Report

Association of Specific Language Impairment (SLI) to the Region of 7q31

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FOXP2 (forkhead box P2) was the first gene characterized in which a mutation affects human speech and language abilities. A common developmental language disorder, specific language impairment (SLI), affects 6%–7% of children with normal nonverbal intelligence and has evidence of a genetic basis in familial and twin studies. *FOXP2* is located on chromosome 7q31, and studies of other disorders with speech and language impairment, including autism, have found linkage to this region. In the present study, samples from children with SLI and their family members were used to study linkage and association of SLI to markers within and around *FOXP2*, and samples from 96 probands with SLI were directly sequenced for the mutation in exon 14 of *FOXP2*. No mutations were found in exon 14 of *FOXP2*, but strong association was found to a marker within the *CFTR* gene and another marker on 7q31, D7S3052, both adjacent to *FOXP2*, suggesting that genetic factors for regulation of common language impairment reside in the vicinity of *FOXP2*.

Specific language impairment (SLI [MIM 602081]) is a developmental language disorder that presents with late onset of expressive language and poor receptive language abilities. This pattern of slow spoken-language development persists through preschool in the absence of hearing loss or neurodevelopmental disorders, including autism (Tomblin et al. 1996). This disorder is common in the population, with a prevalence of 6%–7% (Tomblin et al. 1997; Law et al. 2000). Several family history studies have demonstrated that SLI is familial (Neils and Aram 1986; Tomblin 1989; Lahey and Edwards 1995; van der Lely and Stollwerck 1996). The concordance rate of SLI in twin studies is nearly 100% for MZ and 50%–70% for DZ twins (Bishop et al. 1995; Tomblin and Buckwalter 1998), and SLI has been shown to have moderate-to-high levels of heritability, further supporting a genetic basis for this disorder (Lewis and Thompson 1992; Bishop et al. 1995; Dale et al. 1998).

Molecular genetic studies of speech and language disorders include the report by Fisher et al. (1998) of linkage of a severe autosomal dominant speech and language

disorder to the region of 7q31 (*SPCH1*) in one large pedigree, the KE family. Additionally, Lai et al. (2000) reported an unrelated individual with a similar phenotype who was found to have a translocation in the *SPCH1* region. The breakpoint was located in *FOXP2*, a transcription factor of the extended forkhead family. The affected members of the KE family were found to have a mutation in the DNA-binding domain of exon 14 in this gene (MIM 605317). *FOXP2* is expressed in the developing brain (Shu et al. 2001) and is the first gene directly linked to speech and language disturbances.

Additional studies have further implicated the region of 7q31 in speech and language disorders and in autism, a developmental disorder characterized by impaired language development and social interaction, as well as restricted interests and stereotyped behaviors. Ashley-Koch and colleagues reported a family with two affected children with autism and one affected child with language impairment. This family was found to have a paracentric inversion in the 7q22.1-q31 region. Further study of a set of families with autistic children found significant linkage to markers in this region (Ashley-Koch et al. 1999). A report of two unrelated individuals, one with autism and the other with SLI, described chromosomal rearrangements with breakpoints at 7q31.3 (Warburton et al. 2000). Other studies of autism have also found linkage to regions on 7q, including several genomewide scans (International Molecular Genetic Study of Autism Consor-

tium 1998; Collaborative Linkage Study of Autism [CLSA] et al. 1999; Philippe et al. 1999; International Molecular Genetic Study of Autism Consortium 2001*a*, 2001*b*). Translocation breakpoints in this region in autistic individuals have also been reported (Vincent et al. 2000; Tentler et al. 2001) (fig. 1). The CLSA found that linkage to marker D7S1813 was increased when the autism phenotype was augmented with information concerning family history of language impairment (Bradford et al. 2001). The Autism Genetic Resource Exchange Consortium reported a linkage of D7S3058 to a language item from the Autism Diagnostic Interview-Revised (Lord et al. 1994) concerned with age at first word (Alarcon et al. 2002). Recently, Auranen and colleagues found multipoint linkage to a region centered at D7S2462 and a two-point linkage to D7S1824 for a phenotype that was broadened to contain autism, Asperger syndrome, and developmental aphasia (SLI). No linkage was found to the narrow phenotype of autism on 7q (Auranen 2002). A meta-analysis by Badner and Gershon (2002) of four genomewide linkage scans for autism found evidence for a susceptibility locus at 7q. A study of families with autism found no evidence of linkage or linkage disequilibrium to *FOXP2* or of mutations in the fork-head domain, but undertransmission of one allele was detected in families classified as "language abnormal" (Wassink et al. 2002). A study of probands with moderate-to-severe speech sound disorder found linkage to marker D7S821 located ~16 Mb proximal to *FOXP2* on 7q21.3 (fig. 1). The mutation in exon 14 observed in the KE family was not found in these families (Schick 2002).

