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An Autosomal Genomic Screen For Autism

Collaborative Linkage Study of Autism: Stacey Barrett,[4] John C. Beck,[2] Raphael Bernier,[1] Erica Bisson,[1] Terry A. Braun,[2] Thomas L. Casavant,[2] Deb Childress,[2] Susan E. Folstein,[1*] Melissa Garcia,[3] Mary Beth Gardiner,[3] Stephen Gilman,[1] Jonathan L. Haines,[3] Kelly Hopkins,[3] Rebecca Landa,[4] Nicole H. Meyer,[2] Julie Ann Mullane,[1] Daryl Y. Nishimura,[2] Pat Palmer,[2] Joseph Piven,[2**] Joy Purdy,[3] Susan L. Santangelo,[1,5] Charles Searby,[2] Val Sheffield,[2] Jennifer Singleton,[2] Susan Slager,[2] Tom Struchen,[2] Sarah Svenson,[1] Veronica Vieland,[2] Kai Wang,[2] Brian Winklosky[1]

[1]*New England Medical Center/Tufts University School of Medicine, Boston, Massachusetts*
[2]*University of Iowa College of Medicine, Iowa City, Iowa*
[3]*Vanderbilt University School of Medicine, Nashville, Tennessee*
[4]*The Johns Hopkins University School of Medicine, Baltimore, Maryland*
[5]*Harvard University School of Public Health, Boston, Massachusetts*

Autism is a severe neurodevelopmental disorder defined by social and communication deficits and ritualistic-repetitive behaviors that are detectable in early childhood. The etiology of idiopathic autism is strongly genetic, and oligogenic transmission is likely. The first stage of a two-stage genomic screen for autism was carried out by the Collaborative Linkage Study of Autism on individuals affected with autism from 75 families ascertained through an affected sib-pair. The strongest multipoint results were for regions on chromosomes 13 and 7. The highest maximum multipoint heterogeneity LOD (MMLS/het) score is 3.0 at D13S800 (approximately 55 cM from the telomere) under the recessive model, with an estimated 35% of families linked to this locus. The next highest peak is an MMLS/het score of 2.3 at 19 cM, between D13S217 and D13S1229. Our third highest MMLS/het score of 2.2 is on chromosome 7 and is consistent with the International Molecular Genetic Study of Autism Consortium report of a possible susceptibility locus somewhere within 7q31-33. These regions and others will be followed up in the second stage of our study by typing additional markers in both the original and a second set of identically ascertained autism families, which are currently being collected. By comparing results across a number of studies, we expect to be able to narrow our search for autism susceptibility genes to a small number of genomic regions. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 88:609–615, 1999.

KEY WORDS: affected sib-pair; linkage; autism

INTRODUCTION

Autism is a severe neurodevelopmental disorder defined by social and communication deficits and ritualistic-repetitive behaviors that are detectable in early childhood and continue, with a fairly predictable course, throughout the life span. Based on genetic epidemiological studies, it is now clear that idiopathic autism is strongly influenced by genes [Santangelo and Folstein, 1999]. The ratio of the sibling recurrence risk (6–8%) [Ritvo et al., 1989] to the population prevalence (2–5/10,000) [American Psychiatric Association, 1994] generates a very large sibling risk ratio (λ_S), ranging from 120–400. The MZ and DZ pairwise twin concordance rates of 60% and 0%, respectively [Bailey et al., 1995], suggest a heritability greater than 90%. Although the mechanism of genetic transmission has not yet been determined, oligogenic transmission is suggested by the patterns of inheritance observed in families as well as the greater than 4:1 ratio of concordance for autism in MZ to DZ twins.

Despite this strong genetic influence, the search for autism genes has only recently begun in earnest. Candidate gene studies have provided conflicting evidence for linkage disequilibrium to the serotonin transporter gene on chromosome 17 [Cook et al., 1997;

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*Correspondence to: Susan Folstein, M.D., Department of Psychiatry, New England Medical Center, 750 Washington Street, #1007, Boston, MA 02111. E-mail: susan.folstein@es.nemc.org

**Correspondence to: Joseph Piven, M.D., CB#7250, 7th Floor Neurosciences Hospital, University of North Carolina School of Medicine, Chapel Hill, NC 27599. E-mail: Joe.Piven@css.unc.edu

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Klauck et al., 1997]. Case reports of a possible excess of cytogenetically detectable duplications on chromosome 15q11-13 in autistic individuals have been reported, prompting further study of this region [Baker et al., 1994]. Pericak-Vance et al. found suggestive evidence of linkage (maximum parametric LOD score = 2.6) in 37 sib-pairs to several polymorphisms in this region, including *GABRB3*, the gamma-aminobutyric acid receptor subunit gene [Pericak-Vance et al., 1997]. Subsequently, Cook et al. reported linkage disequilibrium between autism and *GABRB3*, but not in flanking markers [Cook et al., 1998]. A genome screen reported by the International Molecular Genetic Study of Autism Consortium (IMGSAC) in 87 sib-pair families revealed the strongest evidence for linkage on chromosome 7q [IMGSAC, 1998a, 1998b]. Five other regions were also implicated in that study, with lesser support.

