser impairments in general intelligence, gross neurological deficits, uncorrected visual or auditory problems, or emotional disturbances or inadequate schooling (International Classification of Diseases, ICD-10; Dilling *et al*. 1991). Dyslexia is often preceded by disorders in speech and language development. Early precursors are difficulties in auditory processing as speech discrimination, auditory sequential memory, and in rhyming (Bradley & Bryant,

*Corresponding to: Gerd Schulte-Körne, MD, Department of Child and Adolescent Psychiatry and Psychotherapy, Philipps-University Marburg, Hans-Sachs-Str. 4-6, 35033 Marburg, Germany. Phone: +49 (0) 6421 286 6467, Fax: +49 (0) 6421 286 3078. E-mail: schulte1@med.uni-marburg.de

[†]Dyslexia is an often used but not well defined term for a complex disorder which is mainly characterized by a reduced word reading speed and accuracy and difficulties in spelling are frequently associated. The ICD-10 also differentiates a specific spelling disorder that is characterized by a significant impairment in the development of spelling skills in the absence of a history of specific reading disorder (See also Schulte-Körne 2001).

1983; Holopainen *et al.* 2001). Dyslexia occurs in all known languages and is the most common learning disorder, affecting around 5%–10% of school-aged children (Shaywitz *et al.* 1990; Katusic *et al.* 2001). Dyslexia is more often diagnosed in boys than in girls (Liederman *et al.* 2005).

Dyslexia clusters within families (Gilger *et al.* 1994; Schulte-Körne *et al.* 1996; Raskind *et al.* 2000). Twin studies have suggested that the familial clustering is due to genetic factors, with heritability estimates for word reading of between 0%–72% (Plomin & Kovas, 2005) and for spelling of about 48%–69% (Schulte-Körne, 2001*a*). The molecular genetic basis for dyslexia has been studied by genetic linkage analysis, and several chromosomal loci have been identified (Fisher & DeFries, 2002). In addition to the core symptoms of dyslexia, namely reading and spelling deficits, several component phenotypes (e.g. phonological and orthographic processing) have also shown linkage to these chromosomal loci (e.g. Fisher *et al.* 2002).

Amongst other factors, the success of molecular genetic studies is dependent on the phenotype dimension used for the study (Marlow *et al.* 2003). The optimal phenotype for dyslexia would be the psychometric phenotype that is most strongly associated with the genetic variation at a genetic locus. Since the best fitting phenotype dimension is not known beforehand, a typical study investigates a number of phenotype dimensions in parallel. This leads to an inflation of the type I error rate if not adequately corrected for.

One alternative is to use a multivariate model instead (see, e.g., Amos *et al.* 1990). The power of these multivariate methods depends, however, on the correlation between the phenotypes (Evans, 2002). For diseases like dyslexia it may therefore be helpful to discover simple patterns in the relationships among the variables in a first step of factor analysis, since the observable variables might well be explained by a smaller set of variables. The factors can then be used in a second step of linkage analysis. If factors are constructed the multiple testing problem is reduced. Furthermore, if the factors are orthogonal results from linkage analysis may be interpreted more easily (Ziegler & König, 2006).

The aims of our study were first to determine how the different phenotype components are correlated with each other and, specifically, how the core phenotypes of reading and spelling correlate with other phenotype components. Secondly, we aimed to identify patterns in the relationship between phenotype components by performing a principal component analysis (PCA) and, through this, to reduce the number of phenotype components as a guide for future molecular genetic studies. Thirdly, we calculated familiality estimates for individual components, as well as for the identified principal components.

We investigated a large sample of probands with dyslexia and their siblings using a battery of psychometric tests. These tests cover dyslexia related phenotypes that have been found to be correlated with the core symptoms (Gayán & Olson, 2003) and that might characterize dyslexia subtypes (Castles *et al.* 1999). These are phonological decoding, phoneme awareness, orthographic processing, short-term memory and rapid naming. In addition, we investigated mathematical abilities since poor mathematical abilities have been repeatedly found in dyslexia subgroups (Landerl *et al.* 2004). For all analyses we applied age- and IQ-adjusted values, because there is clear empirical evidence that both age (Wadsworth *et al.* 2001) and IQ influence the relationship between the variables (Wadsworth *et al.* 2000; Knopik *et al.* 2002).

Finally, we used the identified factors to re-analyze linkage data that we previously published for chromosome 18p11-q12 (Schumacher *et al.* 2006*b*).

Methods and Materials

Ascertainment of Families

In our German two-centre study, families with at least two siblings of whom at least one was affected with spelling disorder were recruited in the outpatient clinics of the Departments of Child and Adolescent Psychiatry and Psychotherapy at the Philipps University in Marburg and at the Julius-Maximilian University in Würzburg. Potential probands who had difficulties learning to read and spell, or who had just been diagnosed with dyslexia, were referred to the investigators by parents, teachers, special educators or practitioners.

All families were of German descent. All individuals, or in the case of minors younger than 14 years of age their parents, gave written informed consent for participation in the study. The ethics committees of the Universities of Marburg and Würzburg approved the study.

Since clinical studies on dyslexia in Germany usually use spelling disorder as an inclusion criterion, and our previous findings are also based on this selection criterion (see Schulte-Körne *et al.* 1996, 1998b, 2001; Ziegler *et al*. 2005; Schumacher *et al*. 2006*a*), the probands' spelling ability was used as the criterion for inclusion (for diagnostic criteria see the following section). Only probands attending at least the middle of the second grade were included because spelling disorder cannot be reliably diagnosed earlier (Schulte-Körne *et al.* 2001).

In our study families were included if at least one child – the proband – fulfilled the criterion for spelling disorder (see following section), and if there was at least one full sibling willing to participate. Hence, as described elsewhere in detail (Ziegler *et al*. 2005), we used a single proband sib-pair design. In addition both parents had to be available for participation.

From August 2001 until April 2004 all dyslexic children were investigated at one of the Departments of Child and Adolescent Psychiatry with standardized and unstandardized tests, and family and medical histories were collected. To evaluate whether the proband or a sibling had symptoms of ADHD, a standardized clinical interview (DIPS, based on ICD-10 criteria for ADHD, Unnewehr *et al.* 1998) was performed with the mother. If the proband or a sibling fulfilled the diagnostic criteria of ADHD, based on the interview data, the family was excluded from this study since their inclusion could have introduced further heterogeneity into the analysis (Willcutt *et al*. 2002), and symptoms of inattention and hyperactivity might influence child behaviour in the neuropsychological examinations. Additional exclusion criteria were a bilingual education, IQ < 85, an uncorrected disorder of peripheral hearing or vision, a psychiatric or neurological disorder influencing the development of reading and spelling ability, and age greater than 21 years.

Criteria for Dyslexia

The diagnosis of dyslexia was based on the spelling score using the T distribution of the general population. For inclusion in the study the proband had to meet the following discrepancy criterion: based on the correlation between IQ and spelling of 0.4 (Schulte-Körne *et al.* 2001), an anticipated spelling score was calculated. The child was classified as affected if the discrepancy between the anticipated and the observed spelling score was at least one standard deviation.

