Further evidence for a susceptibility locus contributing to reading disability on chromosome 15q15–q21

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Background **Linkage and association studies in dyslexia suggest that a susceptibility locus exists on chromosome 15q15–q21.**

Objective **This study aims to evaluate these findings in an independent sample of dyslexia.**

Methods **We performed linkage and association analyses using 82 families with dyslexia and 19 STR markers covering the target region on chromosome 15q.**

Results **We observed suggestive evidence for linkage at STR-marker D15S143; this was the strongest implicated marker in the previous linkage studies on dyslexia. At the association level, linkage disequilibrium (LD) was found between dyslexia and markers within a circumscribed genomic region recently implicated in two independent studies on dyslexia.**

Conclusion **Our data and the previous reported findings present convincing evidence for a dyslexia-related gene within the identified linkage and LD region on chromosome 15q. However, at this stage it seems difficult to determine whether the linkage and association findings point to more than one susceptibility loci within this region. A definite answer to this question will require systematic single nucleotide polymorphism-based LD mapping within the implicated region, which should lead to the identification of the true dyslexia susceptibility gene(s).** ***Psychiatr Genet*** **18:137–142 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Dyslexia (MIM 6002002) is the most frequently diagnosed learning disorder (Lerner, 1989; Schulte-Körne, 2001); affecting 5–12% of school-age children and is associated with major educational, social, and emotional repercussions (Shaywitz *et al.*, 1990; Katusic *et al.*, 2001). The familial nature of dyslexia was recognized when the disorder was first described and has since become well established (Hinshelwood, 1895; Stephenson, 1907; Fisher and DeFries, 2002). Twin studies have shown that the tendency for familial clustering is primarily because of genetic factors rather than shared environment, with heritability estimates ranging up to 0.70 for spelling and 0.50 for reading (DeFries *et al.*, 1987; Stevenson *et al.*, 1987; Olson and Wise, 1994; Gayan and Olson, 2001; Plomin and Kovas, 2005). The core phenotype of dyslexia is characterized by a lower spelling ability, a lower word reading accuracy, and fluency (Dilling *et al.*, 1991). Several cognitive abilities have been found to be correlated with the core symptoms (Gayan and Olson, 2001) and these might characterize dyslexia subtypes (Bates *et al.*, 2007a). These are phonological decoding, phoneme awareness, orthographic processing, and rapid naming (Schulte-Körne *et al.*, 2007). Genetically, it is likely that multiple genes of small-to-moderate effect are involved in the disease process, with some contributing to general and others to specific phenotypic deficits (Lewitter *et al.*, 1980; Lewis *et al.*, 1993; Wijsman *et al.*, 2000; Schulte-Körne, 2001; Chapman *et al.*, 2003).

Despite the most recent and promising association findings within a dyslexia linkage region on 6p22 (Deffenbacher *et al.*, 2004; Francks *et al.*, 2004; Cope *et al.*, 2005; Meng *et al.*, 2005; Schumacher *et al.*, 2006a), nine other chromosomal regions likely to contain dyslexia genes were suggested through replicated linkage studies and have been listed by the Human Gene Nomenclature Committee (reviewed by Schumacher *et al.*, 2007). Of

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these loci, DYX1 on chromosome 15q15–q21 must be considered as one of the most implicated candidate regions, as several independent studies report on evidence for linkage as well as association within this region (Smith *et al.*, 1983; Grigorenko *et al.*, 1997; Schulte-Körne *et al.*, 1998; Morris *et al.*, 2000; Chapman *et al.*, 2004; Marino *et al.*, 2004; Bates *et al.*, 2007b). According to NCBI Build 36, DYX1 spans 15.9 Mb between STR markers D15S146 (39.7 cM) and D15S121 (47.8 cM). Within this region, a genomic interval covering five adjacent STR markers – D15S146, D15S214, D15S994, D15S508, and D15S182 – showed association in two independent studies using word reading and phonological decoding as dyslexia phenotype (Morris *et al.*, 2000; Marino *et al.*, 2004), whereas a region surrounding STR markers D15S132 and D15S143 was most strongly implicated by linkage studies using spelling disorder as a component of the dyslexia phenotype (Grigorenko *et al.*, 1997; Schulte-Körne *et al.*, 1998).

In this study we aimed to evaluate the region of interest on chromosome 15 in an independent dyslexia sample of German descent and employed a single-proband sib-pair design for linkage and association analysis of quantitative trait loci (QTL) (Ziegler *et al.*, 2005; Schulte-Körne *et al.* 2007; Schumacher *et al.*, 2006b). We included 82 dyslexic children with at least one affected sibling and both parents. In total, we genotyped 19 STR markers covering the whole DYX1 interval and, thereby, focused on both genomic intervals with strongest evidence for linkage and association (Grigorenko *et al.*, 1997; Schulte-Körne *et al.*, 1998; Morris *et al.*, 2000; Chapman *et al.*, 2004; Marino *et al.*, 2004).

