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Report

Replication of Autism Linkage: Fine-Mapping Peak at 17q21

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Autism is a heritable but genetically complex disorder characterized by deficits in language and in reciprocal social interactions, combined with repetitive and stereotypic behaviors. As with many genetically complex disorders, numerous genome scans reveal inconsistent results. A genome scan of 345 families from the Autism Genetic Resource Exchange (AGRE) (AGRE_1), gave the strongest evidence of linkage at 17q11-17q21 in families with no affected females. Here, we report a full-genome scan of an independent sample of 91 AGRE families with 109 affected sibling pairs (AGRE_2) that also shows the strongest evidence of linkage to 17q11-17q21 in families with no affected females. Taken together, these samples provide a replication of linkage to this chromosome region that is, to our knowledge, the first such replication in autism. Fine mapping at 2-centimorgan (cM) intervals in the combined sample of families with no affected females reveals a linkage peak at 66.85 cM, which places this locus at 17q21.

Autism (MIM 209850) is a lifelong neuropsychiatric condition with onset in early childhood. First described in 1943 (Kanner 1943), it is characterized by impairments in language and nonverbal communication, deficits in reciprocal social interactions, and the presence of restricted and repetitive behaviors. Cases of autism may occur in conjunction with chromosomal anomalies, such as duplications on the long arm of chromosome 15q11-13, Rett syndrome (MIM 300005), and fragile-X syndrome (MIM 309550). However, these recognized conditions explain only a small fraction of the observed prevalence of autism, currently estimated to be as high as 3 in 1,000 (Yeargin-Allsopp et al. 2003). Suggestions of a variety of environmental and genetic risk factors for idiopathic autism have resulted in inconsistent findings, and the specific etiologies remain unknown. An autism concordance rate of 92% in MZ twin pairs versus 10% in DZ twin pairs (Bailey et al. 1995) implies that there is a substantial genetic contribution to the risk. However, these very divergent concordance rates indicate that autism is likely to result from the interactive effects of multiple genes, making it genetically complex. Given this level of complexity, it is not surprising that the predisposing genes have thus far remained elusive.

To date, the results of eight independent full-genome scans analyzed for the autism phenotype have been reported (Barrett et al. 1999; Philippe et al. 1999; Risch et al. 1999; Buxbaum et al. 2001; International Molecular Genetic Study of Autism Consortium [IMGSAC] 2001; Auranen et al. 2002; Shao et al. 2002; Yonan et al. 2003). Multiple suggestive but not significant linked loci have emerged from each of these individual studies. A meta-analysis (Badner and Gershon 2002) of four of these autism genome scans (Barrett et al. 1999; Philippe et al. 1999; Risch et al. 1999; IMGSAC 2001) provided evidence of linkage to chromosome 7. Recently, an analysis that considered all eight independent genome scans and focused on detecting common linked regions applied criteria of a maximum LOD score (MLS) >1.5 and a distance of no more than 10 cM between linkage peaks (Smalley et al., in press). The region on chromosome 7 did not satisfy these criteria, and only one region, 17p11-17q11, was linked to autism in more than one of these studies (IMGSAC 2001; Yonan et al. 2003). The lack of consistent linkage results for genetically complex disorders such as autism is not surprising. This is likely due to study differences in such factors as family ascertainment, the instruments used to diagnose autism, the eth-

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nicity of the sample, and the analytic methods employed. Genetic heterogeneity coupled with stochastic fluctuations among samples can also contribute to inconsistent linkage results.

Thus, given the likely genetic complexity of autism and the lack of replication, studies designed to confirm linkage in independent, well-matched samples are critical prior to extensive fine-mapping and association studies. Rules for confirming linkage, developed in the 1970s for Mendelian disorders, preclude the possibility of a replication if there is an overlap in personnel between two studies. These criteria may be too stringent for genetically complex disorders, and Vieland (2001) presents a strong argument for their reformulation. We suggest that an independent sample, from the same cohort, in which family ascertainment, methods of diagnosis, and analytic approaches are identical may be the best sample to use when testing for replication. However, autism cohorts that are large enough to contain independent samples are rare.