Spelling was measured using a grade-appropriate German spelling test (writing to dictation) (Brähler *et al.* 2002) that generates T scores that are distributed normally with mean 50 and variance 100, denoted by N(50,100) in unaffected children. IQ was assessed using one of two Culture Fair Tests (CFT-1; Weiß & Osterland, 1997 or CFT-20; Weiß, 1998) depending on the age of the proband.

Phenotypic Measures

Probands and all siblings were assessed using several psychometric tests. None of these tests were administered to parents. These tests incorporated the relevant aspects of the dyslexia phenotype that have been investigated in genetic linkage and twin studies (Fisher & DeFries, 2002).

Word Reading

A word reading test (Landerl *et al.* 1997) generating T scores that are distributed as N(50,100) in unaffected children was administered. Because there are no standardized German reading tests for children at or above the 5th grade, a non-standardized reading test was performed with these children (Schulte-Körne, 2001*b*). This test requires children to read a list of 48 words as accurately and quickly as possible. The dependent variable was the number of words read correctly in one minute.

Phonological Awareness

Three tests were administered to measure phonological awareness for children from the second to the fourth

grade: a phoneme segmentation, phoneme deletion, and phoneme reversal test. Tests were presented aurally and had to be responded to orally. In the phoneme deletion test children were instructed first to repeat an item (to ensure they had heard it correctly) and then to repeat the pseudoword without the first phoneme; fifteen items were used for this test. In the phoneme segmentation test the task was to split a pseudoword into its phonemes; ten pseudowords were administered. In the phoneme reversal test the children had to switch the first two phonemes of a word (15 real words) (e.g. Leder - elder). For children from the fifth grade, instead of phoneme deletion a word reversal test was administered in order to avoid ceiling effects due to lower task difficulty. For this task the children were required to say a word with the order of its phonemes reversed (e.g. omel – lemo); ten pseudowords were administered. For all tasks practice items were administered to ensure that the child had understood the task. During the test trials no feedback was given. The phonological tests were averaged for both age groups (2nd to 4th grade/5th grade and older) respectively, in order to get one phonological measure. This combined measure was used for subsequent statistical analyses.

Phonological Decoding

For children from the second to fourth grades, a standardized pseudoword reading test (Landerl *et al*. 1997) was administered. This test requires children to read a list of 48 pseudowords as accurately and quickly as possible. The dependant variable was the number of pseudowords read correctly in one minute. Children at or above the fifth grade performed a non-standardized pseudoword reading test. For this task children were required to read a list of pseudowords as accurately and quickly as possible (Schulte-Körne, 2001*b*). The dependent variable was the number of pseudowords read correctly in one minute.

Orthographic Processing

A pseudohomophone test that assesses the ability to discriminate real words (e.g. Wachstum) from pseudohomophones (e.g. Waxtum) was administered and used in a linkage study previously (Schumacher *et al*. 2006*a*,*b*). The pseudohomophones were generated by substituting or adding graphemes into a real word, resulting in a pseudohomophone which sounds identical to the real word but which has incorrect spelling. This test is considered to measure orthographic processing, since the pseudoword and real word sound the same, and phonological analysis of the word cannot discriminate between them. Children heard single words through headphones. After this, a word or a pseudoword corresponding to the audibly presented word appeared on the computer screen. Subjects were asked to press the right button if the word was misspelled, or the left button if the word was spelt correctly. Thirty-five words or pseudowords were presented, one after another in a pseudorandom order.

Rapid Naming

The rapid naming test used for this study was developed based on the work of Denckla & Rudel (1974) and used in a linkage study previously (Schumacher *et al*. 2006*a*,*b*). Four trials naming objects, numbers, letters, and colours were conducted. The trials were printed on a sheet of paper, and children were asked to name them as quickly as possible without making mistakes. Colour naming was measured using circles of five different colours (red, green, brown, blue and black). Number naming was measured using 1-digit numbers (7, 2, 9, 6, 4). Object naming was measured using coloured line drawings of common objects (e.g., scissors, candle, comb, clock, key), and for letter naming single consonants or vowels (p, s, o, a, d) were presented. The raw scores of colour and object naming were combined in order to facilitate the analysis. The combined scores are considered to be a purer measure of naming speed, whereas number and letter naming are more a reflection of speed and fluency, measures that are influenced by exposure to alphabet and print (Meyer *et al*. 1998).

Short Term Memory

Phonological short-term memory was measured using the standardized digit span test from the HAWIK-R (Tewes, 1983; German adaptation of the WISC-R; Wechsler, 1974), which includes forward and backward digit span.

Basic Mathematical Abilities

In collaboration with Brian Butterworth and Karin Landerl (University College, London and University of Tübingen, respectively) we selected some tasks from a previously used test battery (Landerl *et al.* 2004) developed by Brian Butterworth (Butterworth, 2003) and specifically adapted for our study.

Three basic number processing tasks were chosen from the test battery, namely number comparison, addition and multiplication. Since deficits in number processing in children with dyscalculia are difficult to find when untimed conditions are applied (Jordan & Montani, 1997), timed conditions were used.

Number comparison

A group of randomly arranged dots ranging from one to nine were presented on the left hand side of the computer screen, and a written number was presented on the right hand side. Children were asked to compare the number of dots with the written number. If the number of dots equalled the written number, the children had to press the left button of the computer mouse as quickly as possible, and if they were unequal they had to press the right button. Twenty-four trials were presented.

Mental arithmetic

Twenty-four simple additions and 24 simple multiplications were presented in two separate blocks. Numbers from one to 19 were included for additions, single-digit numbers from two to nine for multiplication. No ties (e.g. $5 + 5$, 2×2) were presented, and items were not repeated. Items were presented on the computer screen in the form "$2 + 4 = 6$". Children were asked to press, as quickly as they could without making mistakes, the left mouse button if the result of the addition or multiplication was correct, and the right button if the result was incorrect. The results of these two subtests were combined, since they both represent basic mental arithmetic processing.

Handedness was measured with a self-report handedness questionnaire (Schulte-Körne *et al.* 1998*a*). For all tests that required a button press children were asked to do the task with their preferred hand based on the results of the questionnaire.

Socio-economic status (SES)

Both parents were interviewed about their current occupation and education. This information was then transformed into values on the occupational prestige scale according to Wegener ("Magnitude-Prestigeskala", Wegener, 1988) by the "Zentrum für Umfragen, Methoden und Analysen" (ZUMA) in Mannheim. The Wegener scale renders unstandardized scores that fall roughly between 20 and 200 and reflect the social prestige of an occupation. The Wegener scores were finally transformed into standard T scores using normative data from the large German social survey "Allgemeine Bevölkerungsumfrage 1998" (ALLBUS, ZA-Nr. 3000). Normative data were provided by ZUMA.

Genotyping

To illustrate the use of the phenotype factors in linkage analysis, we re-analyzed data from a subset of 82 families for linkage to a region on chromosome 18p11-q12 (Schumacher *et al.* 2006*b*). Specifically, 14 microsatellites had been genotyped (see Figures 1 and 2), chosen from GDB (http://www.gdb.org.gdb/) with marker positions and distances between them extracted from the Marshfield map (http://research.marshfieldclinic.org/genetics/) and from the UCSC Genome Browser (http://genome.ucsc.edu/cgi-bin/hgGateway). For details of genotyping procedures see Schumacher *et al.* (2006*b*).

