Linkage of Speech Sound Disorder to Dyslexia Candidate Regions

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ABSTRACT

Speech Sound Disorder (SSD) is a developmental disability in learning to produce intelligible speech, noted in the preschool years. In contrast, specific reading disability (dyslexia) is diagnosed at school age and involves difficulty learning to read and spell. SSD has been conceptualized as primarily a motor disorder, while in the majority of cases the core deficit of dyslexia is in the ability to recognize phonemes of language and map them on to letters. Despite these apparent differences, it has been observed that SSD and dyslexia cosegregate, suggesting that they may have common cognitive and genetic etiologies. Sixty-nine families were identified with at least one child between the ages of 5-6 years with a history of moderate to severe SSD, and one sib between the ages of 5-8 years who could be evaluated. Five phenotypes were used, 4 quantitative variables assessing speech sound and phonologic abilities and one categorical phenotype that assigned affection status based on clinical history. Sib-pair linkage analysis was done with markers from 3 chromosomal regions previously linked with dyslexia: 1p36, 6p21.3, and 15q21. Single point analysis was done with SIBPAL (SAGE 4.4), with GENEHUNTER2 and QMS2 used for multipoint analysis. All three regions showed some indication of linkage with SSD phenotypes. The strongest results were for single point analysis of the categorical phenotype and 6p21.3, with highest significance at D6S1571 (p=0.00051). Multipoint analyses (QMS2) were suggestive for 3 of the quantitative phenotypes (p values ranging from 0.02-0.004). For chromosome 15, suggestive results were found for markers including and distal to D15S143, with maximum significance of 0.004 at D15S117 for single point analysis of a standardized articulation test. Suggestive multipoint results (GENEHUNTER2) were also found on chromosome 1 for a nonword repetition test, with a maximum NPL of 1.07 at D1S199. These results support the hypothesis that both dyslexia and SSD share common genetic mechanisms involving phonologic processing. *Supported by NIH-NICHD 2 R01 MH38820 to BFP.*

METHODS

Kindergarten children (between 5-7 years old) with moderate to severe speech sound disorder (SSD) were ascertained through schools and advertisements in Denver. Siblings between 5-8 years old were also recruited regardless of speech characteristics Exclusionary criteria included cognitive, medical or neurosensory problems which would impact speech, and all children were native English speakers. Parents of all subjects gave consent and children gave assent under the approval of IRBs from the University of Denver and the University of Nebraska Medical Center.

Diagnosis was verified by a battery of standardized clinical tests. Phenotypes for linkage analysis included:

- Affected status (DX: based on clinical tests and history)
- Goldman-Fristoe Test of Articulation (GF: quantitative score)
- Shriberg's PCC-R (percent of phonemes correctly articulated)

Two measures of phonologic skills integral to reading were also analyzed:

- Phoneme Awareness (PA: ability to recognize and manipulate speech sounds)
- Non-word Repetition (NW: ability to recall and produce nonsense words)

To determine if there may be genes which influence both reading disability and SSD, buccal samples were obtained for DNA extraction and children and parents were genotyped for microsatellite markers spanning 3 regions suspected to contain genes influencing reading disability: 1p36, 6p21.3, and 15q21. Single- and multi-point sib-pair linkage analysis was done using both regression-based and maximum likelihood methods:

- New Haseman Elston (NHES): single-point regression in SIBPAL, S.A.G.E. 4.4.
- New Haseman Elston (NHEM): multipoint regression from QMS2
- Nonparametric LOD (NPL): multipoint maximum likelihood from GENEHUNTER 2

These approaches compare the sensitivity of multipoint methods, which can increase the informativeness of adjacent markers, with single point methods which are less susceptible to errors in distance estimation or genotyping. Diagnosis was treated as a dichotomous trait, and the other 4 phenotypes were treated as quantitative traits.

RESULTS

This table summarizes the maximum linkage results that were obtained for each marker. Multipoint analyses are also shown graphically for the most significant phenotypes.

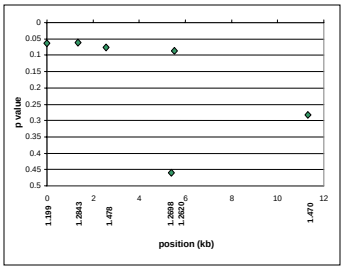
Region	Marker	Phenotype	Analysis	Peak p/LOD
1p36	D1S199	NW	NHES	p=0.06344
	D1S199	NW	GH2	LOD=1.0719
	D1S2843	NW	NHES	p=0.06178
6p21.3	D6S1605	DX	GH2	p=0.04411
	D6S1605	PA	GH2	LOD=1.0059
	D6S1558	GF	NHES	p=0.01270
	D6S1588	GF	NHEM	p=0.00382
	D6S1567-D6S1588	PA	GH2	LOD=1.164649
	D6S1571	DX	NHES	p=0.00051*
	D6S105	GF	NHEM	p=0.02733
	MOG	DX	GH2	p=0.04042
	D6S273	GF	NHEM	p=0.02676
15q21	D15S143	GF	NHES	p=0.02940
	D15S143	GF	NHEM	p=0.03457
	D15S994-D15S1028	GF	GH2	LOD=1.30186
	D15S978-D15S1029	NW	NHEM	p=0.011671
	D15S1029	GF	NHES	p=0.008726
	D15S117	GF	NHES	p=0.004673
	D15S1017-D15S117	GF	GH2	LOD=1.92563