The Autism Genetic Resource Exchange (AGRE) cohort currently consists of ~500 nuclear families, each with a sibling pair that meets narrow, "not quite autism" (NQA), or broad definitions of autism (Geschwind et al. 2001). In these families, ascertained in the United States through a proband with autism spectrum disorder and a potentially affected sibling, the parents or caregivers of each child were queried using the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al. 1994). The ADI-R is constructed to diagnose autism on the basis of the classifications of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (World Health Organization 1992), and the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (American Psychiatric Association 2000). The algorithms associated with the ADI-R are used by AGRE to classify the children into the categories of narrow autism, broad spectrum disorder, or NQA. The specific criteria for classification as NQA are listed on the AGRE Web site. Those who do not satisfy the criteria for narrow autism or NQA are classified as having broad spectrum disorder if they display patterns of impairment consistent with those of pervasive developmental disorders but do not meet the criteria for autism because of their age at onset. Nonidiopathic cases of autism—which include those having a premature birth, evidence of a perinatal insult, another diagnosed psychiatric disorder, a small nuclear ribonucleoprotein polypeptide N (SNRPN) chromosome 15 duplication, fragile-X syndrome, or an abnormal imaging or medical test—were omitted from these analyses. MZ twin pairs were omitted from the linkage analyses, although the DZ twin pairs were retained. AGRE has human subjects' approval from the Western Institutional Review Board, and the current study has the approval of the institutional review board of the University of California at Los Angeles (UCLA).

In a previously reported full-genome–scan linkage analysis of the first 345 families (AGRE_1) with at least broad spectrum disorder that were genotyped for 335 multiallelic markers with a sex-averaged map, an MLS of 2.04 ($P < .002$) was observed at 17q11 (Yonan et al. 2003). Additional 17q11 markers genotyped at intermarker distances of ~2 cM resulted in a multipoint MLS of 2.83 ($P < .00029$) at 52 cM. Since males predominate among autistic children, Stone and colleagues (2004) stratified this sample into 148 sibships with no affected females to explore the possibility that there are male-specific loci contributing to autism. This resulted in an MLS of 4.3, revealing evidence of significant linkage to 17q11 (Stone et al. 2004). In a subsequent analysis of a diagnostic subset of these data, the posterior-probability-of-linkage statistic, which allowed for different male and female recombination fractions and parent-of-origin effects, obtained a peak on chromosome 17 at 45 cM (Bartlett et al. 2005).

Here, we undertook a full-genome scan in an independent sample of 109 sibling pairs with at least broad spectrum disorder from the 91 families of AGRE_2 (table 1). The parents and affected offspring were genotyped for 401 multiallelic markers by the Center for Inherited Disease Research, by use of a marker panel different from the one genotyped in AGRE_1. There were 236 markers common to both scans. The markers had an average spacing of 9 cM, and no intermarker gap was >20 cM. A genotyping error rate of 0.02% was inferred by examination of ~11,000 repeat genotypes, and a 3.22% rate of missing data was observed in these pedigrees. Mendelian errors were identified using the GAS software, and the marker data were replaced with unknown genotypes for these families. Misspecifications

Table 1

Sibships in AGRE_2, Stratified by Sex

Sample and No. of Affected Siblings per Family	No. of Sibships	No. of Individuals	No. of Sib Pairs
AGRE_2:			
2	82	164	82
3	9	27	27
Total	91	191	109
Male[a]:			
2	44	88	44
3	4	12	12
Total	48	100	56
Mixed[b]:			
2	38	76	38
3	5	15	15
Total	43	91	53

[a] Sibships with only affected males.
[b] Sibships with at least one affected female.

The figure is available in its entirety in the online edition of *The American Journal of Human Genetics.*

Figure 1 MLS for a whole-genome scan, by chromosome, of 109 autistic sibling pairs in 91 families in AGRE_2. Those regions showing an MLS >1.0 have been identified with the name of the marker nearest the peak.

of family relationships were tested using the RELCHECK software (Boehnke and Cox 1997; Broman and Weber 1998), and a pair of MZ twins was identified and eliminated, resulting in 109 sib pairs for the analysis. The map order and sex-averaged intermarker distances were estimated using the Marshfield marker map (see Center for Medical Genetics Web site).

