INVITED EDITORIAL
Chromosome 7q: Where Autism Meets Language Disorder?

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On the basis of evidence from twin and family studies, both autism and developmental language disorder—also referred to as specific language impairment (SLI)—are believed to be genetically mediated. The genetic mechanisms involved, however, are not clear. For example, the prevalence of autism is currently estimated at 1/1,000 (Fombonne 1999), whereas the recurrence risk in families is 6%–8% (Santangelo and Folstein 1999). On the basis of combined data from three population-based twin studies, the concordance rate for MZ twins is estimated to be ~65%, contrasted with a concordance rate of 0% in DZ twins (Bailey et al. 1995). Presumably, the DZ rate of 0% is a type II error, since the combined samples contain <100 pairs. Heritability is estimated at >.90, and there is no convincing evidence for perinatal or other environmental risk factors. Genetic modeling based on these data has been consistent with a model of oligogenic inheritance with epistasis (Pickles et al. 1995).

Twin and family studies also suggest a genetic component to the etiology of SLI. Family studies report rates of language and reading disorders in first-degree relatives of children with SLI to be much greater than the estimated population frequency of ~7%. In the only study that used the family study rather than the family history method, 30% of the fathers and brothers and 12% of the mothers and sisters of probands met criteria for SLI (Tomblin and Zhang 1999). Twin studies have found higher MZ than DZ concordance rates. MZ concordance rates are estimated at ~70% and DZ rates are estimated at ~45% (Lewis and Thompson 1992; Bishop et al. 1995; Tomblin and Buckwalter 1998). Heritability estimates calculated from these data (0.45) are somewhat lower than those calculated for autism, and the MZ-DZ proportions of SLI are not inconsistent with single-gene models (Bishop et al. 1995; Tomblin and Pandich 1999).

A number of research groups have been actively searching for genes that contribute to autism and SLI. Two studies in this month's *Journal* report evidence for loci on 7q31 that may be important in the genetic etiologies of autism and SLI. Association of this region with autism has been suggested in four linkage studies (International Molecular Genetic Study of Autism Consortium 1998; Ashley-Koch et al. 1999*a*; Ashley-Koch et al. 1999*b*; Collaborative Linkage Study of Autism 1999; Philippe et al. 1999), prompting the search for autistic individuals who have translocations in this region. In one article, John Vincent and his colleagues report their characterization of a novel gene on 7q31 that they call *RAY1* (2000 [in this issue]). This gene was interrupted at the breakpoint of a translocation found in a person with autism. Unfortunately, they did not find any mutations in the coding regions of this gene in another 27 autistic individuals examined. However, the other side of the translocation occurs at chromosome 13q21, in a region with a suggestive linkage signal for autism (Collaborative Linkage Study of Autism 1999).

In the other article, Lai et al. (2000 [in this issue]) report progress toward narrowing the *SPCH1*-gene region on 7q31. The presence of this locus was inferred from linkage analysis of a single kindred, "KE." First reported in 1998 (Fisher et al. 1998), affected members of the KE family have a severe disorder of speech and language, presumably without any features of autism, although this has not been specifically reported. This disorder segregates as an autosomal dominant trait, and the original LOD score was 6.62. In this month's *Journal,* Lai et al. report substantial progress toward localizing the gene responsible for this family's disorder. They have assembled a contig map of the region and, using positional cloning methods, have narrowed the interval of interest to ~6–7 Mb. They have also analyzed the breakpoints of translocations involving 7q31 from two unrelated cases that were phenotypically similar to affected members of the KE kindred. In one of the two cases, the breakpoint was within their narrowed interval of interest. No mutations in affected members of the KE kindred were found in the known coding regions of the most likely candidate gene, *CAGH44*.

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Given that the two regions of interest overlap substantially, the question arises as to whether there exists a single gene on 7q31 that is involved in both autism and SLI. These two clinical syndromes are, by concept and definition, distinct. Autism is defined by the failure to develop social relationships, with abnormal *social use of language* (pragmatics), while SLI is defined by abnormalities of *language structure,* in the *absence* of autism (Tager-Flusberg 1999). Children with language disorders are, for the most part, said to interact socially within the limitations imposed by abnormalities of verbal fluency, vocabulary, grammar, and phonology (the ability to pronounce words accurately). Children with autism may have perfectly normal fluency, vocabulary, grammar, and phonology, but they have little or no interest in using language for social communication.

