

## Linkage analyses of chromosomal region 18p11-q12 in dyslexia

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**Summary.** Dyslexia is characterized as a significant impairment in reading and spelling ability that cannot be explained by low intelligence, low school attendance or deficits in sensory acuity. It is known to be a hereditary disorder that affects about 5% of school aged children, making it the most common of childhood learning disorders. Several susceptibility loci have been reported on chromosomes 1, 2, 3, 6, 15, and 18. The locus on chromosome 18 has been described as having the strongest influence on single word reading, phoneme awareness, and orthographic coding in the largest genome wide linkage study published to date (Fisher et al., 2002). Here we present data from 82 German families in order to investigate linkage of various dyslexia-related traits to the previously described region on chromosome 18p11-q12. Using two- and multipoint analyses, we did not find support for linkage of spelling, single word reading, phoneme awareness, orthographic coding and rapid naming to any of

the 14 genotyped STR markers. Possible explanations for our non-replication include differences in study design, limited power of our study and overestimation of the effect of the chromosome 18 locus in the original study.

**Keywords:** Linkage analysis, dyslexia, chromosome 18.

### Introduction

Dyslexia is a specific disorder in 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 (ICD-10, Dilling et al., 1991). The prevalence rate is 5–10% of school aged children and adults. Boys are twice more likely to be affected than girls (Rutter et al., 2004). Dyslexia is a complex disorder determined by both genetic and

environmental factors with a poorly understood etiology. It is associated with a high level of social and psychological morbidity for the individual and the family; approximately 40–50% of the individuals have persistent disability into adulthood (Schulte-Körne et al., 2003; Shaywitz et al., 1999).

The familial nature of dyslexia has been recognized since the first description of the disorder (Fisher and DeFries, 2002). Twin studies have shown concordance rates for dyslexia being higher in monozygotic than in dizygotic twins, with heritability estimates ranging up to 0.71 (DeFries and Gillis, 1993).

It is likely that dyslexia is genetically determined by a number of genes with small to moderate effects, with some contributing to general and other to specific phenotypes (Chapman et al., 2003; Gilger et al., 1994; Lewis et al., 1993; Lewitter et al., 1980; Schulte-Körne, 2001a; Wijsman et al., 2000). Therefore, the analysis of multiple features of the component processes specific to dyslexia in linkage studies should facilitate the detection of disease causing genes by reducing the heterogeneity and genetic complexity of the trait. Furthermore, gene-mapping strategies that investigate linkage to quantitative measures of component processes should provide a more powerful tool than strategies only relying on categorical diagnostic criteria, i.e. reading or spelling disorder.

In recent years linkage studies using both, qualitative and quantitative phenotypes, have identified regions likely to contain genes contributing to dyslexia, in particular chromosomal regions 1p36 (Grigorenko et al., 2001; Rabin et al., 1993), 2p11-p16 (Fagerheim et al., 1999; Fisher et al., 2002; Kaminen et al., 2003), 3p12 (Nopola-Hemmi et al., 2001), 6p21 (Cardon et al., 1994; Fisher et al., 1999; Gayan et al., 1999; Grigorenko et al., 1997, 2003; Kaplan et al., 2002), 7q32 (Kaminen et al., 2003), and 15q21 (Chapman et al., 2004; Grigorenko et al., 1997; Marino et al., 2004; Morris et al., 2000; Schulte-Körne et al., 1998). In particular, strong evi-

dence for linkage on chromosomal region 18p11 was observed recently in three large family samples with dyslexia from the UK and USA (Fisher et al., 2002). In the two-point analysis, using the single word-reading measure as phenotypic trait, linkage was strongest in two family sets at STR-marker D18S53. At the same marker strongest evidence for linkage was observed using phonemic-awareness as trait in the second family sample from the UK. The multipoint analysis increased the evidence for linkage on 18p11, pointing to a small chromosomal region at STR-markers D18S464 and D18S53 (Fisher et al., 2002). Based on the NCBI Build 35, both markers are located in close distance to each other, separated by only ~1.5 Mb of genomic DNA (D18S464 at 9.951.258 Mb and D18S53 at 11.482.730 Mb on chromosome 18).

