

ASSOCIATION OF SPECIFIC LANGUAGE IMPAIRMENT WITH LOCI AT 7q3

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Specific Language Impairment (SLI)

Among children with developmental forms of spoken language impairment are those who have normal hearing, no signs of other developmental impairments such as mental retardation, autism, or cerebral palsy, and who have been provided with ordinary rearing experiences. These children present specific language impairment (SLI). They are common in the case loads of speech-language clinicians and are found in disproportionate numbers of programs for children with academic and behavior disorders (Beitchman et al., 1989; Bishop & Adams, 1990; Catts & Kamhi, 1991; Cantwell & Baker, 1991; Stark & Tallal, 1988). Children with specific language impairment present no dysmorphic features, known organ function differences, chromosomal, or genetic markers that allow a diagnosis that is independent of language

Limitations in spoken language development

Children with SLI have been traditionally diagnosed based upon their performance on their performance on standardized measures of expressive and receptive vocabulary, sentence structure, and discourse. Tomblin, et al. (1996) proposed the diagnostic standard for SLI of two spoken language test scores at or below the 10th %ile.

Limitations in phonological memory

Recently, a measure of phonological memory requiring repetition of words varying in length has been found to be highly predictive of clinical diagnoses of SLI (Dollaghan & Campbell, 1998) and Bishop, North, and Donlan (1996) have found high levels of heritabilities for this trait.

Familial Liability for SLI

Several studies have demonstrated that first degree relatives of children with SLI are significantly more likely to have speech, and spoken and written language impairment than relatives of controls without SLI.

Family History Studies

Several of these studies have used the family history method. These studies have found between 20-42% of the first degree relative were affected ($M=28\%$). Relative risk for these family members compared with control families was between 4 and 9.

Family Study

One study has directly examined for SLI in the family members of 48 families ascertained through an affected child (Tomblin & Buckwalter, 1996). These investigators found 22% first degree (29% males, 13% females) were affected with similar rates between the two generations. A segregation analysis (Tomblin & Zhang, In Press) of these pedigrees rejected the hypothesis of no transmission and supported the hypothesis concerning dominance. The hypothesis of no polygenic transmission was not rejected, however, the chi-square was close to a significance level of .05. The hypothesis of a major locus was supported, however, the hypothesis of Mendelian transmission was rejected. These results would suggest a complex mode of transmission.

Twin Studies

The family studies provide evidence of familial aggregation for SLI. Two twin studies (Bishop, North, and Donlan (1995) and Tomblin, Buckwalter, and Zhang (1998) have provided heritability estimates ranging from 45-.77. Thus, these studies suggest that the familial aggregation is substantially genetically influenced.

Linkage of SLI to 7q31 (Fisher et al. 1998)

Pedigree and Phenotype

There has been only one study employing molecular genetic methods to test for linkage or association of loci with SLI. Fisher et al. (1998) have studied a British family that contained 35 family members, 15 of whom were considered to be affected. The phenotype used in this study was not well described by these authors. The affected members were described as having dyspraxia (an impairment of speech planning), impairments of spoken and written language, and some instances of intellectual impairment. Crago and Gopnik (1991) have also described some of these family members as having particular difficulties with the acquisition and use of grammatical rules.

Linkage

A genome wide search resulted in the identification of a 5.6 -cM region of 7q31 that was linked (LOD=6.62 at $\alpha=0.0$) to the speech and language disorder. This locus was named SPCH1. These results provide the first evidence of a region linked to an SLI phenotype. Additional work is needed due to the ambiguity of the phenotype, and the limitation of this study to one kindred. The linkage to the 7q31 region provides an opportunity to examine candidate loci in this region using association methods with samples of SLI cases and normal language control children.

Purpose of Current Study

Use candidate markers in the regions of 7q31 to test the association of spoken language, phonological memory, reading, and speech to this region.

- Can results from the KE family generalize to European decedents in the U.S population?
- Which aspects of this complex phenotype appear to be associated with this region?

Method

Study Sample and Phenotype

Participants

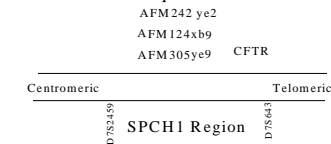
434 2nd grade children participating in a longitudinal study of spoken and written language.

Phenotypes

- Spoken language status in kindergarten or 2nd grade
- Phonological memory
- Reading status in 2nd grade
- Speech sound production in kindergarten

Candidate Loci

Chromosome 7q31 Markers Used



| Locus | Phenotype | Number of Children and Parents Genotyped at Each Locus | | | | | |
|------------|--------------|--|---------|--------|---------|--------|---------|
| | | Child | | Father | | Mother | |
| | | Case | Control | Case | Control | Case | Control |
| AFM 242ye3 | Spoken Lang | 30 | 50 | 17 | 21 | 20 | 33 |
| | Word Recog | 22 | 58 | 15 | 23 | 16 | 37 |
| | Non word Rep | 15 | 65 | 11 | 27 | 10 | 43 |
| | Speech | 6 | 63 | 2 | 32 | 3 | 46 |
| AFM 124xb9 | Spoken Lang | 32 | 45 | 14 | 29 | 18 | 48 |
| | Word Recog | 21 | 56 | 5 | 38 | 12 | 54 |
| | Non word Rep | 14 | 62 | 7 | 36 | 8 | 58 |
| | Speech | 1 | 65 | 2 | 39 | 3 | 56 |
| CFTR | Spoken Lang | 175 | 259 | 47 | 72 | 62 | 92 |
| | Word Recog | 100 | 334 | 27 | 92 | 35 | 119 |
| | Non word Rep | 94 | 330 | 22 | 96 | 28 | 124 |
| | Speech | 1 | 65 | 2 | 39 | 3 | 56 |
| AFM 305ye9 | Spoken Lang | 139 | 206 | 37 | 57 | 3 | 79 |
| | Word Recog | 84 | 261 | 23 | 71 | 33 | 109 |
| | Non word Rep | 77 | 260 | 18 | 75 | 22 | 117 |
| | Speech | 1 | 65 | 2 | 39 | 3 | 56 |