Each genotyped marker was checked for Mendelian incompatibilities using a customized version of the program PedCheck, Version 1.1 (O'Connell & Weeks, 1998). Incompatibilities were either resolved unambiguously or individuals were discarded from further analyses. Double recombinants were identified with Genehunter, Version 2.1 (Kruglyak *et al.* 1996). Allele frequencies were estimated from the sample by allele counting in founder individuals.

Statistical Analyses

To adjust for age and IQ in all of the psychometric tests, we modelled the functional relationship between test scores, age and IQ simultaneously by applying multiple fractional polynomials (Royston & Altman, 1994)

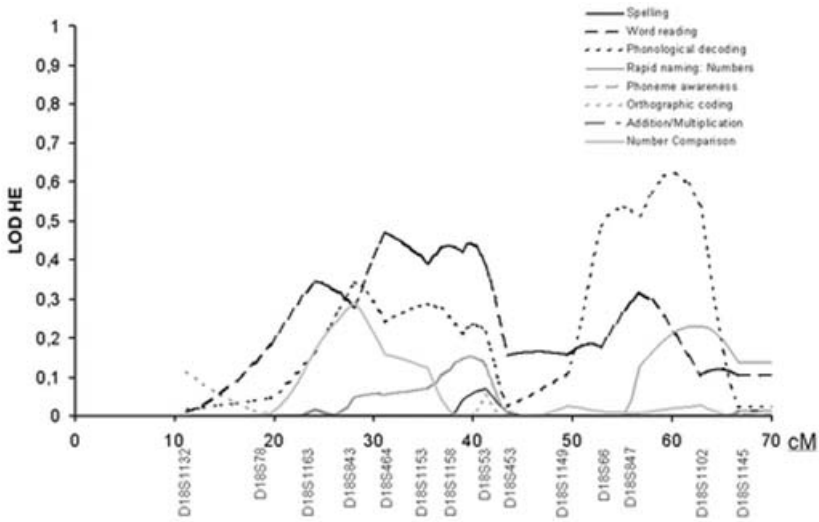

Figure 1 Results from linkage analysis of spelling as well as related phenotypes (word reading, phonological decoding, rapid naming (numbers), phoneme awareness, orthographic coding, addition/multiplication, number comparison) in 82 families with at least one dyslexic child. *HE LOD = Multipoint LOD score from Haseman-Elston algorithm.*

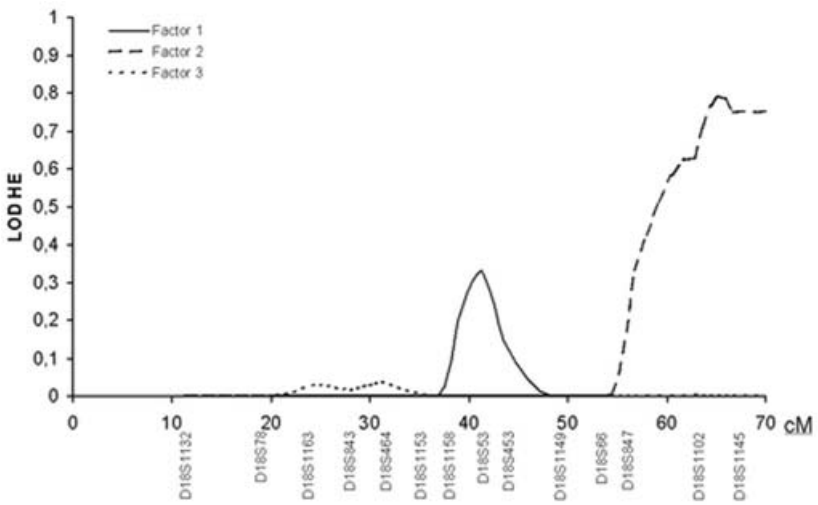

Figure 2 Results from linkage analysis of three factors (factor 1: general dyslexia factor, factor 2: processing speed factor, factor 3: basic mathematical abilities factor) in 82 families with at least one dyslexic child.

without interactions. These models were developed in the subgroup of siblings who were not affected according to our discrepancy criterion for reducing possible effects of dyslexia on the modelled functional relationship. From the resulting models the ordinary individual residuals were used for further analyses. When different tests were administered in different age groups, adjustments were performed within the age groups. To improve comparability between tests the observed scores in all children were linearly transformed, so that they were distributed with a mean of 50 and a standard deviation of 10 in the subgroup of siblings not affected with dyslexia.

For adjusted phenotypes mean and standard deviations were computed for probands and for all of their siblings. To describe the distributions of the phenotypes

in detail, skewness and kurtosis with respective standard errors were computed for probands and for siblings, and we tested for deviations from the normal distribution using the Jarque-Bera test. The relationships between phenotypes were investigated by calculating Pearson correlation coefficients with two-sided p-values between all phenotypes, separately within probands and their siblings. To analyze the relationship between the phenotypes in more detail, a principal components analysis with subsequent varimax rotation was performed in the sibling sample, generating factor scores.

Further, the familiality of single phenotypes and of factors extracted from the principal components analysis was estimated. Specifically, in order to be able to estimate the familiality in sib-pairs in a variance component model the usual restrictions were introduced, i.e., independence of genotypic and environmental variances, no interactions between genotype and environment, and no dominance variance (Ziegler & König, 2006). The resulting estimator is identical to the narrow sense heritability for dizygotic twins if shared environment can be excluded (Khoury *et al*. 1993; Vogel & Motulsky, 1996). Robust confidence intervals for the familiality estimates were obtained by using a jack-knife procedure.

Finally, to analyze the 14 genotyped microsatellites covering approximately a 55 cM (36 Mb) interval on chromosome 18p11-q12, multipoint linkage analyses were carried out with the single phenotypes as well as with the phenotype factors using the traditional Haseman-Elston method (Haseman & Elston, 1972).

Results

A sample of 287 families comprising a total of 574 siblings was investigated. Sibship size ranged from 2 to 5. For families containing more than two siblings the sibling who was closest to the proband in age was selected for the analyses. The mean SES of the fathers and of the mothers was 55.2 ($\pm$12.2) and 53.2 ($\pm$9.1), respectively. Thus the SES was in the normal range, although the mean values were slightly above the mean for both mothers and fathers.

Of the 287 probands (mean age = 12.13, standard deviation = 2.29) 211 were boys, whereas of their siblings (mean age = 13.24, standard deviation = 3.21) only 140 were male. Applying the same diagnostic criteria to the sibling sample we found that 173 of the 287 individuals were also spelling disabled.

Descriptive Statistics

Descriptive statistics for the phenotypic measures and IQ are presented in Table 1 for both probands and siblings. Probands' mean spelling score was more than two standard deviations below the mean (standardized test, Brähler *et al*. 2002). As expected from the single proband sib-pair design, with the sibling not required to be affected, all of the phenotypic measures were lower in probands than in siblings. Furthermore, all measures in the sib-pair sample were below the mean, which was also predicted from our study design (Ziegler *et al*. 2005). In both probands and siblings deviations from the normal distribution were visible for the rapid naming and mathematical phenotypes, which were all skewed to be left. In addition, the IQ was skewed to be right in the probands (Table 1).