In order to evaluate the region of interest on chromosome 18, we employed a single-proband sib-pair (SPSP) design for linkage analysis of quantitative trait loci (QTL) (Ziegler, 1999; Ziegler et al., 2005). We included 82 dyslexic children with at least one sibling and both parents. In this sample, 14 STR-markers were genotyped, covering approximately a 55 cM (36 Mb) interval on chromosome 18p11-q12.

## Material and methods

### *Ascertainment of the families*

Families with at least two siblings were recruited in the Department of Child and Adolescent Psychiatry and Psychotherapy of the Philipps-University in Marburg and in the Department of Child and Adolescent Psychiatry and Psychotherapy of the Julius-Maximilian University in Würzburg. Potential probands who had difficulty in learning how to spell or had been diagnosed as dyslexic were referred to the investigators by parents, teachers, special educators or practitioners.

Because clinical studies on dyslexia in Germany usually base sample selection on spelling disorder and our previous findings all rest on this selection criterion (see Schulte-Körne et al., 1996, 1998), the probands' spelling ability was selected for inclusion (for diagnos-

tic criterion, see following section). Since a spelling disorder cannot be reliably diagnosed earlier, only children visiting a regular primary school (no special school, i.e. for learning disabled children) at at least the middle of second grade were included in the study. All children were investigated at one of the Departments of Child and Adolescent Psychiatry with standardized and unstandardized tests as described below, and family and medical history was collected.

To exclude families in which the proband or a sibling showed symptoms of ADHD, a standardized clinical interview (Unnewehr et al., 1995) was performed with the mother. Reasons for exclusion of comorbid children with dyslexia and ADHD or siblings with ADHD was firstly that both traits might overlap (Willcutt et al., 2002), and secondly that symptoms of inattention and hyperactivity might influence child behavior on the neuropsychological examinations. Additional exclusionary criteria were a bilingual education, IQ below 85, and an uncorrected peripheral hearing and vision disorder or a psychiatric and neurological disorder influencing the development of reading and spelling ability.

Once a proband was identified, all siblings fulfilling the inclusion criteria were invited to participate. In addition, both parents had to be available for participation.

All participants or, in case of children younger than 14 years, their parents gave written informed consent to study participation. The study was approved by ethics committees of the universities Marburg and Würzburg.

The study sample comprised 82 probands (68% males, age =  $12.07 \pm 2.34$ , IQ =  $109.64 \pm 12.8$ ) and 85 siblings (59% males, age =  $13.27 \pm 3.03$ , IQ =  $110.65 \pm 13.12$ ), as well as their parents.

### *Criteria for dyslexia*

The diagnosis of dyslexia was based on the spelling score using the T distribution of the general population. For inclusion on the trial, the following discrepancy criterion had to be fulfilled by the proband: based on an assumed correlation between the intelligence quotient (IQ) and spelling of 0.4 (Schulte-Körne et al., 1998, 2001), an expected spelling score was estimated. The child was classified as affected if the discrepancy between the expected and the observed spelling score was  $\geq 1 \cdot \sigma$ .

Spelling was measured using age appropriate spelling tests (writing to dictation) that render T scores that are distributed as N(50,100) in unaffected children (Schulte-Körne et al., 2001). The (IQ) was assessed using the Culture Fair Test (CFT-1, Weiß and Osterland, 1997, or CFT-20, Weiß, 1998) depending on the proband's age.

### *Phenotypic measures*

Probands and all siblings fulfilling the inclusion criteria were assessed with several psychometric tests, none of which were administered to the parents. These tests targeted different aspects of the dyslexia phenotype with single word reading, phoneme awareness, phonological decoding, rapid naming, and orthographic coding which have been found to be linked to the chromosome 18 locus (Fisher et al., 2002).

#### *Word reading and phonological decoding*

All probands and their siblings performed a single word and non-word reading test (Salzburger Lese- und Rechtschreibtest, Landerl et al., 1997). This test also renders T scores that are distributed as N(50,100) in unaffected children (Landerl et al., 1997). Because there are no standardized German reading or phonological decoding tests for children at or above the fifth grade, an unstandardized reading test was administered to these children (Schulte-Körne et al., 2004).

This test requires children to read a list of 48 words and 48 pronounceable non-words as accurately and quickly as possible. The depending variables were the number of words and non-words read correctly in one minute. Population data and age corrections were not available for this test.

