A Genome-scan for Shared Autism Spectrum Disorder and Specific Language Impairment Loci

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abstract

Background: The genetic basis of autism spectrum disorders (ASDs) is still largely unknown as is possible shared etiologies of ASDs and specific language impairment (SLI), a neurodevelopmental disorder of language that is not accounted by low IQ or other cognitive impairments. In order to elucidate shared loci, a genome scan was conducted on pedigrees ascertained using a novel sampling design - pedigrees that were ascertained for both ASD and SLI probands in each pedigree. **Methods**: Affymetrix Axiom Array SNP genotyping provided data for both linkage and association analysis on 51 families with both ASD and SLI (+27 families without an SLI proband). The posterior probability of linkage (PPL) framework was used. It is the only implementation of a joint categorical-quantitative analysis method that allows for persons with ASD to be coded as "affected due to being beyond a unknown threshold" while all other family members are analyzed using quantitative trait values on 3 factors scores derived from performance on 22 language and literacy tests. Analysis of language and reading impairment as categorical traits was also conducted. **Results**: Categorical trait analysis showed large peaks for both language and reading impairment on chromosomes 15 (PPL=55%, 78 Mb, build 37) and 16 (PPL=37%, 20Mb, build 37), respectively. These results explicitly assume ASD is etiologically the same as language or reading impairment. Analysis of the 3 factors scores did not yield large linkage peaks, though GWAS of the same data did indicate strong evidence for LD (PPLD=81%, 184 Mb, build 37) on chromosome 4. **Discussion**: These data provide evidence for shared etiology of ASD and SLI since a lack of genetic overlap would be expected to reduce power due to the incorrect diagnostic classification of coding both ASD and SLI affected as done here. The peak locations are not known ASD or SLI loci, but this may be expected since this unique sampling design is most powerful where other studies are least powerful. Further mapping efforts are warranted to elucidate these loci and determine their effects in ASD alone, SLI alone and jointly.

background

Specific Language Impairment (SLI) is a heritable developmental language disorder occurring in absence of frank neurological or cognitive impairment.

Autism is a disorder of neural development characterized by impaired social interaction and communication, and by restricted and repetitive behavior.

Previous studies showed that a subgroup of children with autism overlap with SLI in language ability, perhaps through shared genetic etiology (Kjelgaard & Tager-Flusberg 2001; Tager-Flusberg & Joseph 2003) though the issue is debated at length (Tomblin 2011).

The **New Jersey Language and Autism Genetics Study (NJLAGS)** project was designed to address the question of shared genetic etiology by directly testing such overlap in the pedigrees that have both disorders.

methods

Families:
- 54 families, 427 subjects (304 with behavioral data)
- Ascertained through a proband with autism and at least one additional family member meeting the study criteria for SLI

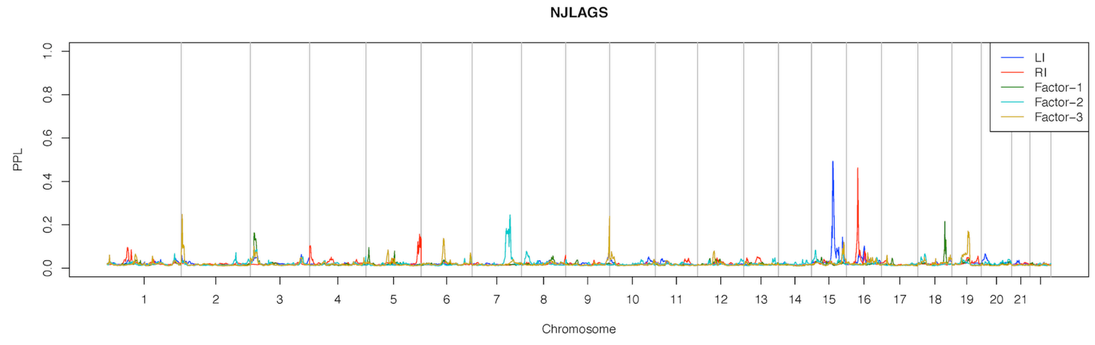
Proband criteria:
- Autism proband met criteria for Autistic Disorder on 2-3 of: 1) Autism Diagnostic Interview (ADI-R), 2) Autism Diagnostic Observation Schedule (ADOS), 3) DSM-IV
- SLI proband met these criteria: 1) Clinical Evaluation of Language Fundamentals (CELF) Composite score of <= 85, 2) Wechsler Intelligence Test Performance IQ >= 80, 3) No language relevant neurological or structural deviations, 4) Native English speaker.