Correlations between Phenotypes

In order to explore the relationship between the various phenotypic measures, Pearson correlation coefficients are displayed in Table 2a and b. Table 2a shows the correlations within probands, and Table 2b shows those within their siblings. In general, the correlation coefficients within siblings were higher than within probands, which can be explained by the restricted variance within our proband sample. Examination of the relationships suggested a pattern of two groups of phenotypes that are highly correlated. The first consists of spelling, word reading, phonological decoding, orthographic processing, and phonological awareness, and the second of addition/multiplication, number comparison, rapid naming (numbers), and rapid naming (symbols/colours). An exception is the rapid naming test (letters), which is highly correlated with every other test.

Principal Component Analysis

In order to investigate the relationships amongst our phenotypes in more detail, a principal component analysis using age and IQ corrected phenotype measures was performed.

Table 1 Descriptive statistics for probands and siblings[a]

	Probands (n = 287)				Siblings (n = 287)			
	Mean (SD)	Skewness (SE)	Kurtosis (SE)	p	Mean (SD)	Skewness (SE)	Kurtosis (SE)	p
IQ	109.86 (12.23)	0.54 (0.14)	−0.06 (0.29)	0.0009	111.70 (12.32)	0.15 (0.14)	−0.45 (0.29)	0.1712
Spelling	29.76 (6.00)	−0.26 (0.14)	−0.17 (0.29)	0.1732	41.16 (9.52)	0.24 (0.14)	0.36 (0.29)	0.1137
Word Reading	35.05 (11.17)	0.30 (0.14)	0.28 (0.29)	0.0695	44.56 (11.97)	−0.10 (0.14)	−0.75 (0.29)	0.0259
Phonological Decoding	37.85 (10.44)	−0.06 (0.14)	0.33 (0.29)	0.4747	45.06 (11.06)	0.08 (0.14)	0.58 (0.29)	0.1138
Phonological Awareness	39.63 (9.19)	−0.22 (0.14)	−0.24 (0.29)	0.2364	46.79 (8.19)	−0.70 (0.14)	0.24 (0.29)	<0.0001
Orthographic Processing	32.86 (11.21)	0.04 (0.14)	0.10 (0.29)	0.9118	42.59 (12.11)	−0.28 (0.14)	−0.32 (0.29)	0.0835
RN: Numbers	44.02 (13.44)	−1.42 (0.14)	3.71 (0.29)	<0.0001	48.32 (10.26)	−1.25 (0.14)	2.24 (0.29)	<0.0001
RN: Letters	41.54 (13.14)	−1.72 (0.14)	5.81 (0.29)	<0.0001	46.90 (11.66)	−2.72 (0.14)	13.89 (0.29)	<0.0001
RN: Symbols/Colours	43.93 (9.91)	−0.81 (0.14)	1.14 (0.29)	<0.0001	48.31 (8.96)	−0.60 (0.14)	0.92 (0.29)	<0.0001
Short Term Memory	42.59 (8.52)	0.21 (0.14)	−0.03 (0.29)	0.3536	46.90 (9.37)	−0.10 (0.14)	−0.19 (0.29)	0.6307
Addition/Multiplication	44.71 (10.36)	−2.11 (0.14)	10.47 (0.29)	<0.0001	48.21 (9.38)	−1.08 (0.14)	2.73 (0.29)	<0.0001
Number Comparison	46.99 (11.29)	−0.60 (0.14)	0.59 (0.29)	<0.0001	49.49 (10.28)	−0.37 (0.14)	0.89 (0.29)	0.0003

[a]Spelling and short term memory: T scores; word reading and phonological decoding. T scores for subjects of grade 2 – 4. Subjects of grade 5 and above: scores yielding mean = 50 and standard deviation = 10 for the subgroup of siblings not affected with dyslexia. All other phenotypes: scores that yield mean = 50 and standard deviation = 10 for unaffected siblings. SD = standard deviation, SE = standard error, p = p values from Jarque-Bera test.

The analysis yielded three factors with an eigenvalue above 1 after varimax rotation. Table 3 shows the factor loadings.

Spelling, word reading, phonological decoding, phonological awareness, orthographic processing, and short-term memory characterize factor 1 (Table 3). Word reading and phonological decoding have significant loadings on both factors 1 and 2. Factor 2 is additionally characterized by the three rapid naming variables. Finally, factor 3 is characterized by the two basic mathematical abilities variables.

Factor 1, which accounts for about 27% of the total variance, includes all the variables directly related to spelling and reading, and is best characterized as a general dyslexia factor. Factor 2, accounting for 24% of the total variance, includes all speed variables, except for the basic number processing tests which make up factor 3.

Familiality

Familiality of the phenotypic components was estimated in all children, using all phenotypes and factor scores generated from the PCA analysis. It was moderate to high for all components, with the highest estimates found for spelling (Table 4).

The familiality of basic mathematical abilities was very similar to the familiality of word reading and phonological decoding. Finally, the familiality of the three principle component factors (Table 3) was estimated. The general dyslexia factor and the speed of processing factor gave intermediate estimates, while the basic mathematical abilities factor showed lower familiality.

Figure 1 shows the multipoint LOD scores for all single phenotypes with LOD scores > 0, showing that no LOD score exceeded 0.6. The respective multipoint LOD scores for the phenotype factors are displayed in Figure 2, showing maximal LOD scores of 0.33, 0.79, and 0.04 for factors 1, 2, and 3, respectively. Hence, corroborating our previous results, we failed to detect linkage to chromosome 18p11-q12 in our sample of 82 nuclear families (Schumacher *et al.* 2006*b*). Our results therefore have consistently failed to replicate the strong evidence for linkage to this region obtained in three independent samples from the UK and the US (Fisher *et al.* 2002).

Table 2a Correlation of age- and IQ-adjusted phenotypes within probands[b]

	Spelling	Word Reading	Phonological Decoding	Orthographic Processing	Phonological Awareness	Short Term Memory	Addition/ Multiplication	Number Comparison	Rapid Naming: Letters	Rapid Naming: Numbers
Word Reading	0.48 ****									
Phonological Decoding	0.41 ****	0.79 ****								
Orthographic Processing	0.42 ****	0.33 ****	0.30 ****							
Phonological Awareness	0.34 ****	0.35 ****	0.29 ****	0.13						
Short Term Memory	0.32 ****	0.24 ****	0.22 ***	0.31 ****	0.38 ****					
Addition/Multiplication	0.18 **	0.23 ****	0.14 *	0.21 ***	0.05 -	0.15 *				
Number Comparison	0.14 *	0.11 -	0.14 *	0.20 ***	0.03 -	0.23 ****	0.44 ****			
Rapid Naming: Letters	0.40 ****	0.47 ****	0.54 ****	0.30 ****	0.28 ****	0.28 ****	0.34 ****	0.27 ****		
Rapid Naming: Numbers	0.27 ****	0.46 ****	0.54 ****	0.22 ***	0.26 ****	0.32 ****	0.29 ****	0.28 ****	0.73 ****	
Rapid Naming: Symbols/Colours	0.29 ****	0.36 ****	0.33 ****	0.21 ***	0.18 **	0.34 ****	0.28 ****	0.38 ****	0.52 ****	0.58 ****