*(maximum significance; all other markers except D6S258 showed p<0.05)

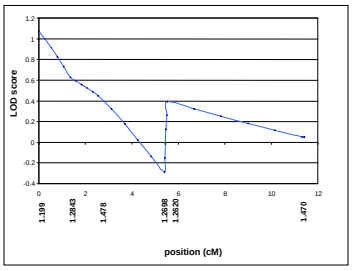
Chromosome 1p36

Linkage of markers in this region, particularly D1S199, has been reported for dyslexia, particularly with a Phonological Decoding (nonword reading) phenotype[1,2]. Results are shown for single point analysis with the New Haseman Elston procedure and NPL multipoint analysis with GENEHUNTER2 with the Nonword Repetition phenotype. Although linkage is not strong, a LOD score over 1.0 indicates replication of the dyslexia linkage.

Chromosome 1: Nonword Repetition, Single point (NHE)



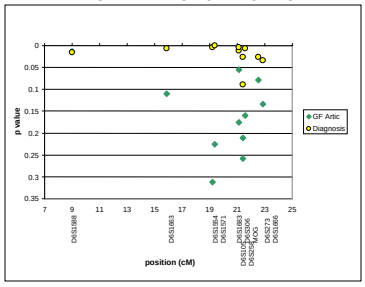
Chromosome 1: Nonword Repetition, Multipoint (GH2)



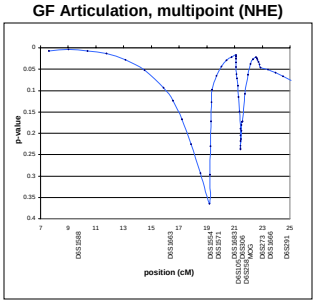
Chromosome 6p21.3

This region has shown both linkage and association to dyslexia phenotypes in several independent studies[1,3,4,5] (see Poster 1919). The most likely region of linkage for dyslexia is between markers D6S1597-D6S1571, peaking at D6S1554. Results with SSD phenotypes are similar, particularly with regression-based methods. Interestingly, analyses of dyslexia have also shown two peaks in some studies. Selection of families for increased severity (at least 1 SD below the mean) increased the significance of the linkage for the GF Articulation phenotype slightly (e.g., for D6S1558, p=0.0018). Such selection also results in increased evidence for chromosome 6 linkage in our families with dyslexia.

Chromosome 6: GF Articulation, single point (NHE) Diagnosis, single point (NHE)



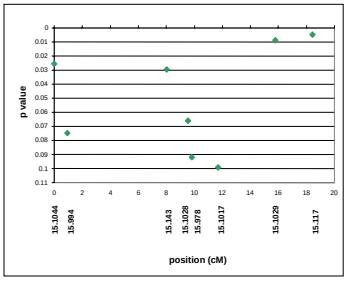
Chromosome 6: GF Articulation, multipoint (NHE)



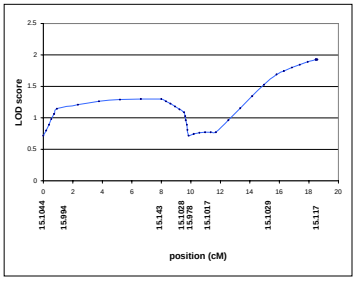
Chromosome 15q21

Linkage and association of dyslexia with chromosome 15q markers has been observed in several studies[1,6,7] and recently a candidate gene has been identified[8] (see presentation 111). The studies by Grigorenko et al. showed significant results with D15S143, while the candidate gene, identified through a translocation family, is distal to that marker. The region of linkage seen with SSD starts at D15S143 and continues distally.

Chromosome 15: Nonword Repetition, single point (NHE)



Chromosome 15: GF Articulation, multipoint (GH2)



CONCLUSIONS

The Speech Sound Disorder phenotypes show evidence of linkage to the candidate regions for dyslexia. This could indicate that the same genes influence both disorders. The possibility of separate but linked genes cannot be ruled out, although it seems unlikely that such groups of genes would be present in all 3 regions. A more parsimonious explanation is that dyslexia and speech sound disorder share neurological functions that are disrupted by genes in these regions.

- These results are consistent with the hypothesis that both disorders have a phonologic basis. Further studies will be needed to determine the genetic and/or environmental factors that result in SSD in some families, with others showing more reading problems.

- These same regions have *not* been implicated in specific language impairment (SLI)[9], which also shows comorbidity with SSD and RD, suggesting that there are additional genetic influences on these disorders.

References

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