We report here the results of our initial genomic screen for genes underlying autism. We identified several regions of interest, with the strongest results on chromosomes 13 and 7.

MATERIALS AND METHODS

Sample

Seventy-five families with at least two children with autism (including three families with three autistic children) comprise the sample for this study. The families were recruited from three regions of the United States (Midwest, New England, and mid-Atlantic states) through three clinical data collection sites: the University of Iowa, Tufts University-New England Medical Center, and Johns Hopkins University. All probands met algorithm criteria of the Autism Diagnostic Interview-Revised (ADI-R) [Lord et al., 1994] and were at least 3 years old. All probands were assessed with the Autism Diagnostic Observation Schedule (ADOS) [Lord et al., 1989] or a later revision (ADOS-G). Nonverbal IQ estimates were based on available medical records. When medical records were unavailable, minimal IQ estimates were made using the Vineland Adaptive Behavior Scales [Sparrow et al., 1985] and Raven's Progressive Matrices Form Board [Raven, 1956]. Most probands underwent a standardized physical exam for evidence of neurocutaneous abnormalities, localizing neurological signs and dysmorphology. Families were excluded if (1) either proband had evidence of a medical condition associated with autism by history or exam (such as tuberous sclerosis or fragile X syndrome); (2) either proband had evidence of gross central nervous system injury by history or exam; (3) either proband experienced a severe perinatal event; or (4) both probands had nonverbal IQ estimates below 30. The rationale for these exclusion criteria was to decrease sample heterogeneity (e.g., there may be genetic factors unique to families in which both probands have severe/profound mental retardation). Fragile X was ruled out, in at least one autistic child per family, by earlier testing (available through the medical record) or by screening in our laboratory.

Genotyping

Blood samples were taken from all available first-degree relatives. In almost all cases at least two affected siblings and both parents were sampled. DNA from each subject was prepared from whole blood using standard nonorganic protocols. In a small number of cases lymphoblastoid cell lines have been initiated [Anderson and Gusella, 1984]. Short tandem repeat polymorphic markers (STRPs) spanning the genome were utilized for the genomic screening. These markers represent a modified version of Weber set 9 (www.marshmed.org/genetics). The majority of these STRPs are tri- and tetranucleotide repeat polymorphisms developed by the Cooperative Human Linkage Center [Sheffield et al., 1995]. A total of 403 markers were genotyped with an average spacing of 9 cM. An additional 13 markers were added in two regions of particular interest: on chromosome 13, where we obtained our highest signal, and on chromosome 7, based on the reported finding of the IMGSAC [1998a, 1998b].

Genotyping was performed at the University of Iowa (even numbered chromosomes) and Vanderbilt University (odd numbered chromosomes) using essentially the same protocol. Polymerase chain reaction (PCR) amplification of STRPs was performed with 20 ng of genomic DNA in 8.4 μL reactions containing 1.25 μL of PCR buffer (100 mM Tris-HCl [pH 8.8], 500 mM Kcl, 15 mM $MgCl_2$, 0.01% gelatin [w/v], 200 μM each of dATP, dCTP, dGTP and dTTP, 2.5 pmol of each primer and 0.25 unit of Taq DNA polymerase). Samples were amplified for 35 cycles at 94°C for 30 s, 55°C for 30 s, and 72°C for 30 s. PCR products were electrophoresed on 6% polyacrylamide gels containing 7.7 M urea at 60 W for approximately 2 hrs. Gels were silver stained using the method of Bassam et al. [Bassam et al., 1991]. Gels were either transferred to Whatmann paper (Vanderbilt) or the images were captured using a CCD camera (Iowa). In both cases the gels were scored independently by two observers. Genotyping data were entered into a locally developed genotyping and data management system at each site. The database system GenoMap [Scheetz et al., 1998] was used at the Iowa site and for coordination of all data handling across the two sites; the LAPIS database system was used at the Vanderbilt site [Haynes et al., 1995].