Several recent studies of SLI have not found linkage or association to *FOXP2* or chromosome 7. Newbury et al. (2002) studied 210 individuals from 43 families with SLI recruited by the Newcomen Centre at Guy's Hospital, London; by the Cambridge Language and Speech Project (CLASP) from three special schools for language disorder; and from Afasic, a support organization for people with developmental and language impairments. They found no association between quantitative language scores of probands with SLI and six markers within *FOXP2* and no mutations in the forkhead domain; they also found no association between autism and *FOXP2* markers and no mutations in autism probands (Newbury et al. 2002). Meaburn et al. (2002) also studied 270 children with SLI and did not find the mutation in exon 14 of *FOXP2* that was present in the KE family. The SLI Consortium of Newbury et al. used the samples from the Guy's Hospital and CLASP cases to perform a genomewide scan that identified two loci on 16q and 19q involved in SLI; no evidence of linkage was found to 7q (The SLI Consortium 2002). Another genomewide scan performed by Bartlett et al. (2002) detected a significant LOD score on chromosome 13q21 but not at 7q.
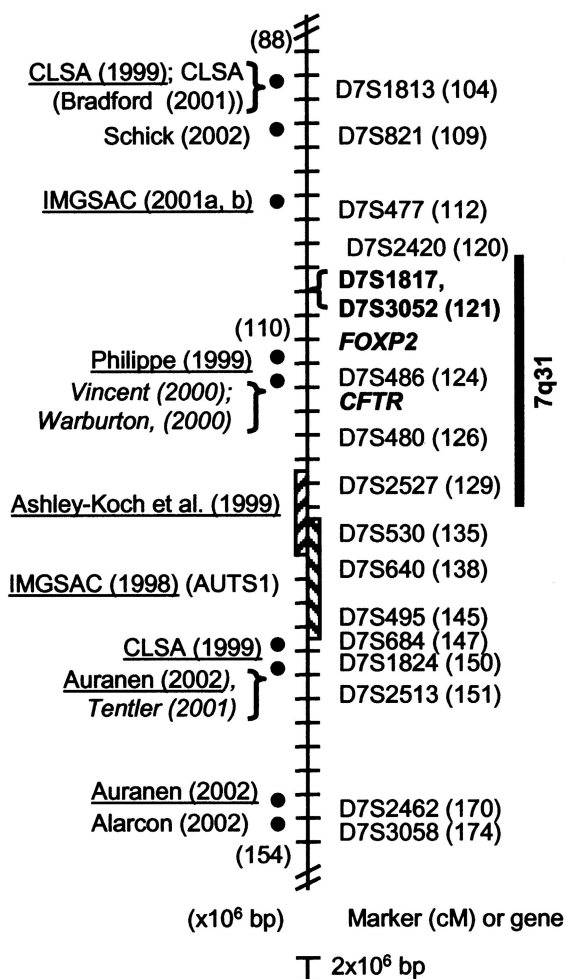

Figure 1 Autism and language studies of chromosome 7, long arm, from 88–154 × 10⁶ bases. All base-pair positions, in parentheses on the left, are based on the Human Genome Browser as of November 2002. Marshfield marker name and centimorgan position are listed on the right side, along with the position of *FOXP2* and *CFTR*. Markers used in this study are in bold type. Published studies of autism or language disorders with significant linkage or association to specific markers (*filled circle*) or to regions (*crosshatched line*) are listed along the left side. Genomewide scans are underlined, and reports of translocations are in italics.