As in the original analysis of AGRE_1 (Yonan et al. 2003), multipoint MLSs were generated for AGRE_2, by the Genehunter software (Kruglyak et al. 1996), at 1-cM intervals along the chromosomes. No regions of significant linkage were observed for AGRE_2, and only two loci exhibited LOD scores exceeding the replication threshold of 1.4 ($P < .01$) posed by Lander and Kruglyak (1995). The complete results of this scan can be found in figure 1. A 12-cM region on 3p14-3p12 had a peak at 105 cM near *D3S2406,* with an MLS of 1.8, but there was no evidence of linkage to that chromosomal region in AGRE_1. However, a 25-cM region with all LOD scores >1.4 on 17q11-23 had a peak at 61 cM with an MLS of 1.9 near *D17S1299* (fig. 2). To assess whether the linkage signal was derived from the 48 families with no affected females (table 1), as seen in AGRE_1 (Stone et al. 2004), we applied the same strategy to AGRE_2 on chromosome 17. Strikingly, multipoint analyses of AGRE_2 stratified into the 56 sibling pairs from the sibships containing no affected females revealed an MLS of 4.1 with a linkage peak at 61 cM in 17q21. Figure 2 shows the MLS plots for AGRE_2 stratified into 56 pairs from the 48 sibships with no affected females, for the 53 pairs from the 43 sibships with at least one affected female, and for their combination of 109 pairs from the 91 sibships. These linked regions show a considerable overlap, and it is likely that the 9-cM separation between the peak LOD scores is due to the differences between the two samples in the distributions of markers in this region.

We examined the linkage evidence in detail to evaluate whether these study samples together provide a statistical replication of linkage to a single locus on 17q11-21, although we recognized that the replication would

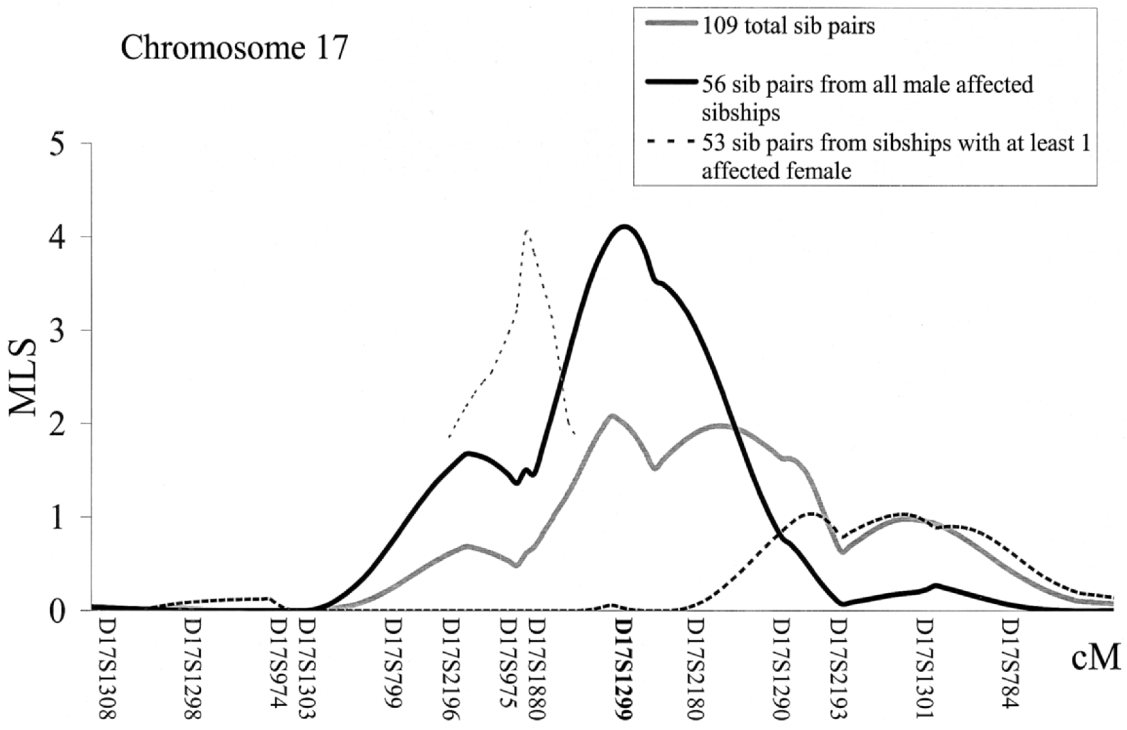

Figure 2 Chromosome 17 linkage-analysis MLSs of 109 autistic sibling pairs from AGRE_2 (*gray line*). MLSs obtained by stratifying the sibships into those with no autistic females are indicated by a black line. MLSs from sibships with at least one autistic female are indicated by a dashed line. The additional gray dashed peak represents the location and MLS plot from the analysis of AGRE_1 sibships with no affected females. The peak marker is in boldface type.