Notwithstanding the clear diagnostic distinction, there is, in practice, considerable overlap between the phenotypes of the two disorders. While abnormalities of language structure are not essential to the diagnosis of autism, a substantial number of children with autism do have abnormalities of fluency, vocabulary, grammar, and phonology (Tager-Flusberg 1999). Perhaps a third of children with autism never develop speech at all (Rapin 1997). Language abnormalities are also found in family members. About 25% of the parents and siblings of autistic children, compared with 5%–10% of controls, have delayed onset of speech or trouble learning to read (Fombonne et al. 1997; Folstein et al. 1999). Family members with such a history have lower verbal intelligence scores and score worse on spelling and on difficult reading tests, compared to family members without developmental delays of language onset and reading (Folstein et al. 1999). This is suggestive of a relationship between autistic language impairment and the language impairment of SLI.

Given the report of linkage to 7q31 in the KE family and a positive test for association in another sample of children with SLI (Tomblin et al. 1998), the Collaborative Linkage Study of Autism tested the hypothesis that the weakly positive linkage signal they obtained at 7q22-31 could be attributed to a subset of their 75 multiplex families in which both probands had markedly delayed onset of speech. In this analysis, they classified any parent who had delayed speech or trouble with reading or spelling as affected. The 50 families in which both probands had delayed onset of speech accounted for virtually all of the signal at 7q31, and the LOD for the 50 families was higher than that for the combined sample (Collaborative Linkage Study of Autism 1999, unpublished data). This finding supports the possibility that a locus near 7q31 is one of the causes of both autism and SLI. However, the region suggested by the Collaborative Linkage Study of Autism linkage data and by other genome screens for autism is not nearly as well localized as is the *SPCH1* area, and the possibility exists that the regions responsible for the two phenotypes may not represent the same locus.

Just as there is a greater-than-expected prevalence of language disorder in the families of autistic children, there also appears to be a greater-than-expected prevalence of autism in the siblings of probands with SLI. In an epidemiologically ascertained sample of children with SLI, Tomblin and colleagues evaluated the siblings of SLI probands for autism. They found a prevalence of autism among the siblings of SLI probands of ~3% (Hafeman and Tomblin 1999). This is the same prevalence of autism that is seen in the sibs of autistic probands and is much higher than what would be expected by chance, given the prevalence of autism in the general population (~0.1%).

Not only are there more than the expected number of families who have children with both disorders, but there are some cases in which the features of both autism and developmental language disorder overlap. In a pioneering study that compared children with autism to children with developmental language disorder, Rutter and his colleagues found that they could not assign some of the children into a distinct diagnostic category (Bartak et al. 1975, 1977; Cox et al. 1975). The children from this study have recently been reexamined as adults, and it is interesting to note that even those subjects who were unequivocally diagnosed with language disorders without autistic features during childhood have had significant social difficulties as adults (Howlin et al., in press).

Although some of the data are circumstantial or preliminary, autism and SLI appear to be genetically related; both disorders occur much more often than expected by chance within the same family, and some cases exist that have phenotypes that cannot be distinctly differentiated. Thus, it is tempting to speculate that the two conditions have some genes in common (Folstein 1999). This would be consistent with the oligogenic models proposed for autism, where genes that confer susceptibility—which are expected to be common in the population—assort in various combinations, leading, perhaps, to a range of phenotypes including those as severe as autism and SLI. Other phenotypic evidence also supports this idea. Some individuals with very mild autism, recently called Asperger syndrome, have entirely normal structural language but have marked rigidity, circumscribed interests, and very poor social instincts (Wing 1981, 1986; Klin et al. 2000). Similar, but milder, traits have been observed in the parents and siblings of autistic probands in several case-control studies. These traits are called "the Broader Autism Phenotype" (Eisenberg 1957; Landa et al. 1991, 1992; Gillberg et al. 1992; Ozonoff et al. 1993; Bolton et al. 1994, 1998; DeLong 1994; Le Couteur et al. 1996; Fombonne et al. 1997; Folstein et al. 1999).