The present study reports the results of genotyping samples from children with SLI and their family members, as well as control samples for markers on chromosome 7, including markers within and adjacent to *FOXP2*. This study also reports the results of direct sequencing of probands for exon 14 of *FOXP2*, the location of the mutation that was present in the KE family (Lai et al. 2001). The participants of the present study consisted of probands identified in a population-based study of children with and without language impairment who are being followed during their school years. The probands were identified when they were in kindergarten from a

sample of children enrolled in schools in Iowa and Illinois. All 7,218 children from the chosen communities were given a language-screening test. Those who failed and one-third of those who passed were sampled for a more complete language, speech, hearing, and IQ assessment. By use of this information, children were diagnosed with respect to their language status, in accordance with a system described by Tomblin et al. (1996). The results of the screening and diagnosis were published in a study that found a 7.4% incidence of SLI in that group (Tomblin et al. 1997). The parents of 1,744 participants who received the diagnostic evaluations were asked to participate in a registry for future research. From this registry, 604 children were sampled to participate in a longitudinal study. This sample consisted of all children who were language impaired and for whom assent was obtained, as well as a random sample of those children with assent who were developing typically. Phenotypic measures were obtained in second grade for all these children (table 1). Information was also collected on the language phenotype of the siblings of the probands through assessment with one of three language batteries, depending upon the siblings' ages (table 2). High between-battery correlations had been obtained with these tests, indicating that they were testing the same traits in siblings and probands. Performance IQ (PIQ) was assessed by the performance battery of Wechsler Intelligence Scale for Children-Third Edition (Wechsler 1991). Only children with a PIQ >70 were included in the statistical analysis. A composite language score of 1.14 SDs below the mean for second grade was used for diagnosis of SLI for the discrete language phenotype (Tomblin et al. 1996). The institutional review board approved this study, and all individuals or their guardians provided written informed consent for participation in the study.

Using buccal swabs or blood samples obtained from the affected and control probands and their family members, DNA was extracted using standard procedures. The samples were genotyped for microsatellite repeats in chromosome 7 by amplification of the region by PCR. The PCR product was run on denaturing 6% polyacrylamide gel, and bands were visualized via silver staining. All samples were genotyped for a tetranucleotide repeat (GATT) in the *CFTR* gene, a marker chosen for ease in genotyping on sequencing gels (Gasparini et al. 1991) as well as its location in the region of critical interest, 3 Mb distal to *FOXP2* on 7q31. Next, two tetranucleotide repeat CHLC markers in 7q31, D7S1817 and D7S3052, located 5 Mb proximal to *FOXP2*, were used to genotype all samples using standard CHLC PCR conditions (Murray et al. 1994). Using a GATA repeat in intron 2 of *FOXP2* with primers designed by Wassink et al. (2002), all samples—including those from affected individuals, their family members, and controls—were genotyped, for a total of 1,608 genotyped individuals. By use of the published sequence of *FOXP2* available on the Human Genome Gateway Browser and Sequencher 4.1, six additional tetranucleotide repeats were found within the intronic regions of *FOXP2*, as described by Lai et al. (2001). Primers were designed to amplify these microsatellite repeats, and genotypes were generated for a subset of samples. These genotypes were used to calculate the degree of linkage disequilibrium between the seven markers in *FOXP2* using the GOLD program (Abecasis and Cookson 2000). Two markers, both TTTA repeats within the intronic regions between exons 1 and 2 and exons 3a and 3b of *FOXP2* (Lai et al. 2001; Bruce and Margolis 2002), were not in linkage disequilibrium with the GATA repeat and were used to genotype samples from families with siblings. A total of 781 samples were genotyped for all three markers. These genotypes were analyzed again to confirm that the additional mark-

Table 1

Language Measures for Probands

	LANGUAGE MEASURE		
TEST	Receptive	Expressive	Composite[a]
Vocabulary	PPVT-R[b]	CREVET[c]	Vocabulary composite
Sentence use	CELF-III[d] (sentence structures, concepts and directions)	CELF-III[d] (word structure, recalling sentences)	Sentence composite
Narration	CELF-III[d] (listening to paragraphs)	Narrative generation (total clauses)	Narrative composite
Composite[a]	Receptive composite	Expressive composite	Total composite

NOTE.—Language measures employed for diagnosis of language impairment and the assignment of these measures to a matrix consisting of language modality and language domain from which marginal composite scores were computed. The language measures consisted of: *Peabody Picture Vocabulary Test-Revised* (Dunn and Dunn 1981), *Comprehensive Receptive Expressive Vocabulary Test* Expressive subtest (Wallace and Hammill 1994), and the sentence structure, concepts and oral directions, word structure, recalling sentences, and listening to paragraphs of the *Clinical Evaluation of Language Fundamentals-3* (Semel et al. 1995). Narrative expression employed a story-generation task, which was transcribed and coded for total clauses (Hunt 1970). The total composite score derived from these tests was standardized by being referenced to the normal norm.