Table 2

Allele Sharing at 17p11-q21 in AGRE_1, Stratified by Sex

Position (cM)	Marker	Proportion of Alleles Shared IBD (*P*) for	
		Total Sample	Male[a]
44		.54 (.007)	.57 (.003)
46		.55 (.005)	.58 (.002)
48	*D17S1871*	.55 (.003)	.58 (.001)
50	*D17S1824*	.56 (.002)	.58 (.001)
51	*D17S1294*	.56 (.002)	.58 (.001)
52	*D17S1800*	.56 (.002)	.59 (.0009)
53	*D17S798*	.55 (.005)	.59 (.0009)
54		.54 (.01)	.58 (.001)
56	*D17S1293*	.53 (.04)	.57 (.004)
58		***.53 (.05)***	***.56 (.008)***
60		.53[b]	.55 (.02)
62	*D17S1299*	.53[b]	.55 (.04)
64		.53[b]	.54 (.04)

Note.—Linkage at position 58 (shown in bold italics) is replicated in AGRE_1 and AGRE_2 families with only affected males.

[a] Sibships with no affected females.

[b] Not significant.

not occur at the linkage peak in either sample. We applied a formal criterion of significant linkage of $P < .000022$ in one sample and $P < .01$ in a second sample (Lander and Kruglyak 1995). Multipoint identical-by-descent (IBD) allele-sharing statistics and their *P* values were generated across the linked regions in AGRE_1 and AGRE_2 separately, through use of the GENIBD and SIBPAL programs of the Statistical Analysis for Genetic Epidemiology (SAGE) software. For the affected sibling pairs from AGRE_1, table 2 reports IBD allele-sharing estimates and their corresponding *P* values at 2-cM intervals and the genotyped markers for the total sample and for the sibships that have no affected females. For AGRE_2, table 3 reports the same information at 4-cM intervals and genotyped markers and includes the IBD allele-sharing estimates for the sibships that have at least one affected female. These statistics are reported for the regions with linkage, beginning at 44 cM, where AGRE_1 showed significant allele sharing ($P < .01$). Table 2 reports these statistics up to 64 cM, for comparison with the results at the peak marker in AGRE_2. Statistics in table 3 extend to 84 cM, beyond which the *P* value is >.01. At position 58 cM, the proportions of IBD allele sharing of .65 with $P = .00002$ and .56 with $P = .008$ in families with no affected females indicate that AGRE_2 linkage is replicated by AGRE_1 at the genomewide level of significance (tables 2 and 3).

Although linkage was replicated statistically, the peaks from the two samples did not coincide. To resolve this difference, we undertook additional fine mapping of 13 multiallelic markers in the combined AGRE samples. The original genome scans of the two samples used different marker sets with different and uneven distributions of intermarker distances. Those markers were excluded from these new analyses. The fine-mapping markers were selected using the criterion that any bias that could be introduced by their distribution or informativeness be minimized. The markers are between positions at 48 and 82 cM, have ~2–3-cM intervals, and have an expected multipoint information content of ⩾.70 or better in the combined sample. Two additional markers, at 24 and 100 cM, serve as anchors.

With use of the Genehunter software (Kruglyak et al. 1996), multipoint and single-point MLS scores were generated at 1-cM intervals across the region from 24 to 100 cM by use of a sex-averaged map of the separate and combined samples of the sibships containing no affected females. Plots of the multipoint MLSs in the separate and combined stratified samples are shown in figure 3. Whereas peaks seen in the original genome scans of AGRE_1 and AGRE_2 are observed at *D17S1294* at 51 cM and at *D17S1299* at 61 cM, respectively, in the present fine-mapping analysis, the most significant LOD score of 4.1 is at marker *D17S2180,* at a distance of 66.85 cM from the p telomere. A 1-LOD drop includes the peak from the second scan, with an MLS of 3.6 at *D17S1299*. The proportion of multipoint allele-sharing IBD in the combined sample estimated at *D17S2180* is .59 ($P = .00002$), by use of the SIBPAL software of the SAGE package. The analogous single-point estimate is .58 ($P = .00002$).