[b]Pearson correlation coefficients (two-sided p-values) within probands: *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, ****: $p < 0.0001$

Table 2b Correlation of age-and IQ adjusted phenotypes within siblings[c]

	Spelling	Word Reading	Phonological Decoding	Orthographic Processing	Phonological Awareness	Short Term Memory	Addition/ Multiplication	Number Comparison	Rapid Naming: Letters	Rapid Naming: Numbers
Word Reading	0.54 ****									
Phonological Decoding	0.46 ****	0.75 ****								
Orthographic Processing	0.59 ****	0.56 ****	0.44 ****							
Phonological Awareness	0.42 ****	0.45 ****	0.35 ****	0.40 ****						
Short Term Memory	0.37 ****	0.33 ****	0.28 ****	0.32 ****	0.40 ****					
Addition/Multiplication	0.19 **	0.29 ****	0.24 ****	0.25 ****	0.12 *	0.14 *				
Number Comparison	0.01 -	0.10 -	0.07 -	0.04 -	−0.03 -	0.06 -	0.56 ****			
Rapid Naming: Letters	0.26 ****	0.40 ****	0.46 ****	0.31 ****	0.28 ****	0.15 **	0.39 ****	0.16 **		
Rapid Naming: Numbers	0.24 ****	0.46 ****	0.46 ****	0.30 ****	0.25 ****	0.26 ****	0.40 ****	0.17 **	0.65 ****	
Rapid Naming: Symbols/Colours	0.24 ****	0.38 ****	0.41 ****	0.24 ****	0.26 ****	0.28 ****	0.39 ****	0.27 ****	0.55 ****	0.57 ****

[c]Pearson correlation coefficients (two-sided p-values) within siblings: *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, ****: $p < 0.0001$

Table 3 Principal Component Analysis[d]

Variable	Factor 1	Factor 2	Factor 3
Spelling	**0.82**		
Word Reading	**0.69**	**0.48**	
Phonological Decoding	**0.54**	**0.59**	
Orthographic Processing	**0.75**	0.19	
Phonological Awareness	**0.68**	0.17	
Short Term Memory	**0.62**		0.14
Rapid Naming: Letters	0.14	**0.83**	0.14
Rapid Naming: Numbers	0.16	**0.83**	0.14
Rapid Naming: Symbols/Colours	0.16	**0.70**	0.29
Addition/Multiplication	0.14	0.33	**0.79**
Number comparison			**0.90**
Explained variance by factor	26.7%	23.8%	14.5%

[d]Loadings > 0.35 are given bold, loadings < 0.10 not shown.

Discussion

A battery of psychometric tests covering different dyslexia related phenotypic components was applied to a large sample of 287 German dyslexia families. Since molecular genetic studies have reported linkage and association of the core symptoms of dyslexia and related phenotypes (Cardon *et al.* 1994, 1995; Gayán *et al.* 1999; Fisher *et al.* 1999, 2002; Grigorenko *et al.* 2000, 2001, 2003; Petryshen *et al.* 2002; Kaplan *et al.* 2002; Francks *et al.* 2004; Raskind *et al.* 2005) we systematically investigated the relationship between these components.

The gender ratio (males/females) in the proband sample is 2.8:1, corresponding to the findings reported in families (e.g. Schulte-Körne *et al.* 1996) as well as in epidemiological samples (Rutter *et al.* 2004).

The average proband scores on all reading and spelling related measures and mathematical abilities were below the mean, with the lowest score obtained for spelling. This finding can be explained by the diagnostic inclusion criterion of an IQ-discrepant spelling disorder. Also, the sibling scores on all phenotypic measures were below the mean. Although the siblings were not phenotypically selected for inclusion in the study (single proband sib-pair design, Ziegler *et al.* 2005) this result was expected, due to the fact that the siblings' families were selected through an affected proband and the familiality of dyslexia related phenotypes is well known (e.g. Marlow *et al.* 2001).

The correlation between the phenotypes was investigated in the proband and sibling samples, leading to a comparably wide range of correlation coefficients (0–0.7). In general, the correlations were lower in the proband sample as compared to the sibling sample. This might be explained by our sample recruitment strategy. Since probands were selected based on poor spelling, the spelling variance in the probands' sample was smaller than in the siblings' sample, where no such selection was applied. Because of the correlations amongst spelling and the other variables, variances of all these variables

Table 4 Familiality Estimates

Measure	Familiality	95% confidence interval	p-value
Spelling	0.63	0.23–1.00	0.0002
Word Reading	0.36	0.12–0.61	0.0016
Phonological Decoding	0.40	0.17–0.64	0.0005
Phonological Awareness	0.39	0.17–0.61	0.0001
Orthographic Processing	0.25	0.01–0.49	0.0138
Rapid Naming: Letters	0.42	0.17–0.67	<0.0001
Rapid Naming: Numbers	0.36	0.18–0.54	0.0001
Rapid Naming: Symbols/Colours	0.45	0.12–0.58	<0.0001
Addition/Multiplication	0.36	0.14–0.73	0.0002
Number Comparison	0.35	0.24–0.64	0.0003
Short Term Memory	0.40	0.13–0.68	0.0004
Factor 1 (General Dyslexia Factor)	0.43	0.14–0.73	0.0002
Factor 2 (Processing Speed Factor)	0.44	0.24–0.64	0.0016
Factor 3 (Basic Mathematical Abilities Factor)	0.31	0.11–0.50	0.0005

were most likely decreased, leading to lower correlations in the probands' sample than in the siblings' sample.

We investigated the structure of the phenotypes further by performing principal components analysis (PCA) for siblings. A further aim of the PCA was to generate factor scores that were subsequently used for familiality estimation.

Three factors were identified, with the first factor appearing to be a general dyslexia factor involving the core symptoms of reading and spelling, and the related variables phonological and orthographic processing. This dyslexia factor resembles the general factor of reading ability described by Marlow *et al.* (2001), who found only one factor that accounted for over half of the total variance. In our analysis we integrated a measure that mainly covers the speed of processing aspect. It has been hypothesized that rapid naming measures a process that explains variance of the reading and spelling phenotype, in addition to phonological and orthographic processing (Bowers, 1995). We found evidence for this hypothesis since the rapid naming variables mainly load onto the second factor of the PCA. However, those two variables (word reading and phonological decoding), which are speed measures, also load onto the second factor. Thus, the second factor is a speed of processing factor independent of the material that has to be named. Interestingly, we found a third factor that appears to be a general factor of basic mathematical abilities. All the other variables showed no or only marginal loadings on this factor. This finding, and the low correlation between reading/spelling and mathematical abilities, suggest a low dependency of these cognitive abilities.

To explore the heritable nature of related phenotypes familiality was estimated for all the phenotype measures, as well as for the factor scores derived from the PCA. We calculated familiality estimates not only for the phenotypes, but also for our factor scores, because the phenotype variables underlying each factor represent a bundle of components in and of themselves, e.g., word reading reflects not only speed but also reading. Generating a factor of all speed-related variables should potentially lead to a more stable, reliable, and pure representation of the speed aspect.