Researchers in autism genetics are hoping to use the

emerging information about other disorders and the reliably measurable language and personality traits found in family members of autistic probands (Folstein et al. 1998; Folstein and Santangelo 2000) as a means of adding power to linkage analysis in this condition in which large kindreds are rare, and even affected sib pairs are fairly sparse.

References

Ashley-Koch A, Wolpert CM, Menold MM, Zaeem L, Basu S, Donnelly SL, Ravan SA, et al (1999*a*) Genetic studies of autistic disorder and chromosome 7. Genomics 61:227–236

Ashley-Koch A, Zaeem L, Menold MM, Basu S, Donnelly SL, Ravan SA, Powell CM, et al (1999*b*) Autistic disorder and chromosome 7: evidence for a paternal effect (abstracts for 7th World Congress of Psychiatric Genetics). Mol Psychiatry Suppl 4:S15

Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, Rutter M (1995) Autism as a strongly genetic disorder: evidence from a British twin study. Psychol Med 25:63–77

Bartak L, Rutter M, Cox A (1975) A comparative study of infantile autism and specific development receptive language disorder. I. The children. Br J Psychiatry 126:127–145

——— (1977) A comparative study of infantile autism and specific developmental receptive language disorders. III. Discriminant function analysis. J Autism Childhood Schizophr 7:383–396

Bishop DVM, North T, Donlan C (1995) Genetic basis of specific language impairment: Evidence from a twin study. Dev Med Child Neurol 37:56–71

Bolton P, Macdonald H, Pickles A, Rios P, Goode S, Crowson M, Bailey A, et al (1994) A case-control family history study of autism. J Child Psychol Psychiatry 35:877–900

Bolton PF, Pickles A, Murphy M, Rutter M (1998) Autism, affective and other psychiatric disorders: patterns of familial aggregation. Psychol Med 28:385–395

Collaborative Linkage Study of Autism (1999) An autosomal genomic screen for autism. Am J Med Genet 88:609–615

Cox A, Rutter M, Newman S, Bartak L (1975) A comparative study of infantile autism and specific developmental receptive language disorder. II. Parental characteristics. Br J Psychiatry 126:146–159

DeLong R (1994) Children with autistic spectrum disorder and a family history of affective disorder. Dev Med Child Neurol 36:674–687

Eisenberg L (1957) The fathers of autistic children. Am J Orthopsychiatry 127:715–724

Fisher SE, Vargha-Khadem F, Watkins KE, Monaco AP, Pembrey ME (1998) Localisation of a gene implicated in a severe speech and language disorder [published erratum appears in Nat Genet (1998) 18:298]. Nat Genet 18:168–170

Folstein SE (1999) Autism. Int Rev Psychiatry 11:269–277

Folstein SE, Bisson E, Santangelo SL, Piven J (1998) Finding specific genes that cause autism: a combination of approaches will be needed to maximize power. J Autism Dev Disord 28:439–445

Folstein SE, Santangelo S (2000) Does Asperger syndrome aggregate in families? In: Klin A, Volkmar FR, Sparrow SS (eds) Asperger syndrome. Guilford Press, New York, pp 159–171

Folstein SE, Santangelo SL, Gilman SE, Piven J, Landa R, Lainhart J, Hein J, et al (1999) Predictors of cognitive test patterns in autism families. J Child Psychol Psychiatry 40: 1117–1128

Fombonne E (1999) The epidemiology of autism: a review. Psychol Med 29:769–786

Fombonne E, Bolton P, Prior J, Jordan H, Rutter M (1997) A family study of autism: cognitive patterns and levels in parents and siblings. J Child Psychol Psychiatry 38:667–684

Gillberg C, Gillberg IC, Steffenburg S (1992) Siblings and parents of children with autism: a controlled population- based study. Dev Med Child Neurol 34:389–398