#### *Phoneme awareness*

Three tests were administered to measure the spectrum of phonological awareness of children from second to fourth grade. The tests were presented aurally and were to respond to orally. They included a phoneme segmentation task, a phoneme deletion task, and a phoneme reversal task. For children from the fifth grade upward, a phoneme segmentation test, a phoneme reversal test, and a phoneme binding and word reversal test were administered.

#### *Orthographic coding*

A pseudohomophone test was administered which assesses the ability to discriminate real words from pseudohomophones. These pseudohomophones were generated by substituting or adding graphemes in a real word resulting in a pseudohomophone that sounds very similar to the real word, but is orthographically wrong. This test is considered to measure orthographic processing because pseudowords and real words sound the same, and the phonological analysis of the word cannot discriminate between them. The children heard single words with headphones at a sound pressure of 70 dB. After this, a word or a pseudoword corresponding to the

word presented auditorily appeared on the computer screen. The subjects were asked to press the right button if the word was a pseudoword, the left button if the word was a real word. Thirty-five words or pseudowords were presented one after another in a pseudorandom order. The number of correct responses (i.e. number of real words which were recognized as correctly spelled, maximally 20) was recorded by the computer. The test was started after four practice trials.

### Rapid naming

The rapid naming test used for this study was developed on the basis of the work of Denckla and Rudel (1974). Four trials, naming objects, number, letters, and colors were conducted. Each trial consisted of items that were arrayed in consecutive rows. Each row consisted of five items which were repeated in a different order for a total of ten rows. The trials were printed on a sheet of paper, and children were asked to read them as quickly as they could without making mistakes. A stopwatch was used to measure the time taken by the child to name all stimuli of the entire list. A practice item was given before starting the tests.

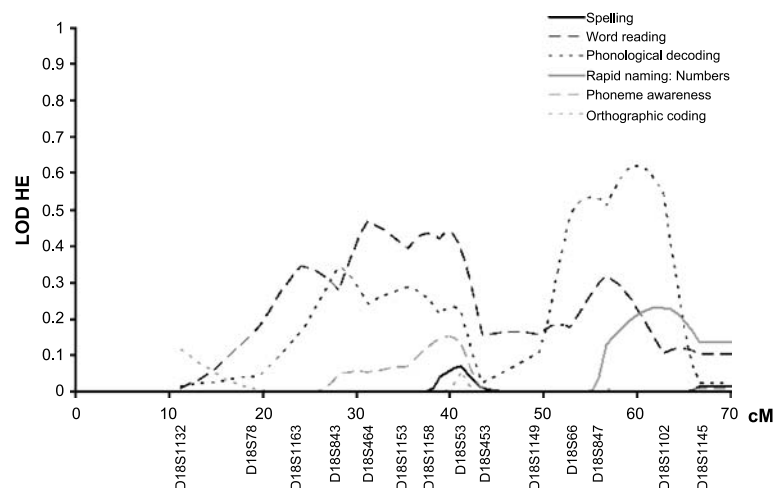
Color naming was measured by rectangles of five different colors (red, green, brown, blue, and black). Each color was presented in a pseudorandom order with the provision that no item appeared twice in succession.

Number naming was measured with 1-digit numbers (7, 2, 9, 6, 4) in the same way as color naming.

Object naming was measured with colored line drawings of common objects (i.e. scissors, candle, comb, clock, key), for letter naming single consonants or vowels (p, s, o, a, d) were presented.

### Genotyping

Data on STR-marker (see Fig. 1) were chosen from GDB (<http://www.gdb.org.gdb/>), marker positions and distances between them were extracted from the Marshfield-map (<http://research.marshfieldclinic.org/genetics/>) and from the UCSC Genome Browser (<http://genome.ucsc.edu/cgi-bin/hgGateway>). Primer pairs were obtained from MWG Biotech (Germany) with the forward primer of each pair labeled with FAM, TET or HEX fluorescent dyes. Polymerase chain reactions (PCRs) were performed in 10 µl reaction volumes containing 80 ng of genomic DNA, 10 pmol of each primer, 1.5 mM MgCl<sub>2</sub>, 4 mM of each dNTP, and 0.8 U Taq DNA polymerase (Gibco). All PCRs were performed on MJ Research thermocyclers with an initial denaturation stage at 95°C for 5 min followed by 30 cycles (30 s at 95°C, 30 s at 50–65°C, 30 s at 72°C) and a final extension step at 72°C for 5 min. Reactions for each marker were performed separately, with products being multiplexed into size-specific sets prior to gel electrophoresis. ROX-labeled molecular weight markers were run in each lane. Markers were typed on an ABI-377 DNA Sequencer using Genescan and Genotyper software (Applied Biosystems). Detailed information on PCR-amplification, genotyping procedure and genotype calling can be obtained on request. Each genotyped marker was checked for Mendelian incompatibilities using a customized version of the program PEDCHECK, Version 1.1 (O'Connell and 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).