These familiality estimates could be interpreted as heritability estimates, and are identical to those of dizygotic twins if absence of shared environment is assumed. In general, we found moderate to high familiality of all components. The highest familiality was estimated for spelling ($h^2 = 0.63$), a result that was comparable to the heritability estimates reported in a UK family study ($h^2 = 0.72$) (Marlow *et al.* 2001) and a UK twin study ($h^2 = 0.72$) (Stevenson *et al.* 1987). In comparison to the other dyslexia related phenotypes, spelling seems to be one of the most heritable phenotypes, rendering it a promising candidate phenotype for gene identification studies. In line with this hypothesis, we have recently shown that the gene doublecortin-domain-containing-2 (DCDC2) on chromosome 6p21-p22 shows strongest association with an IQ-discrepant spelling phenotype (Schumacher *et al.* 2006*a*). To date only two twin studies concerning mathematical disabilities have been published. Heritability estimates reported in the Colorado Twin Study of Reading Disability (Alarcón *et al.* 1997) was 0.38 for a composite mathematics score that was computed by summing each individual's subtests scores. These subtests included tasks such as counting, written computations, geometry, and trigonometry. Although we only applied a few tasks that are similar to this test battery, we found familiality estimates in our study that were comparably high. More recently, findings from the Twins' Early Development Study (TEDS) were consistent with a higher heritability of low mathematical performance ($h^2 = 0.65$) (Oliver *et al.* 2004). This higher heritability is not surprising given the differences between the sample recruitment strategies. The group heritability was estimated in the twin pairs with at least one twin being characterized by low mathematics performance. In our study, and the study of Alarcón and colleagues (1997), however, mathematical abilities were investigated in a sample of individuals with dyslexia. Thus, one possible reason for the higher estimates found in the TEDS is that this was a more homogenous sample of individuals with low mathematical performance. Since the heritability estimates for all these studies also denote that at least 40% of the variance of mathematical disabilities must be explained by shared and non-shared environment, it is essential to also consider environmental factors, e.g. quality of teaching, as causal factors for mathematical disabilities (Kameenui & Griffin, 1989; Newman & Stevenson, 1989).

Because estimates of familiality depend on the specific ascertainment scheme employed, the severity of

affection influences familiality at both the phenotypic and the molecular genetic level. Hence, if affection is defined with stricter criteria, recurrence risk estimates for dyslexia (Ziegler *et al.*, 2005) and also for other complex diseases increase (Ziegler *et al.* 1997); the findings for *DCDC2* were predominantly based on more severely affected families (Schumacher *et al.* 2006*a*).

There is an ongoing discussion as to whether the nature of dyslexia is influenced by different language environments. Whereas behavioural studies suggest that the nature of dyslexia might differ between the orthographies (Landerl *et al.* 1997; Seymour *et al.* 2003), neuroimaging studies have found evidence for a universal neurobiological deficit in dyslexia (Paulesu *et al.* 2001). Furthermore, because linkage of dyslexia to a candidate gene region on chromosome 15 was replicated in individuals speaking different languages and learning different orthographies (English, Finnish, German, Italian) one might assume that different orthographies have only a minor influence on the genetics of dyslexia (Smith *et al.* 1983; Grigorenko *et al.* 1997; Nopola-Hemmi *et al.* 2001; Schulte-Körne *et al.* 1998*a*; Marino *et al.* 2004). In order to analyse the influence of two different orthographies on some of our findings, we compared our study results with results from a study that investigated English-speaking children with dyslexia (Marlow *et al.* 2001). Interestingly, the principal component analysis in the UK sample revealed one factor that could best be explained as a general dyslexia factor, since word reading, spelling, phoneme awareness and orthographic processing load onto it. This factor is very similar to the general dyslexia factor found in our study, since the same variables load onto it. As we investigated more components of the dyslexia phenotype, we found that phonological decoding and short-term memory also load onto this general dyslexia factor. The second consistency between the studies is the comparably high heritability for spelling (UK $h^2 = 0.72$, Germany $h^2 = 0.63$). Thus, more than 60% of the variance of spelling can be explained by genetic factors. Although there are also some inconsistencies between these studies, this comparison further strengthens the view that the influence of different orthographies on the genetic findings is small.

Recently, a cognitive-genetic model of 'generalist genes' was proposed by Plomin & Kovas (2005), which suggests that the same genes affect most cognitive abilities and disabilities. The finding of a high genetic correlation between reading and mathematics in the study by Plomin & Kovacs (2005), ranging between 0.41 and 0.98, supported this model. In our study we found medium to high intercorrelations between the different reading related measures, suggesting a common variance between these cognitive dimensions. In contrast to the prediction of the 'generalist genes' model, however, we did not find evidence for an overlap of reading related measures and basic mathematical abilities.

Finally, the various correlated dyslexia related component phenotypes can be condensed into three factors which all are moderately heritable. Since no single measure reflects the complex phenotype completely, these composite phenotypes are more suitable for genetic analysis. Therefore, in a future genome screen of the German families described here we will analyse these factors, as well as applying multivariate analysis of quantitative traits as suggested by Marlow *et al.* (2003), who have demonstrated the validity of these methods in molecular genetic studies. Our study in which we applied factors to linkage data from chromosome 18p11-q13 (Schumacher *et al.* 2006*b*), however, did not lead to an improvement of the results. This was not unexpected, since the investigation of individual components had not shown any evidence for linkage. The proof of principle for our sample will come from the comparison of different methods on a systematic genome-wide scale.

Acknowledgments

We are very grateful to all families who participated in this study. We thank Maike Preis and Jutta Hülsmann for the collection of blood samples and for testing the subjects. We thank Karin Landerl and Brian Butterworth for their help with the basic mathematical tasks.

This research was funded by the Deutsche Forschungsgemeinschaft. M.M.N. was supported by the Alfried Krupp von Bohlen und Halbach-Stiftung.

References

Alarcón, M., DeFries, J. C., Light, J. C. & Pennington, B. F. (1997) A twin study of mathematics disability. *J Learn Disabil* **30**, 617–623.

Amos, C. I., Elston, R. C., Bonney, G. E., Keats, B. J. & Berenson, G. S. (1990) A multivariate method for

detecting genetic linkage, with application to a pedigree with an adverse lipoprotein phenotype. *Am J Hum Genet* **47**, 247–254.

Bowers, P. G. (1995) Tracing symbol naming speed's unique contributions to reading disabilities over time. *Reading and Writing* **7**, 189–216.

Bradley, L. & Bryant, P. (1983) Categorising sounds and learning to read: a causal connection. *Nature* **301**, 419–421.

Brähler, E., Holling, V., Leutner, D. & Petermann, F. (2002) *Brickenkamp Handbuch psychologischer und pädagogischer Tests*. Göttingen: Hogrefe.

Butterworth, B. (2003) *Dyscalculia Screener*. London: NFER Nelson.

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.

Cardon, L. R., Smith, S. D., Fulker, D. W., Kimberling, W. J., Pennington, B. F. & DeFries, J. C. (1995) Quantitative trait locus for reading disability: correction. *Science* **268**, 1553.