Some factors contributing to this successful stratification strategy have been discussed in detail by Stone et

Table 3

Allele Sharing at 17p11-q23 in AGRE_2, Stratified by Sex

Position (cM)	Marker	Proportion of Alleles Shared IBD (*P*) for		
		Total Sample	Male[a]	Mixed[b]
44	*D17S2196*	.56 (.04)	.63 (.003)	.47
48		.55 (.05)	.62 (.004)	.47
52	*D17S1880*	.55 (.04)	.61 (.005)	.49
56		.57 (.008)	.64 (.0001)	.49
58		***.58 (.004)***	***.65 (.00002)***	***.49***
60		.59 (.003)	.67 (.00001)	.48
61	*D17S1299*[c]	.59 (.003)	.68 (.000009)	.48
64		.58 (.004)	.67 (.00001)	.47
66	*D17S2180*	.58 (.007)	.67 (.00004)	.47
68		.58 (.004)	.66 (.00006)	.48
72		.58 (.002)	.63 (.0003)	.51
76		.58 (.002)	.61 (.003)	.54
80		.59 (.003)	.59 (.02)	.57
81	*D17S1290*	.59 (.004)	.58 (.03)	.57
84		.57 (.007)	.56[d]	.57

Note.—Linkage at position 58 (shown in bold italics) is replicated in AGRE_1 and AGRE_2 families with only affected males.

[a] Sibships with no affected females.

[b] Sibships with at least one affected female.

[c] Peak marker.

[d] Not significant.

