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0002-9297/98/6301-0042$02.00

Am. J. Hum. Genet. 63:279–282, 1998

Evidence for Linkage of Spelling Disability to Chromosome 15

To the Editor:

Dyslexia (reading and spelling disability) is one of the most frequently diagnosed disorders in childhood. It is generally agreed that dyslexia has a substantial genetic contribution, although the exact mode of inheritance remains obscure. The phenotype of dyslexia is complex, and different phenotype dimensions can be distinguished. In the *Journal,* Grigorenko et al. (1997) recently reported linkage for distinct components of dyslexia to chromosomes 6 and 15: the phonological-awareness phenotype was mapped to chromosome 6p21-p22, and the single word–reading phenotype was assigned to chromosome 15q21. The chromosome 6 linkage of phonological awareness was supported by multipoint affected-pedigree-member analysis using markers D6S109, D6S461, D6S299, D6S464, and D6S306. With chromosome 15 markers and the single word–reading phenotype, a LOD score of 3.15 was obtained for marker D15S143 at a recombination fraction (θ) of 0, under an autosomal dominant–inheritance model.

We conducted a linkage study for another component of dyslexia—namely, spelling disability—in seven multiplex families from Germany. Twin studies of dyslexia

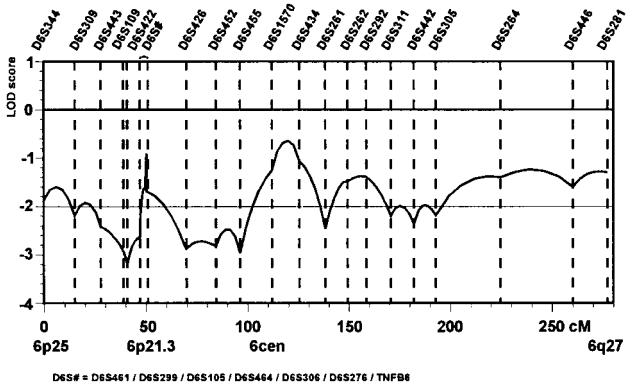

Figure 1 Graphic representation of parametric multipoint linkage analysis of chromosome 6 markers and spelling disability.

have indicated that deficits in spelling are substantially heritable and that the heritability of spelling deficits is higher than the heritability of reading deficits (Stevenson et al. 1987; DeFries et al. 1991). In the families in our study, we genotyped 26 microsatellite markers covering the entirety of chromosome 6 and 13 microsatellite markers covering the entirety of chromosome 15. The highest density of markers was in the regions where Grigorenko et al. (1997) had obtained positive results.

Seven families were chosen from our study sample (Schulte-Körne et al. 1996). Selection criteria were an extended family history of spelling disability and a pedigree suggestive of autosomal dominant transmission (e.g., a three-generational history of familial spelling problems). Diagnosis was based on psychometric tests (IQ test and spelling test) and on a questionnaire (Schulte-Körne et al. 1997). For children to grade 6, the spelling test required the spelling of 30–40 words with specific difficulties with regard to German spelling rules and the German language. For children beyond grade 6 and for adults, a standardized German word–recognition test (Jäger and Jundt 1981) was administered. The nonverbal Culture Fair Intelligence Test (CFT) (Weiß and Osterland 1977; Weiß 1987) was chosen as intelligence test, in order to reduce the influence of verbal abilities and cultural and educational influences on IQ-test performance. Individuals were classified as affected either if their actual spelling achievement (percentile rank as measured by the spelling test) was $\geqslant 1$ SD below the expected spelling achievement based on IQ or if, on the basis of the questionnaire data (adults only; $n = 9$), they had a history of spelling disorder. This definition includes compensated adults (those with a history of spelling disorder but with a discrepancy <1 SD).

Expected spelling achievement was computed by use of a regression model (spelling on IQ) with an assumed .42 correlation between the two measures (Glogauer 1977). The regression equation was derived from a large normative German sample that was independent from our sample. The underlying regression equation is as follows: spelling (T-norm) .42 × (SD IQ/SD spelling) × (IQ − 100) + residual (Schulte-Körne et al. 1996).

After informed consent had been obtained, EDTA blood samples were collected from 67 family members. Of these, 51 were classified as affected. Lymphocyte DNA was extracted by standard methods. Microsatellite markers were typed by use of a model 377 Applied Biosystems automatic sequencer.

Parametric two-point linkage analysis was performed with the LINKAGE package (Lathrop et al. 1984). Parametric and nonparametric multipoint linkage analyses were performed with the GENEHUNTER program (Kruglyak et al. 1996). The *P* values were based on an exact test as described by Kruglyak et al. (1996). For the parametric analyses, the following assumptions were made: autosomal dominant inheritance, disease penetrance .91, phenocopy rate .11, and disease-allele frequency .0298.