Castles, A., Datta, H., Gayán, J. & Olson, R. K. (1999) Varieties of developmental reading disorder: genetic and environmental influences. *J Exp Child Psychol* **72**, 73–94.

O'Connell, J. R. & Weeks, D. E. (1998) PedCheck: a program for identification of genotype incompatibilities in linkage analysis. *Am J Hum Genet* **63**, 259–266.

Denckla, M. & Rudel, R. G. (1974) Rapid automatized naming of pictured objects, colors, letters and numbers by normal children. *Cortex* **10**, 86–202.

Dilling, H., Mombour, W. & Schmidt, M. H. (1991) *International Classification of Mental Diseases, ICD-10, German edition*. Bern: Huber.

Evans, D. M. (2002) The power of multivariate quantitative-trait loci linkage analysis is influenced by the correlation between variables. *Am J Hum Genet* **70**, 1599–1602.

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 quantitative-trait locus on chromosome 6p influences different aspects of developmental dyslexia. *Am J Hum Genet* **64**, 146–156.

Fisher, S. E. & DeFries, J. C. (2002) Developmental dyslexia: genetic dissection of a complex cognitive trait. *Nat Rev Neurosci* **3**, 767–780.

Fisher, S. E., Francks, C., Marlow, A. J., MacPhie, I. L., Newbury, D. F. Cardon, L. R., Ishikawa-Brush, Y., Richardson, A. J., Talcott, J. B., Gayán, J., Olson, R. K., Pennington, B. F., Smith, S. D., DeFries, J. C., Stein, J. F. & Monaco, A. P. (2002) Independent genome-wide scans identify a chromosome 18 quantitative-trait locus influencing dyslexia. *Nat Genet* **30**, 86–91.

Francks, C., Paracchini, S., Smith, S. D., Richardson, A., Scerri, T. S. Cardon, L. R., Marlow, A. J., MacPhie, I. L., Walter, J., Pennington, B. F., Fisher, S. E., Olson, R. K., DeFries, J. C., Stein, J. F.& Monaco, A. P. (2004) A 77-kilobase region of chromosome 6p22.2 is associated with dyslexia in families from the United kingdom and from the United States. *Am J Hum Genet* **75**, 1046–1058.

Gayán, J. & Olson, R. K. (2003) Genetic and environmental influences on individual differences in printed word recognition. *J Exp Child Psychol* **84**, 97–123.

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. *Am J Hum Genet* **64**, 157–164.

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

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. *Am J Hum Genet* **60**, 27–39.

Grigorenko, E. L., Wood, F. B., Meyer, M. S., Pauls, J. E., Hart, L. A. & Pauls, D. L. (2001) Linkage studies suggest a possible locus for developmental dyslexia on chromosome 1p. *Am J Med Genet* **105**, 120–129.

Grigorenko, E. L., Wood, F. B., Meyer, M. S. & Pauls, D. L. (2000) Chromosome 6p influences on different dyslexia-related cognitive processes: further confirmation. *Am J Hum Genet* **66**, 715–723.

Grigorenko, E. L., Wood, F. B., Golovyan, L., Meyer, M., Romano, C. & Pauls, D. L. (2003) Continuing the search for dyslexia genes on 6p. *Am J Med Genet* **118**, 89–98.

Haseman, J. K. & Elston, R. C. (1972) The investigation of linkage between a quantitative trait and a marker locus. *Behav Genet* **2**, 3–19.

Holopainen, L., Ahonen, T. & Lyytinen, H. (2001) Predicting delay in reading achievement in a highly transparent language. *J Learn Disabil* **34**, 401–413.

Jordan, N. & Montani, T. (1997) Cognitive arithmetic and problem solving: A comparison of children with specific and general mathematics difficulties. *J Learn Disabil* **30**, 624–634.

Kameenui, E. J. & Griffin, C. C. (1989) The national crisis in verbal problem solving in mathematics: A proposal for examining the role of basal mathematics programs. *The Elementary School Journal* **89**, 575–593.

Kaplan, D. E., Gayán, J., Ahn, J., Won, T. W., Pauls, D., Olson, R. K., DeFries, J. C., Wood, F., Pennington, B. F., Page, G. P., Smith, S. D. & Gruen, J. R. (2002) Evidence for linkage and association with reading disability on 6p21.3-22. *Am J Hum Genet* **70,** 1287–1298.

Katusic, S. K., Colligan, R. C., Barbaresi, W. J., Schaid, D. J. & Jacobsen, S. J. (2001) Incidence of reading disability in

a population-based birth cohort. *Minn Mayo Clin Proc* **76**, 1081–1092.

Khoury, M. J., Beaty, T. H.& Cohen, B. H. (1993). *Fundamentals of Genetic Epidemiology*. New York: Oxford University Press.

Knopik, V. S., Smith, S. D., Cardon, L., Pennington, B., Gayán, J., Olson, R. K. & DeFries, J. C. (2002) Differential genetic etiology of reading component processes as a function of IQ. *Behav Genet* **32**, 181–198.

Kruglyak, L., Daly, M. J., Reeve-Daly, M. P. & Lander, E. S. (1996) Parametric and nonparametric linkage analysis: a unified multipoint approach. *Am J Hum Genet* **58** 1347–1363.

Landerl, K., Wimmer, H. & Moser, E. (1997) *Salzburger Lese- und Rechtschreibtest*. Bern: Huber.

Landerl, K., Bevan, A. & Buttherworth, B. (2004) Developmental dyscalculia and basic numerical capacities: a study of 8-9-year-old students. *Cognition* **93**, 99–125.

Liederman, J., Kantrowitz, L. & Flannery, K. (2005) Male vulnerability to reading disability is not likely to be a myth: a call for new data. *J Learn Disabil* **38**, 109–129.

Marino, C., Giorda, R., Vanzin, L., Nobile, M., Lorusso, M. L., Baschirotto, C., Riva, L., Molteni, M. & Battalia, M. (2004) A locus on 15q15-15qter influences dyslexia: further support from a transmission/disequilibrium study in an Italian speaking population. *J Med Genet* **41**, 42–46.

Marlow, A. J., Fisher, S. E., Richardson, A. J., Francks, C., Talcott, J. B. Monaco, A. P., Stein, J. F. & Cardon, L. R. (2001) Investigation of quantitative measures related to reading disability in a large sample of sib-pairs from the UK. *Behav Genet* **31**, 219–230.

Marlow, A. J., Fisher, S. E., Francks, C., MacPhie, I. L., Cherny S. S. Richardson, A. J., Talcott, J. B., Stein, J. F., Monaco, A. P. & Cardon, L. R. (2003) Use of multivariate linkage analysis for dissection of a complex cognitive trait. *Am J Hum Genet* **72**, 561–570.

Meyer, M. S., Wood, F. B., Hart, L. A. & Felton, R. H. (1998) Longitudinal course of rapid naming in disabled and nondisabled readers. *Ann of Dyslexia* **48**, 91–114.

Newman, R. S. & Stevenson, H. W. (1989) Children's achievement and causal attributions in mathematics and reading. *J Exper Educ* **58**, 197–212.

Nopola-Hemmi, J., Myllyluoma, B., Haltia, T., Taipale, M., Ollikainen, V. Ahonen, T., Voutilainen, A., Kere, J. & Widen, E. (2001) A dominant gene for developmental dyslexia on chromosome 3. *J Med Genet* **38**, 658–664.