Materials and methods

Ascertainment of the families, diagnostic criteria, and phenotypic measures

In a German bicenter study, families with at least one affected child were recruited in the Departments of Child and Adolescent Psychiatry and Psychotherapy at the Universities of Marburg and Würzburg. These families are part of a larger study (Schumacher *et al.*, 2006a; Schulte-Körne *et al.*, 2007). All individuals, and in the case of children younger than 14 years their parents gave written informed consent for participation in the study. The study was approved by the ethics committees of the Universities Marburg and Würzburg.

From our family sample 82 families with at least two affected siblings were selected for this study. The sample characteristics were as follows: 82 affected probands [68% males, mean age = 12.07 ± 2.34, mean intelligence quotient (IQ) = 109.64 ± 12.8] and 85 affected siblings (59% males, mean age = 13.27 ± 3.03, mean IQ = 110.65 ± 13.12), as well as their parents (a total 331 individuals). The diagnostic inclusion criteria and phenotypic measures have been described in detail (Schumacher *et al.*, 2006a; Schulte-Körne *et al.*, 2007) and are given briefly: the diagnosis of dyslexia was based on the spelling score using the T distribution of the general population. For the diagnosis of dyslexia, the child had to meet the following discrepancy criterion: on the basis of 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 dyslexic if the discrepancy between the anticipated and the observed spelling score was of at least one standard deviation.

In addition, probands and all siblings fulfilling the inclusion criteria were assessed with several psychometric tests. These tests targeted different aspects of the dyslexia phenotype, with word reading, phoneme awareness, phonological decoding, rapid naming, and orthographic coding.

Word reading

Among all additional assessed phenotypes, reading disability was of particular interest in studying chromosome 15, as strong DYX1 association has been found using this dyslexia component (Morris *et al.*, 2000; Marino *et al.*, 2004). Within our sample, word reading was assessed as follows: all probands and their siblings performed a single word and nonword 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). As there are no standardized German reading tests for children at or above the fifth grade, an unstandardized reading test was administered to these children (Schumacher *et al.*, 2006b). This test requires children to read a list of 48 words and 48 pronounceable nonwords as accurately and quickly as possible. The dependent variables were the number of words and nonwords read correctly in one minute. Population data and age corrections were not available for this test.

Genotyping

In total, 19 STR markers spanning the DYX1 region (between D15S1031 and D15S1036) were chosen from the Human Genome Database. Marker positions and distances between them were extracted from the Marshfield map and from the UCSC Genome Browser. Primer pairs were obtained from MWG Biotech (Edersberg, Germany) with the forward primer of each pair labeled with fluorescent dyes. Polymerase chain reactions (PCRs) were performed using MJ Research thermocyclers (Global Medical Instrumentation Inc., Ramsey, Minnesota, USA). The amplified markers were typed on an ABI-377 DNA sequencer (Applied Biosystems, Foster City, California, USA) 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). 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 among tests, the observed scores in all children were linearly transformed so that in the unaffected siblings they were distributed with mean $\sigma = 50$ and $\sigma = 10$. To analyze the linkage of the qualitative affection status of dyslexia as described above, we conducted two-point and multipoint analyses using the maximum likelihood binomial 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). On the genomic level, the analyzed markers span a region of 35.79 cM with an average intermarker distance of $\sim$1.88 cM. We therefore considered a two-point logarithm of the odds (LOD) score of more than 1.32 as significant evidence of linkage according to Lander and Kruglyak (Lander and Kruglyak, 1995). Associations for quantitative traits were tested using the method of Rabinowitz as implemented in quantitative transmission/disequilibrium test (Monks and Kaplan, 2000) based on 10 000 permutations. Haplotype analysis was done using quantitative pedigree disequilibrium test PHASE (Dudbridge, 2003). No adjustments for multiple testing of different phenotypes were carried out in linkage or association analyses.

Results

At the linkage level, we obtained the strongest linkage signals using spelling disorder as phenotypic trait. Three markers fulfilled the criteria for suggestive evidence for linkage. Two of them, D15S143 and D15S1032, are located at 45.62 cM and two-point LOD scores of 1.31 and 0.99 were observed (Table 1). For the third STR-marker, D15S182, a two-point LOD-score of 1.24 was found; D15S182 is located at 40.25 cM according to the Marshfield Map (Table 1) and maps within the region, for which we observe strong association evidence (see below and Table 2). For all other markers, two-point LOD scores were below the threshold for suggestive linkage evidence. In addition, no linkage evidence was observed using the word reading, phonological decoding, phonological awareness, rapid naming, and orthographic processing (data not shown).