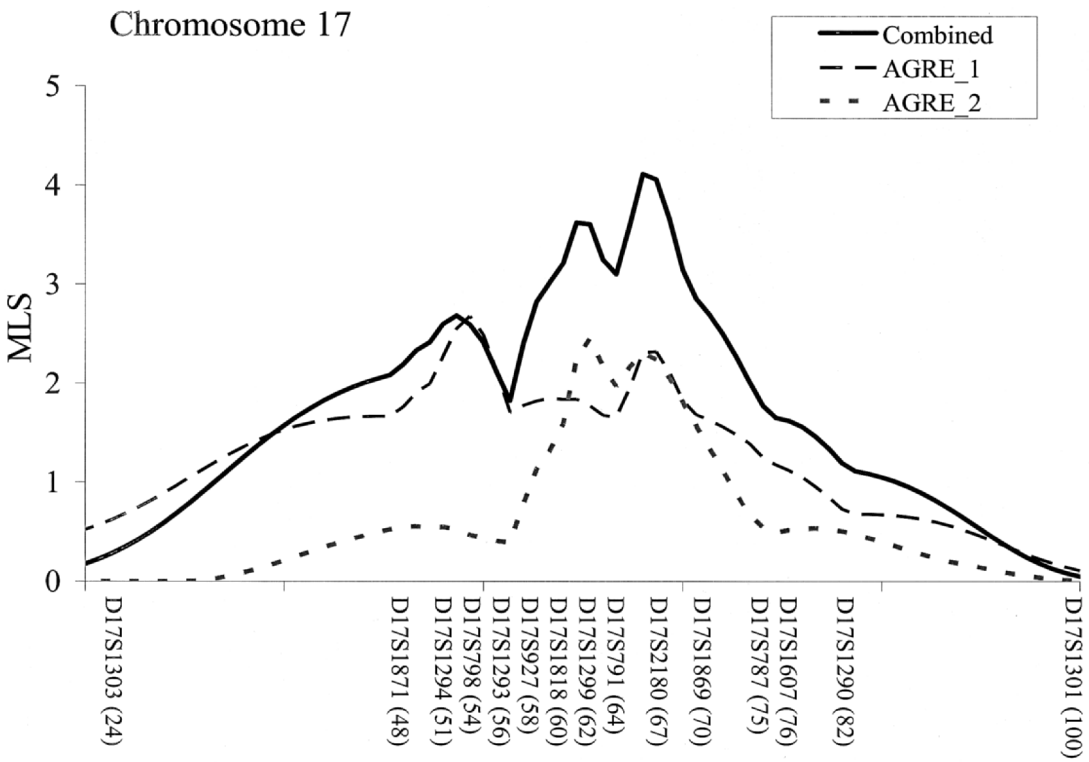

Figure 3 Chromosome 17q fine-mapping linkage-analysis MLSs of 220 autistic sibling pairs with no affected females from AGRE_1 and AGRE_2 separately (*black and gray dashed lines,* respectively) and combined (*solid black line*). Markers and their distances from the p telomere (in parentheses) appear on the horizontal axis.

al. (2004). They include the fact that male and female brains have different structures and function differently and that the incidences of autism and other neurodevelopmental disorders are different between males and females. Here, we turn to the reported analyses of other genetically complex diseases for additional insight. We first note that there have been similar sex-stratification analyses that resulted in positive sex-specific linkage and association findings for other complex traits. In a linkage and association analysis of the insertion-deletion polymorphism of the angiotensinogen-converting enzyme (*ACE*) gene, male-specific association and linkage findings were seen for blood pressure traits in humans (O'Donnell et al. 1998). In a complementary study, gene-targeting experiments in mice provided additional evidence that functional inactivation of the *ACE* gene contributes to blood-pressure levels in males but not in females (Krege et al. 1995). Loughlin and colleagues (2000) were able to remove heterogeneity from a linkage analysis of osteoarthritis and chromosome 2q by use of sex stratification, and the positive linkage signal was observed when the affected individuals were limited to males. In a study of the linkage of inflammatory bowel disease to the HLA region, sex stratification removed heterogeneity and improved the LOD score from 1.2 to 4.5 in the male-only sibships (Fisher et al. 2002). In each case, the mechanism by which the sex effect operates needs additional investigation.

For possible positional candidate genes, the serotonin transporter gene (*SLC6A4*), which codes for a protein controlling the reuptake of serotonin in the synapse (Murphy et al. 2004), is at 49 cM, under the original peak in AGRE_1. It has been investigated by association studies of the combined AGRE_1 and AGRE_2 samples. No evidence for allelic association was observed between the putative functional promoter variant (5-HTTLPR) and autism spectrum disorder; however, evidence of association was observed with two SNPs (A. Yonan and C. Gilliam, personal communication). Given the peak in the combined AGRE_1 and AGRE_2 samples, it is of interest that a recent report addressed the sex-specific genetic architecture of whole-blood serotonin levels in 806 Hutterites from a single pedigree (Weiss et al. 2005). This trait is sexually dimorphic, and a QTL for male serotonin levels was identified on 17q, with the linkage peak at 66 cM, very close to the one identified in the present study. An association with a SNP in the integrin $\beta 3$ (*ITGB3*) gene under the peak at 66 cM was reported by the same group (Weiss et al. 2004). *ITGB3* is a biologically plausible candidate for autism susceptibility be-

cause it is a cell-adhesion molecule involved in nervous system development, including the processes of cell proliferation, migration, differentiation, and synapse maturation (Sajid et al. 2002). This gene provides a good positional candidate for follow-up studies of the combined sex-stratified AGRE sample, since its disruption would clearly affect brain development and functioning, although potentially in a subtle manner.

In conclusion, linkage analyses of 109 autistic sibling pairs from 91 AGRE families in combination with analyses of those pairs from an independent sample of 345 families from the same cohort establish three points. First, stratification of families with autism into only those with affected males reveals significant linkage to 17q11-21 in both samples, supporting the value of this approach. Second, linkage to 17q11-21 is replicated at the genomewide level of significance; this provides the first formal replication of a locus for idiopathic autism. Third, the multipoint linkage evidence in the combined sample localizes the peak to 17q21.

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Electronic-Database Information

The URLs for data presented herein are as follows:

AGRE, http://www.agre.org

Center for Inherited Disease Research, http://www.cidr.jhmi.edu/

Center for Medical Genetics, http://research.marshfieldclinic.org/genetics/ (for the Marshfield marker maps)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for autism, Rett syndrome, and fragile-X syndrome)

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