Oliver, B., Harlaar, N., Hayiou-Thomas, M. E., Kovas, Y., Walker, S. O., Petrill, S. A., Spinath, F. M., Dale, P. S. & Plomin, R. (2004) A twin study of teacher-reported mathematics performance and low performance in 7-year-olds. *J Edu Psychol* **96**, 504–517.

Paulesu, E., Démonet, J. F., Fazio, F., McCrory, E., Chanoine, V., Brunswick, N., Cappa, S. F., Cossu, G., Habib, M., Frith, C. D. & Frith, U. (2001) Dyslexia: cultural diversity and biological unity. *Science* **291**, 2165–2167.

Petryshen, T. L., Kaplan, B. J., Hughes, M. L., Tzenova, J. & Field, L. L. (2002) Supportive evidence for the DYX3 dyslexia susceptibility gene in Canadian families. *J Med Genet* **39**, 125–126.

Plomin, R. & Kovas, Y. (2005) Generalist genes and learning disabilities. *Psychol Bull* **131**, 592–617.

Raskind, W. H., Hsu, L., Berninger, V. W., Thomson, J. B. & Wijsman, E. M. (2000) Familial aggregation of dyslexia phenotypes. *Behav Genet* **30**, 385–396.

Raskind, W. H., Igo, R. P., Chapman, N. H., Berninger, V. W., Thomson, J. B., Matsushita, M., Brkanac, Z., Holzman, T., Brown, M. & Wijsman, E. M. (2005) A genome scan in multigenerational families with dyslexia: Identification of a novel locus on chromosome 2q that contributes to phonological decoding efficiency. *Mol Psychiatry* **10**, 699–711.

Royston, P. & Altman, D. G. (1994) Regression using fractional polynomials of continuous covariats: Parsimonious parametric modelling. *Appl Stat* **43**, 429–467.

Rutter, M., Caspi, A., Fergusson, D., Horwood, L. J., Goodman, R. Maughan, B., Moffitt, T. E., Meltzer, H. & Caroll, J. (2004) Sex differences in developmental reading disability: new findings from 4 epidemiological studies. *J Am Med Assoc* **291**, 2007–2012.

Schulte-Körne, G., Deimel, W., Muller, K., Gutenbrunner, C. & Remschmidt, H. (1996) Familial aggregation of spelling disability. *J Child Psychol Psychiatry* **37**, 817–822.

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

Schulte-Körne, G., Grimm, T., Nöthen, M. M., Müller-Myhsok, B., Cichon, S., Vogt, I. R., Propping, P., Remschmidt, H. (1998b) Evidence for linkage of spelling disability to chromosome 15. *Am J Hum Genet* **63**, 279–282.

Schulte-Körne, G., Deimel, W. & Remschmidt, H. (2001) Diagnosis of reading and spelling disorder. *Z Kinder Jugendpsychiatr Psychother* **29**, 113–116.

Schulte-Körne, G. (2001a) Annotation: Genetics of reading and spelling disorder. *J Child Psychol Psychiatry* **42**, 985–997.

Schulte-Körne, G. (2001b) *Lese-Rechtschreibstörung und Sprachwahrnehmung-Psychometrische und neurophysiologische Untersuchungen zur Legasthenie. (Dyslexia and Speech Perception)*. Münster: Waxman Verlag.

Schumacher, J., Anthoni, H., Dahdouh, F., König, I. R., Hillmer, A., Kluck, N., Manthey, M., Plume, E., Warnke, A., Remschmidt, H., Hülsmann, J., Cichon, S., Lindgren, C. M., Propping, P., Zucchelli, M., Ziegler, A., Peyrard-Janvid, M., Schulte-Körne, G., Nöthen, M. M. & Kere, J. (2006a) Strong genetic evidence for *DCDC2* as a susceptibility gene for dyslexia. *Am J Hum Genet* **78**:52–62.

Schumacher, J., König, I. R., Plume, E., Propping, P., Warnke, A., Manthey, M., Duell, M., Kleensang, A., Repsilber, D., Preis, M., Remschmidt, H., Ziegler, A., Nöthen, M. M. & Schulte-Körne, G. (2006b) Linkage analyses of chromosomal region 18p11-q12 in dyslexia. *J Neural Transm* **113**, 417–423.

Seymour, P. H. K., Aro, M. & Erskine, J. M. (2003) Foundation literacy acquisition in European orthographies. *Br J Psychol* **94**, 143–174.

Shaywitz, S. E., Shaywitz, B. A., Fletcher, J. M. & Escobar, M. D. (1990) Prevalence of reading disability in boys and girls. *J Am Med Assoc* **264**, 998–1002.

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.

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

Tewes, U. (1983) *HAWIK-R. Hamburg-Wechsler Intelligenztest für Kinder*. Bern: Hans Huber.

Unnewehr, S., Schneider, S. & Margraf, J. (1998) *Kinder-DIPS: diagnostisches Interview bei psychischen Störungen von Kindern und Jugendlichen*. Berlin: Springer.

Vogel, F. & Motulsky A. G. (1996). *Human Genetics: Problems and Approaches*. Heidelberg: Springer-Verlag.

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

Wadsworth, S. J., Corley, R. P., Hewitt, J. K. & DeFries, J. C. (2001) Stability of genetic and environmental influences on reading performance at 7, 12, and 16 years of age in the Colorado Adoption Project. *Behav Genet* **31**, 353–359.

Wechsler, D. (1974) *Examiner's Manual: Wechsler Intelligence Scale for Children–Revised*. New York: The Psychological Corporation.

Wegener, B. (1988) *Kritik des Prestiges*. Opladen: Westdeutscher Verlag.

Weiß, R. H. (1998) *Grundintelligenztest Skala 2 (CFT 20)*. Göttingen: Hogrefe.

Weiß, R. H. & Osterland, J. (1997) *Grundintelligenztest Skala 1 (CFT 1)*. Göttingen: Hogrefe.

Willcutt, E. G., Pennington, B. F., Smith, S. D., Cardon, L. R., Gayán, J., Knopik, V. S., Olson, R. K. & DeFries, J. C. (2002) Quantitative trait locus for reading disability on chromosome 6p is pleiotropic for attention-deficit/hyperactivity disorder. *Am J Med Genet* **114**, 260–268.

Ziegler, A., Schäfer, H. & Hebebrand, J. (1997) Risch's lambda values for human obesity estimated from segregation analysis. *Int J Obes Relat Metab Disord* **21**, 952–953.

Ziegler, A., König, I. R., Deimel, W., Plume, E., Nöthen, M. M., Propping, P., Kleensang, A., Müller-Myhsok, B., Warnke, A., Remschmidt, H. & Schulte-Körne, G. (2005) Developmental dyslexia – recurrence risk estimates from a German bi-center study using the single proband sib pair design. *Hum Hered* **5**, 136–143.

Ziegler, A. & König, I. R. (2006) *A Statistical Approach to Genetic Epidemiology: Concepts and Applications*. Weinheim: Wiley-VCH.

Received: 20 March 2006
Accepted: 7 July 2006