Table 1 Two-point linkage analysis using spelling disorder as phenotypic trait

STR-marker	Genetic position (Marshfield map) (cM)	Cytogenetic band	Two-point LOD-Scores
D15S1031	21.58	15q13.3	0
D15S971	31.46	15q14	0.226
D15S1012	35.95	15q14	0.092
D15S641	39.72	15q15.1	0.646
D15S146	39.72	15q15.1	0.668
D15S214	40.25	15q15.1	0.229
D15S994	40.25	15q15.1	0.128
AFM196XB8	40.25	15q15.1	0.542
D15S508	40.25	15q15.1	0.019
D15S182	40.25	15q15.3	**1.246**
AFM189XG5	41.86	15q21.1	0.456
D15S659	43.47	15q21.1	0.179
D15S132	44.90	15q21.1	0.312
D15S143	45.62	15q21.1	**1.310**
D15S1028	45.62	15q21.1	0.057
D15S1032	45.62	15q21.2	**0.995**
D15S1016	47.29	15q21.3	0.874
D15S117	51.21	15q22.1	0.103
D15S1036	57.37	15q22.2	0.262

In bold, two-point LOD-Scores are given exceeding the threshold of suggestive linkage evidence.
LOD, 'logarithm of the odds'?

At the association level, we observed the strongest and most consistent LD pattern with word reading. Within the same interval on chromosome 15q15, where Morris *et al.* (2000) and Marino *et al.* (2004) previously reported an association with reading disability), alleles of three STR markers were significantly under-transmitted to the probands (Table 2). The most significant association result was obtained for AFM189XG5 ($P = 0.0003$). In addition, alleles of two adjacent STR markers within the previously described LD region showed a significant over-transmission to the probands (Table 2). The strongest LD was observed for allele 7 at AFM196XB8 ($P = 0.004$, Table 2). The haplotype analysis supported our association results. Again, using the word reading as trait, four 2-marker haplotypes appeared to be significantly under-transmitted to the offspring (Table 2). Three of them showed overlapping association pointing to an under-transmitted haplotype 6-3-6-4 at a marker combination AFM196XB8-D15S508-D15S182-AFM189XG5 (Table 2). Consistent with the single-marker analysis, haplotypes 8-3 at D15S994-D15S641, 3-7 at D15S641-AFM196XB8 and 7-2 at AFM196XB8-D15S508 were significantly over-transmitted to the probands with reading disability (Table 2), pointing to an over-transmission of haplotype 8-3-7-2 at D15S994-D15S641-AFM196XB8-D15S508. Although the three most associated alleles and markers for reading disability also produced significant results using the spelling phenotype (Table 2), all other components of the phenotypic dyslexia spectrum failed to produce a consistent association picture within the DYX1 LD region (data not shown).

Table 2 Single marker and haplotype association analysis using word reading as phenotypic trait

STR-marker	D15S146	D15S214	D15S994[a]	D15S641	AFM196XB8[a]	D15S508	D15S182	AFM189XG5[a]	D15S659		
Physical position (build 36)	37 911 333	38 187 526	38 369 344	39 631 200	40 418 751	41 365 306	42 253 500	43 232 871	44 161 167		
Cytogenetic band	15q15.1	15q15.1	15q15.1	15q15.1	15q15.1	15q15.1	15q15.3	15q21.1	15q21.1		
Single marker analysis (associated allele *P* values)											
Alleles associated with lower phenotype values		7 ($P=0.041$)	6 ($P=0.008$)[a]					4 ($P=0.0003$)[a]			
Alleles associated with higher phenotype values			8 ($P=0.048$)		7 ($P=0.004$)[a]						
2-marker sliding window haplotype analysis (associated alleles)										*P* value	Global *P* value
Haplotypes associated with lower phenotype values		3	6		6	3				0.029	
						3	6			0.005	0.022
							6	4		0.013	
										0.039	0.036
Haplotypes associated with higher phenotype values			8	3						0.031	
				3	7					0.006	0.015
					7	2				0.015	0.022

[a]STR-markers and alleles, which showed also positive association using spelling disorder as phenotypic trait; D15S994, under-transmission of allele 6 ($P=0.013$); AFM196XB8, over-transmission of allele 7 ($P=0.028$); AFM189XG5, under-transmission of allele 4 ($P=0.002$).