[a] Tests in any row were combined to form subcomposite scores for that domain of language, and tests in any column were combined to form subcomposite scores for that modality. All tests were combined to form the total composite score.

[b] Peabody Picture Vocabulary Test-Revised (Dunn and Dunn 1981).

[c] Comprehensive Receptive Expressive Vocabulary Test Expressive subtest (Wallace and Hammill 1994).

[d] Clinical Evaluation of Language Fundamentals-3 (Semel et al. 1995).

Table 2

Language Measures for Siblings at Different Age Levels

Age Group (year/month)	Test
4/0–6/11	TOLD-2:P[a] (picture vocabulary, oral vocabulary, grammatic understanding, sentence imitation, grammatic completion)
7/0–8/11	PPVT-R[b] and CELF-III[c] (sentence structures, concepts and directions, word structures, recalling sentences, listening to paragraphs)
9/0–14/11	PPVT-R[b] and CELF-III[c] (formulated sentences, concepts and directions, recalling sentences, listening to paragraphs)

NOTE.—A composite language score was derived from the scores on the tests given to each sibling and standardized by being referenced to the national norm of the test.

[a] Test of Language Development-2:Primary (Newcomer and Hammill 1988).

[b] Peabody Picture Vocabulary Test-Revised (Dunn and Dunn 1981).

[c] Clinical Evaluation of Language Fundamentals-3 (Semel et al. 1995).

ers were not in linkage disequilibrium with the GATA repeat and therefore would provide additional information to test for association. Primers and PCR conditions are available upon request.

The genotypes from the GATT repeat in *CFTR,* D7S1817, D7S3052, and the GATA and the two TTTA repeats in *FOXP2* were analyzed for sib-pair linkage using SAGE SIBPAL2 with both continuous and discrete language traits (SAGE 2001). In the analysis, the language phenotype was adjusted according to the specific language battery used and the race of the siblings. Two dummy variables were created to designate which of the three batteries of language testing was given (one for probands and siblings age 7–8 years, another for siblings age 4–6 years, and a third for siblings age 9–14 years). These were used as covariates for the analysis for sibpair linkage. Two dummy variables for race were created and also used as covariates (one for African Americans and the other for minorities other than African American, such as Hispanic or Asian). Using both continuous language scores and the discrete language phenotype from second grade, there was no significant linkage using sib-pair analysis with and without covariates for 244 to 294 sibling pairs (on the basis of the number of sibling pairs successfully genotyped for each marker), except for the GATT marker in *CFTR,* which had a *P* value of .036 for the discrete language phenotype. This value is not significant, however, after correction for multiple testing. The genotypes from parents and affected children were also used to test for association using both the discrete language phenotype and the continuous language scores. Affected family–based controls (AFBAC) analysis and the extended transmission/disequilibrium test (ETDT) for multiple alleles were used with the discrete language phenotype, and the quantitative transmission/disequilibrium test (QTDT) was used with the continuous language scores (Sham and Curtis 1995; Thomson 1995*a*, 1995*b*). The transmission/disequilibrium test (TDT) was chosen because it utilizes a simple family triad structure and heterozygous parents (the families tested consisted mainly of nuclear families), whereas AFBAC was chosen to include both heterozygous and homozygous parents. The numbers of triads for the TDT and for AFBAC are included in table 3. No results were significant for the QTDT. The results for the ETDT and AFBAC are listed in tables 3 and 4. No marker in *FOXP2* was significant overall. Results for the ETDT and AFBAC showed that both D7S3052 and the *CFTR* marker were significantly associated with the discrete language phenotype. When the ETDT and AFBAC were performed with parental-origin-specific alleles for D7S3052, the paternal alleles were significant for both the ETDT and AFBAC, but maternal alleles were not. For the *CFTR* marker, a significant result was obtained for paternal alleles with the ETDT and for maternal alleles with AFBAC. The ETDT algorithm used does not test the effect difference between paternal and maternal alleles. The interaction analysis between parent origin and the effect of allele type performed by the AFBAC analysis did not reveal any significant interaction, which means that the effect of allele type did not change significantly across parent origins.