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

Allele frequencies were estimated from the sample by allele counting in founder individuals.

### *Statistical analysis*

Age corrections were available for the spelling and IQ tests. Hence, individual values were transformed into age corrected scores. To adjust for age in the other tests, we modelled the relationship between test scores and age by applying fractional polynomials (Royston and Altman, 1994) and used the residuals for further analyses. To improve comparability between tests, the observed scores in all children were linearly transformed so that in the unaffected siblings, they were distributed with mean  $\mu = 50$  and  $\sigma = 10$ .

To analyze linkage of the qualitative affection status dyslexia as described above, we conducted two-point and multipoint analyses using the maximum likelihood binomial (MLB) statistics (Abel and Müller-Myhsok, 1998). In addition, multipoint linkage analyses were carried out with spelling as well as the related phenotypes as quantitative traits using the traditional Haseman-Elston method (Haseman and Elston, 1972).

The analyzed 14 markers span a region of approximately 55 cM with an average inter-marker distance of  $\sim 3$  cM (see Fig. 1, distances according to Haldane map). Thus, we considered a multipoint LOD score  $> 1.50$  as significant evidence of linkage according to Lander and Kruglyak (1995). No adjustments for multiple testing of different phenotypes were carried out in linkage analyses.

## **Results**

Using the qualitative discrepancy criterion for dyslexia, two-point LOD scores were calculated. For markers D18S1132 and D18S78, LOD scores were 0.49 and 0.32, respectively. For all other markers, two-point LOD scores equaled 0. Figure 1 displays multipoint LOD scores of the spelling as well as all related quantitative phenotypes with LOD scores  $> 0$ . Upon use of the quantitative measure for spelling and all other phenotypes, neither LOD score exceeded 0.6. Thus, we failed to detect linkage to chromosome 18p11-q12 in our sample of 82 nuclear families.

## **Discussion**

Recently, Fisher et al. (2002) reported strong evidence for linkage of dyslexia between chromosomal region 18p11 and dyslexia in

three independent family samples from the UK and US. The highest linkage peaks were obtained at STR-markers D18S464 and D18S53, which cover a small region on chromosome 18p11.2. In order to replicate their findings in a German sample, we analyzed a total of 82 sib-pair families with dyslexia using 14 STR-markers, covering a 36 Mb region on chromosome 18p11-q12. Using a battery of component processes as quantitative traits, we were unable to confirm linkage in the two-point or multipoint linkage analyses.

The linkage of single word reading and phoneme awareness to chromosome 18p11 has been reported by the group of Fisher et al. (2002). Their sample was ascertained through probands whose reading ability was impaired relative to their IQ. Although the ascertainment scheme is similar to our own, we defined the phenotype based on spelling disorder. Single word reading and writing to dictation (spelling) have been found to be only moderately correlated, and the common variance of both measures is low (between 25 and 30%, Schulte-Körne, 2001b). Thus, failure to replicate linkage to chromosome 18 may be due to the different phenotype definition.

In addition, we cannot rule out the possibility that the genetic effect was too small to be detected in our sample. Fisher et al. (2002) analyzed 195 sib-pairs from the UK and 180 sib-pairs from the US whereas in our study 82 sib-pairs were available for linkage analyses.

Recently, another study failed to replicate the findings reported by Fisher et al. (2002) (Chapman et al., 2004). Their linkage sample consisted of 111 families with dyslexia and the ascertainment procedure was similar to the ascertainment of the UK study (Fisher et al., 2002). Since the sample size of 111 families is considerably high in order to detect linkage, and the phenotype definition was similar to the phenotype used in the study from Fisher et al. (2002) (single

word reading), we assume – together with our findings – that the putative disease gene on chromosome 18p11 might confer a smaller risk to the development of dyslexia as suggested in the original study (Fisher et al., 2002). In this case, much larger linkage samples would be needed to detect these effects.

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