Hafeman L, Tomblin B (1999) Autistic behaviors in the sublings of children with specific language impairment. Mol Psychiatry Suppl 4:S14

Howlin P, Mawhood L, Rutter M. Autism and developmental language disorder—a comparative follow-up study in early life. II. Social, behavioral, and psychiatric outcomes. J Child Psychol Psychiatry (in press)

International Molecular Genetic Study of Autism Consortium (1998) A full genome screen for autism with evidence for linkage to a region on chromosome 7q. Hum Mol Genet 7: 571–578

Klin A, Sparrow S, Marans WD, Carter A, Volkmar FR (2000) Assessment issues in children and adolescents with Asperger syndrome. In: Klin A, Volkmar FR, Sparrow S (eds) Asperger syndrome. Guilford Press, New York, pp 309–339

Lai CSL, Fisher SE, Hurst JA, Levy ER, Hodgson S, Fox M, Jeremiah S, et al (2000) The *SPCH1* region on human 7q31: genomic characterization of the critical interval and localization of translocations associated with speech and language disorder. Am J Hum Genet 67:357–368 (in this issue)

Landa R, Folstein SE, Isaacs C (1991) Spontaneous narrative-discourse performance of parents of autistic individuals. J Speech Hear Res 34:1339–1345

Landa R, Piven J, Wzorek MM, Gayle JO, Chase GA, Folstein SE (1992) Social language use in parents of autistic individuals. Psychol Med 22:245–254

Le Couteur A, Bailey A, Goode S, Pickles A, Robertson S, Rutter M (1996) A broader phenotype of autism: the clinical spectrum in twins. J Child Psychol Psychiatry 37:785–801

Lewis BA, Thompson LA (1992) A study of developmental speech and language disorders in twins. J Speech Hear Res 35:1086–1094

Ozonoff S, Rogers SJ, Farnham JM, Pennington BF (1993) Can standard measures identify subclinical markers of autism? J Autism Dev Disord 23:429–441

Philippe A, Martinez M, Guilloud-Bataille M, Gillberg C, Rastam M, Sponheim E, Coleman M, et al (1999) Genome-wide scan for autism susceptibility genes. Hum Mol Genet 8:805–812

Pickles A, Bolton P, Macdonald H, Bailey A, Le Couteur A, Sim CH, Rutter M (1995) Latent-class analysis of recurrence risks for complex phenotypes with selection and measure-

ment error: a twin and family history study of autism. Am J Hum Genet 57:717–726

Rapin I (1997) Current concepts: autism. N Engl J Med 337: 97–104

Santangelo SL, Folstein SE (1999) Autism: a genetic perspective. In: Tager-Flusberg H (ed) Neurodevelopmental disorders. MIT Press, Cambridge, MA, pp 431–447

Tager-Flusberg H (1999) A psychological approach to understanding the social and language impairments in autism. Int Rev Psychiatry 11:325–334

Tomblin J, Nishimura C, Zhang X, Murray JC (1998) Association of developmental language impairment with loci at 7q3. Am J Hum Genet Suppl 63:A312

Tomblin JB, Buckwalter PR (1998) Heritability of poor language achievement among twins. J Speech Lang Hear Res 41:188–199

Tomblin JB, Pandich J (1999) Lessons from children with specific language impairment. Trends Cogn Sci 3:283–285

Tomblin JB, Zhang X (1999) Language patterns and etiology in children with specific language impairment. In: Tager-Flusberg H (ed) Neurodevelopmental disorders. MIT Press, Cambridge, MA, pp 361–382

Vincent JB, Herbrick J, Gurling HMD, Bolton PF, Roberts W, Scherer SW (2000) Identification of a novel gene on chromosome 7q31 that is interrupted by a translocation breakpoint in an autistic individual. Am J Hum Genet 67:510–514 (in this issue)

Wing L (1981) Asperger's syndrome: a clinical account. Psychol Med 11:115–129

——— (1986) Clarification on Asperger's syndrome. J Autism Dev Disord 16:513–515