Analyses

- Case-Control
- Affected Family Based Control (AFBC)

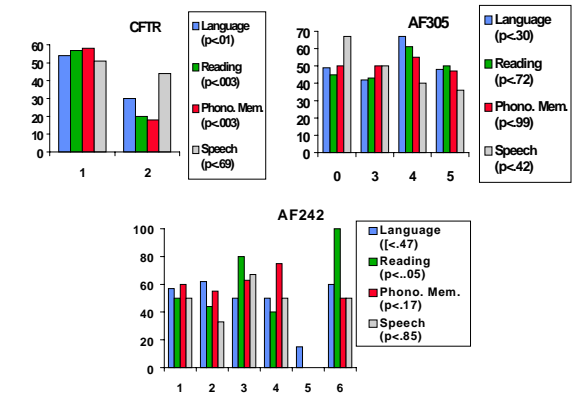
Results

Case-Control Comparison

| A Allele | Language | | Reading | | Phonological Memory | | Speech | |
|----------------|----------------------------|---------|----------------------------|---------|----------------------------|---------|----------------------------|---------|
| | Case | Control | Case | Control | Case | Control | Case | Control |
| CFTR | | | | | | | | |
| 1 | 300 | 425 | 175 | 532 | 184 | 542 | 18 | 599 |
| 2 | 18 | 93 | 28 | 136 | 24 | 116 | 8 | 136 |
| | $2^{*} 2.2 \times 10^{-4}$ | | $2^{*} 2.2 \times 10^{-4}$ | | $2^{*} 2.2 \times 10^{-4}$ | | $2^{*} 2.2 \times 10^{-4}$ | |
| AFM 305 | | | | | | | | |
| 0 | 14 | 61 | 28 | 51 | 26 | 52 | 4 | 62 |
| 1 | 57 | 82 | 31 | 108 | 23 | 104 | 7 | 107 |
| 2 | 57 | 96 | 32 | 127 | 23 | 123 | 8 | 126 |
| 3 | 11 | 90 | 18 | 123 | 18 | 128 | 10 | 140 |
| 4 | 53 | 100 | 33 | 125 | 33 | 121 | 7 | 129 |
| | $2^{*} 4.1 \times 10^{-6}$ | | $2^{*} 4.1 \times 10^{-6}$ | | $2^{*} 1.1 \times 10^{-4}$ | | $2^{*} 1.1 \times 10^{-4}$ | |
| AFM 242 | | | | | | | | |
| 0 | 12 | 30 | 23 | 56 | 1 | 33 | 1 | 34 |
| 1 | 12 | 19 | 24 | 19 | 9 | 27 | 4 | 24 |
| 2 | 11 | 24 | 15 | 15 | 10 | 25 | 4 | 26 |
| 3 | 9 | 21 | 23 | 7 | 4 | 26 | 1 | 23 |
| 4 | 10 | 17 | 24 | 20 | 2 | 27 | 2 | 21 |
| | $2^{*} 1.6 \times 10^{-4}$ | | $2^{*} 1.6 \times 10^{-4}$ | | $2^{*} 1.1 \times 10^{-4}$ | | $2^{*} 1.6 \times 10^{-4}$ | |
| AFM 124 | | | | | | | | |
| 0 | 2 | 11 | 3 | 10 | 3 | 10 | 1 | 12 |
| 1 | 7 | 14 | 4 | 17 | 2 | 18 | 0 | 16 |
| 2 | 14 | 10 | 9 | 18 | 1 | 20 | 1 | 18 |
| 3 | 28 | 20 | 18 | 20 | 12 | 22 | 0 | 20 |
| 4 | 12 | 25 | 8 | 30 | 7 | 31 | 0 | 31 |
| | $2^{*} 1.4 \times 10^{-6}$ | | $2^{*} 1.2 \times 10^{-6}$ | | $2^{*} 1.1 \times 10^{-4}$ | | $2^{*} 1.6 \times 10^{-4}$ | |

Weak evidence for an association between CFTR and language, reading, and phonologic memory.

AFBAC



AFBAC supports an association between the CFTR region and spoken language, phonological memory, and reading, but no association with speech.

Discussion

The phenotypes of SLI are concerned with limitations in spoken language acquisition having to do with vocabulary and grammar, reading impairment, and poor phonological memory. Each of these was associated with allelic variation of CFTR using AFBAC and weakly associated in the case-control analysis. The SLI phenotype does not include deficits in speech sound production and this was not associated with CFTR or loci in the 7q31 region. The coherence of the patterns of phenotypic associations with CFTR and the similar pattern for the case-control is encouraging.

Conclusions

- The linkage of the D7S527-D7S53 region to speech and/or language reported by Fisher et al. (1998) was supported for the phenotype of language, but not speech.
- Loci closely linked to the CFTR region may be associated with elevated liability for poor language skills in the general population.
- A confirmatory study using independent samples at CFTR is warranted.

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