Discussion

In this study, 19 STR markers covering the DYX1 locus were genotyped in a sample of at least 82 dyslexic siblings and both parents, all of German descent. These families represent an independent sample compared with our multiplex families, for which we have previously reported DYX1 linkage evidence (Schulte-Körne *et al.*, 1998). At the linkage level, we obtained the strongest results using spelling disorder as phenotypic trait. The highest two-point LOD score of 1.31 was found at STR marker D15S143. Although in itself it is not sufficient to claim significant evidence for linkage (defined by a two-point LOD score of ≥ 1.32), Grigorenko *et al.* (1997), Schulte-Körne *et al.* (1998), and Chapman *et al.* (2004) obtained their strongest linkage results – LOD scores of 3.15, 1.78, and 2.34 – at exactly the same STR marker, D15S143. Therefore, our sample represents the fourth sample pointing to a susceptibility gene for dyslexia near marker D15S143. Close to this finding, we observed an association within a 5-Mb region on DYX1 using word reading as phenotypic trait. This finding corresponds exactly with the association results, which were previously reported in this region. Morris *et al.* (2000) performed a two-stage association study using reading disability as a phenotypic trait and observed an association with D15S994 in their initial sample (101 triads of UK origin). Although they failed to replicate this finding in the second sample of 77 UK triads, the three-marker haplotype D15S146-D15S214-D15S994 was significantly associated in both samples (initial sample: global *P* value of 0.03, replication sample: global *P* value of 0.006). Although we found an association at two of these markers in the single marker analysis, we failed to observe an association at the haplotypic level ($P = 0.070$ for haplotype 5-3-6 at D15S146-D15S214-D15S994). A second study used a sample of 121 Italian triads with reading disability and observed significant association at the STR marker D15S214 ($P = 0.03$; Marino *et al.*, 2004). By performing haplotype analysis, they found an association with the three-marker haplotype D15S214-D15S508-D15S182 (global *P* value of 0.005). Compared with our allele destination, they observed the haplotypes 6-3-6 ($P = 0.020$) and 6-2-7 ($P = 0.016$) to be under-transmitted, whereas the haplotype 3-3-7 ($P = 0.04$) appeared to be over-transmitted to the affected offspring (Marino *et al.*, 2004). By testing this haplotype combination we found the haplotypes 3-3-6 ($P = 0.043$) and 7-3-6 ($P = 0.020$) to be under-transmitted to our affected probands. Given that the distance between D15S214 and D15S508 is 3.1 Mb, one could speculate that population-specific recombination events occurred between both markers resulting in different under-transmitted alleles at D15S214. In contrast, D15S508 and D15S182 are separated by only 0.88 Mb, and the same haplotype, namely 3-6, is under-transmitted to the affected offspring in the Marino *et al.* (2004) and our study. Together with the significant association results we observed using additional markers, our data produced evidence for a gene related to lower word reading ability within this identified LD region. The fact that we failed to find positive linkage signals within this region using word reading is not conflicting in this context and must be attributed to the power restrictions of linkage analysis.

Another study has reported a positive association with dyslexia using markers on chromosome 15q21. In a Finnish case–control sample Taipale *et al.* (2003) found significant association at the single marker and haplotype level analyzing eight single nucleotide polymorphism markers within the gene DYX1C1. However, the results of the six following association studies using independent dyslexia samples of predominantly European origin and single nucleotide polymorphisms at the DYX1C1 locus must be viewed as being negative (see review Schumacher *et al.*, 2007). DYX1C1 lies at 53.5 Mb on 15q21 and outside of the previously observed DYX1 linkage peaks.

Our analyzed markers in this study were therefore not selected covering the DYX1C1 locus. The closest markers were D15S1016 (at 51.3 Mb) and D15S117 (at 56.2 Mb), which both produced negative association results in this study. However, on the basis of the distance between these STRs and DYX1C1 it is difficult to determine if our results represent a negative replication of the Taipale *et al.* study.

In conclusion, our association results point to a susceptibility gene mainly for the dyslexia component of word reading located in the same 5 Mb region, which was previously implicated in this dyslexia phenotype (Morris *et al.*, 2000; Marino *et al.*, 2004). According to the UCSC RefSeq Genes track, which assembles all known protein-coding genes taken from the NCBI mRNA reference sequences collection (RefSeq), this genomic interval contains at least 70 genes, several of which are known to be expressed in the central nervous system. On the basis of our results and on the findings previously reported, the identified LD region on DYX1 must be considered as one of the most promising locus for systematic LD association studies at present in the field of dyslexia genetic research.

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Web Resources

The URL for data in this article is as follows:

Human Gene Nomenclature Committee: *http://www.gene.ucl.ac.uk/nomenclature/*
Human Genome Database (GDB): *http://www.gdb.org.gdb/*
Marshfield-map: *http://research.marshfieldclinic.org/genetics/*
NCBI Online Mendelian Inheritance in Man (OMIM): *http://www.ncbi.nlm.nih.gov/Omim*
UCSC Genome Browser: *http://genome.ucsc.edu/*

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