In addition to association and linkage analysis, a subset of probands was also analyzed by direct sequencing for mutations in exon 14 of *FOXP2,* the site of mutation in the KE family (Lai et al. 2001). Primers were designed for amplification of exon 14 and at least 150 bases in the surrounding intron-exon boundaries. Of the 96 probands analyzed, no mutations were found in exon 14, but three rare variants were found outside the coding region. One variant, a G→A substitution, was found in intron 13, 9 bases before the start of exon 14. Two variants were found in intron 14, a T→C substitution and a C→T substitution located 24 and 43 bases from the end of exon 14, respectively. None of these variants were found in 92 control samples. One of these variants, the T→C substitution, was reported +24 bases from exon 14 in a proband with SLI (Newbury et al. 2002). This substitution and the substitution in intron 13 occur in nucleotides that are conserved in the mouse genome (GenBank accession number CAAA01121518.1). Given

Table 3

Results of ETDT for the Six Markers Using Discrete Language Phenotypes

		ETDT Results (P)		
Marker	N^a	All Data	Paternal Data	Maternal Data
D7S1817	133	.3827	.1513	.0304
D7S3052	104	.0003[b]	.0022[c]	.1217
FOXP2 intron 1 TTTA	95	.0661	.1564	.1700
FOXP2 GATA	114	.2743	.2473	.4742
FOXP2 intron 3 TTTA	76	.8941	.5042	.7794
CFTR GATT	58	.0014[b]	.0055[c]	.0212

[a] Number of family triads with heterozygous parents.

[b] Significant at level of $P < .01$ after Bonferroni correction for the number of markers (i.e., 6).

[c] Significant at level of $P < .05$.

that these variants occur in a region of high homology (166/176 bases), it is possible that these intronic regions are involved in splicing or regulatory mechanisms. Functional studies will be necessary to determine the significance of these changes.

In the present study, significant association was found between the language phenotype and the marker D7S3052. According to the most recent map on the Genome Browser from November 2002, the location of this marker is <5 Mb proximal to *FOXP2*. In an examination of the region of chromosome 7q31 surrounding the marker D7S3052 using the Genome Browser, the closest candidate gene found was *IMMP2L,* located <1 Mb distal to the marker. This gene, a homologue of the yeast inner mitochondrial membrane peptidase subunit-2, has been implicated in Gilles de la Tourette syndrome (GTS [MIM 137580]), a neurologic disorder with motor and vocal tics and behavioral abnormalities, on the basis of several studies of patients with translocations at 7q31 (Boghosian-Sell et al. 1996; Petek et al. 2001). Additional genes in this region include *Dna*J (*Hsp*40) homologue, subfamily B, member 9 (*Dna*JB9), and neuronal cell adhesion molecule (*NRCAM*). Significant association was also found to a marker in *CFTR,* which is located <1 Mb distal to *WNT2* (wingless-type MMTV integration site family member). A study of autism found significant association between an SNP in the 3′ untranslated region of *WNT2* and a subset of families with autism with a more severe language impairment (Wassink et al. 2001).

Previous studies had suggested that this region of chromosome 7 is a hot spot for imprinting, with a difference in the expression of the maternal and paternal alleles. The Ashley-Koch et al. (1999) study of autism and chromosome 7 found a difference in the parental contribution for the association between the significant markers and autism, with the majority of effect from paternal alleles. There was also evidence of an increase in the recombi-

nation rate of the region in autistic families versus controls, which mirrors the higher recombination rate in the male versus the female map. Genomic imprinting on chromosome 7 has also been implicated in Russell-Silver syndrome (MIM 180860), and an imprinted gene has been identified in the region of 7q32 (Kobayashi et al. 1997; Nakabayashi et al. 2002). A study of genes and expressed sequence tags in chromosome 7 found differences in hypermethylation of maternal and paternal chromosomes (Hannula et al. 2001). Our study did not find a significant interaction between the effect of transmitted alleles and the parental origin. This may be due to insufficient power to detect modest or small interactive effects.

Recently, the TDT has been criticized for being biased by possible genotyping errors (Mitchell et al. 2003). Further analysis was done comparing the results of the TDT from controls and their heterozygous parents with the results from case subjects. Though the sample size was much larger for the TDT with control subjects than with case subjects, the results with control subjects were not significant for all the six markers, including D7S3052 and the *CFTR* marker, which were significant for case subjects. This provides support that significant association was not due to genotyping errors.