On chromosome 6, no significant evidence for linkage was obtained. None of the two-point LOD scores was >0.24 (results not shown). The parametric multipoint analysis showed negative results over the entirety of chromosome 6 (fig. 1). A maximum multipoint LOD score of −0.64 was observed between D6S1570 and D6S434 on the long arm of chromosome 6. A second relative peak, of −0.95, was observed between D6S105 and D6S464 at 6p22-p21. Nonparametric analysis also failed to reveal significant evidence for linkage. The maximum multipoint LOD score peaked at 0.39 ($P = .30$) between D6S1570 and D6S434 and at 0.70 ($P = .21$) between D6S105 and D6S464. Although the data for chromosome 6 were negative, results for chromosome 15 markers supported a locus on 15q21. The two-point LOD scores for spelling disability and markers on chromosome 15q are shown in table 1. The highest two-point LOD score was 1.26 with marker D15S143, at $\theta = 0$. A multipoint LOD score of 1.78 ($P = .0042$) was

Table 1

Results of Two-Point Linkage for Chromosome 15 Markers

	LOD Score at θ =			
Marker	0	.01	.05	.1
D15S214	−.43	−.36	−.15	.01
D15S132	.44	.46	.49	.46
D15S143	1.26	1.23	1.09	.88
D15S126	−.03	.03	.17	.24
D15S117	-1.13	−.97	−.51	-0.17

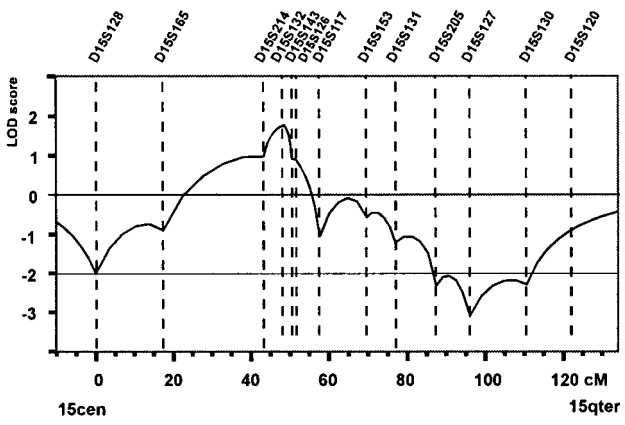

Figure 2 Graphic representation of parametric multipoint linkage analysis of chromosome 15 markers and spelling disability.

achieved with a maximum multipoint LOD score at D15S132 (fig. 2). Linkage to chromosome 15 was also supported by nonparametric analysis. The multipoint maximum LOD score peaked at 2.19 ($P = .03$) at marker D15143.

Our results confirm those of Grigorenko et al. (1997), supporting linkage between chromosome 15q21 markers and dyslexia. The P value of .0042, equivalent to the LOD score of 1.78, obtained in the multipoint LOD-score analysis meets the criteria for confirmation of linkage (Lander and Kruglyak 1995). Given that a third independent study (Smith et al. 1991) had shown linkage of dyslexia to the same chromosomal region, this locus might be considered an established locus for the disorder. The convergence of our results and the findings by Smith et al. (1991) and Grigorenko et al. (1997) is especially interesting, considering that different phenotype definitions were applied. However, spelling and reading disability are strongly correlated ($r = .50 - .80$) (Malmquist 1958), and the results suggest that at least some of the shared variance is responsible for linkage of both phenotypes to chromosome 15. In our study, we found no convincing evidence for linkage of spelling disability to markers on chromosome 6. Although phonological awareness and spelling disability are also moderately correlated ($r = .55$; authors' unpublished data), our results are at least suggestive of the possibility that the shared variance probably is not responsible for the linkage to chromosome 6. However, if the gene residing on chromosome 6 has only a minor effect on spelling disability, then our sample size might have been too small for detection of such an effect. The latter explanation might be supported by a previous study of reading disability, in which evidence for quantitative-trait loci on chromosome 6p21.3 was revealed in a large sample of sib pairs (Cardon et al. 1994). Interestingly, our own results show a relative peak in the same region of chromosome 6.

In conclusion, our results do not support a strong effect by a putative chromosome 6 dyslexia gene on the phenotype of spelling disability. However, we present independent evidence in support of a dyslexia gene on chromosome 15q21. This gene seems to be relevant for spelling (our results) as well as for word reading (Smith et al. 1991; Grigorenko et al. 1997).

Acknowledgments

We are extremely grateful to the families who participated in this work. We appreciate the assistance of Katarina Müller and Wolfgang Deimel (Marburg). This work was supported by Deutsche Forschungsgemeinschaft grants Re 471/9-1 and Schu 988/2-1//2-3.

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