Phenotypes:
- Language Impairment (**LI**): CELF <= 85
- Reading Impairment (**RI**): Single word reading <= 85
- Language-based learning impairment (**LLI**): *Either* RI *or* LI, *or* both
- Three factor scores derived by maximizing genetic correlation of 21 language/ literacy measures

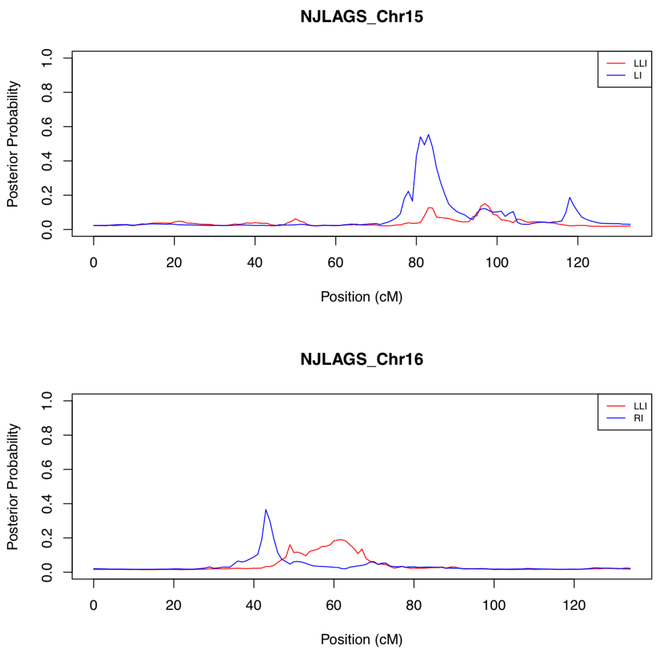
Genotyping:
Affymetrix Axiom 1.0 arrays were used to generate 567,893 SNP genotypes
Quality control and linkage marker selection as per Simmons et al (2010)

Statistical analysis:
Conducted with the PPL framework (Vieland in press)

results



Both categorical traits, LI and RI, yielded strong evidence for linkage on chromosome 15q24-25 and 16p12 respectively (above).



The linkages appear specific to LI and RI (left), and use of combination phenotype that includes both diagnoses, LLI, greatly reduces both linkage signals.

Additionally, setting either proband's affection status to missing also attenuates the linkage signal (not shown).

Use of the dense SNP data for family-based association analysis did not yield strong evidence for association to any genes under the linkage peaks.

GWAS analysis of the array data yielded only large PPLD (81%), at rs12646153, 20kb downstream of inhibitor of growth family member 2 (ING2)

discussion

- ❑ Two clear linkage peaks are observed in autism/SLI pedigrees with language phenotypes from the SLI literature
- ❑ The linkage signals depend on both the SLI and autism probands indicating shared etiology
- ❑ Phenotypic specificity is demonstrated by both the lack of overlap in the linkage signals for LI and RI, as well as the superset of the affected individuals LLI
- ❑ GWAS data awaits further validation

references

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acknowledgements

We would like to thank the participating families whose time and cooperation made this work possible. Family collection was supported by the National Institute of Mental Health R01MH070366 and ongoing work is funded by RC1MH088288.

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