Linkage or association of SLI to *FOXP2* was not observed in this study, supporting the results reported in a previous study with a smaller sample size (Newbury et al. 2002). There were no mutations found in exon 14 of *FOXP2,* as was similarly reported in the linkage study and in a sequencing study (Meaburn et al. 2002; Newbury et al. 2002). The very large size of *FOXP2* (>600 kb) and the recent discovery of additional exons made gene sequencing impractical (Bruce and Margolis 2002). There was, however, very significant association even after the correction for the multiple comparisons done between SLI and two other markers on chromosome 7q31 located 5 Mb proximal and 3 Mb distal to *FOXP2*. This is the first study to report association of SLI to this region, whereas previous genomewide scans did not find significant linkage to chromosome 7 (Bartlett et al. 2002; The SLI Consortium 2002). The TDT is more sensitive in the setting of linkage disequilibrium than linkage analysis in detecting genetic effects too weak to be identified by linkage, as may be seen in genes involved in complex human diseases, and association tests require vastly smaller sample sizes than linkage (Risch and Merikangas 1996). The results in the present study may indicate the presence not of a major locus but, rather, one or more regions that modify language phenotypes. The effects of these loci may be too weak to be detected by linkage using the number of sib pairs in our study, but they were detectable by association tests. Both of these markers lie within a region that has been implicated in other studies of speech and language impairment, including the study by Schick et al. (2002) of linkage of a

Table 4

Results of AFBAC for the Six Markers Using Discrete Language Phenotypes

		AFBAC RESULTS (*P*)				
MARKER	N^a	All Data	Paternal Data	Maternal Data	Interaction between Transmitted Data and Parent Origin	Interaction between Nontransmitted Data and Parent Origin
D7S1817	142	.7480	.3159	.9789	.4928	.4974
D7S3052	140	.0096	.0033[b]	.2073	.0375	.2177
FOXP2 intron 1 TTTA	90	.0716	.7323	.0141	.8474	.0369
FOXP2 GATA	135	.0507	.7383	.0258	.5486	.4683
FOXP2 intron 3 TTTA	89	.9484	.6481	.3934	.0903	.1483
CFTR GATT	164	<.0001[c]	.0650	<.0004[c]	.9285	.2438

[a] Number of families with heterozygous and homozygous parents.
[b] Significant at level of $P < .05$.
[c] Significant at level of $P < .01$ after Bonferroni correction for the number of markers (i.e., 6).

specific speech phenotype to marker D7S821 at 7q21.3. The *FOXP2* gene is large—at least 600 kb, according to recent findings (Bruce and Margolis 2002)—and patterns of linkage disequilibrium are often saltatory and population dependent. It seems plausible that mutations outside known coding sequences and involving one or more regulatory regions would be candidates for the milder phenotype described in the present study, when compared with the severe language and speech disruptions seen in the KE family. Comprehensive studies of linkage disequilibrium across the 8 Mb defined here, as well as extensive sequencing of all of *FOXP2*—including regulatory regions defined via human-animal model homologies—can now be undertaken to identify one or more specific etiologic variants. It is also possible that one or more genes, other than *FOXP2,* in this region may be involved in the speech/language phenotypes. The significant association to the markers on 7q31 was found using the discrete language phenotype, and additional phenotypic definition may also help in localization. The lack of linkage or association when using quantitative language scores supports the theory that language disorder is distinct rather than just the lower end of the continuum and that the relationship is not linear, as has been reported in a twin study of language delay (Dale et al. 1998). Further investigation of this region is warranted to investigate the genetic component of SLI.

Acknowledgments

Electronic-Database Information

URLs for data presented herein are as follows:

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for the mouse genome [accession number CAAA01121518.1])
Marshfield Medical Research Foundation Center for Medical Genetics, http://research.marshfieldclinic.org/genetics/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for specific language impairment, *FOXP2,* GTS, and Russell-Silver syndrome)
Statistical Analysis for Genetic Epidemiology (SAGE), http://darwin.cwru.edu/octane/sage/sage.php (for release 4.3)
UCSC Human Genome Project Working Draft, http://genome.cse.ucsc.edu/ (for November 2002 assembly)

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