Statistical Analysis

(i) Establishing regions of interest for follow-up at Stage 2. Our initial screening strategy entailed calculating an affected sib-pair (ASP) test at each marker, for our Stage 1 data. Any region yielding a p-value ≤ 0.10 would then be retained for follow-up in an independent set of families, currently being collected, for a Stage 2 analysis. We conducted the initial screen using a simple recessive LOD score which, for data such as ours, is equivalent to the ASP test of the hypothesis that the mean number of alleles shared identical by descent is 1 [Knapp et al., 1994]. This test has been shown to be the most powerful ASP test over a range of models [Blackwelder and Elston, 1985]. The maximum LOD score is approximately distributed as a χ^2 (one sided) with one degree of freedom, and accordingly a LOD threshold of 0.36 was used for initial screening purposes. LOD scores were calculated using the MLINK subroutine of the LINKAGE package [Lathrop et al., 1985].

TABLE I. Sample Demographics

Families in screen	75[a]
Total individuals genotyped	298[a]
Autistic probands	152[a]
Males	123
Females	29
Age range (yrs) at ADI	3.0–31.0
Ethnicity	
Caucasian	94.7%
African-American	2.6%
Asian	1.3%
Hispanic	1.3%
Other	0%
Probands by IQ group	
<30	7%
29–49	21%
50–69	33%
70+	34%
Not known	5%
Parental occupation (primary provider)	
Professional/Intermediate	49%
Nonmanual skilled	16%
Manual skilled	17%
Partly skilled/unskilled	16%
Chronically unemployed	1%
No work due to physical/emotional illness	1%
Parental education (primary provider)	
Graduate degree	17%
College degree	42%
Partial college	19%
High school	22%
<High school	0%

[a]One family was not genotyped on the even chromosomes, lowering the total number of families, individuals, and probands for the even chromosome analyses to 74, 295, and 151, respectively.

(ii) Measuring evidence for linkage in the Stage 1 sample. Increased power to detect linkage may be achieved by calculating LOD scores under a dominant as well as a recessive model (as above) [Durner et al., 1999; Vieland et al., 1992], and by explicitly allowing for locus heterogeneity. Consequently, we calculated two LOD scores, one for a dominant model and one for a recessive model, allowing for locus heterogeneity via the admixture model of Smith [Smith, 1963]. Both two-point and multipoint versions of this analysis were run. We report later in this article the higher of the two multipoint scores at each locus, and refer to this as the MMLS/het statistic [Greenberg, 1989; Hodge et al., 1997]. All offspring in our families were affected, all parents were designated as phenotypically unknown, and the low population prevalence of autism means that allowing for intrafamilial phenocopies is unnecessary. Therefore, only one parameter is involved in specification of the genetic model for these analyses, viz., the disease allele frequency. We set this frequency to arbitrarily high values of 0.10 for the recessive model and 0.04 for the dominant. Two-point analyses were run using the MLINK and HOMOG subroutines of the LINKAGE package [Lathrop et al., 1985]; multipoint MMLS/het analyses were run in GENEHUNTER [Kruglyak et al., 1996], with scores calculated at each marker locus and at 10 points between markers. We also report NPL p-values as calculated by GENEHUNTER.

We note that 4.6 times the two-point admixture LOD score is approximately distributed as a χ^2 with between 1 and 2 degrees of freedom, while 4.6 times the multipoint admixture LOD score is approximately distributed as a χ^2 with 1 degree of freedom (because only the admixture parameter α is estimated). But for the MMLS/het statistic, a correction is needed to the corresponding χ^2 distribution to compensate for our having calculated two LOD scores (one dominant, one recessive) at each locus. Hodge et al. [1997] showed that (under homogeneity) adding 0.3 to the ordinary significance cut-off is a conservative correction for the two tests. At the one locus where we have evidence of linkage in the Stage 1 data set (see below), we also maximized the LOD score over the sole parameter of the genetic model (disease allele frequency), which allows us to evaluate the evidence for linkage at (or near) the true point of maximum likelihood. This technique has been shown to be a mathematically correct way to estimate the gene frequency [Hodge and Elston, 1994; Vieland and Hodge, 1996], assuming that there really is linkage, and it has been shown to yield good param-

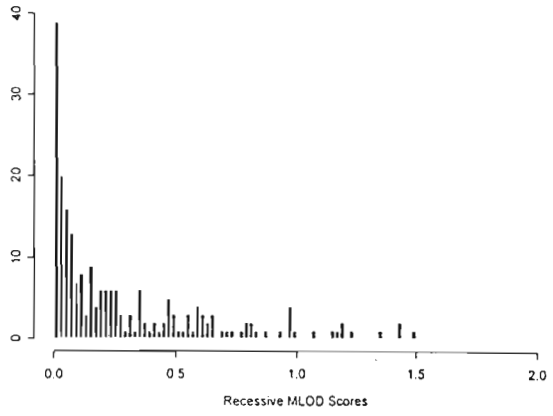

Fig. 1. Frequency distribution of two-point recessive maximum homogeneity lod scores (ASP tests).

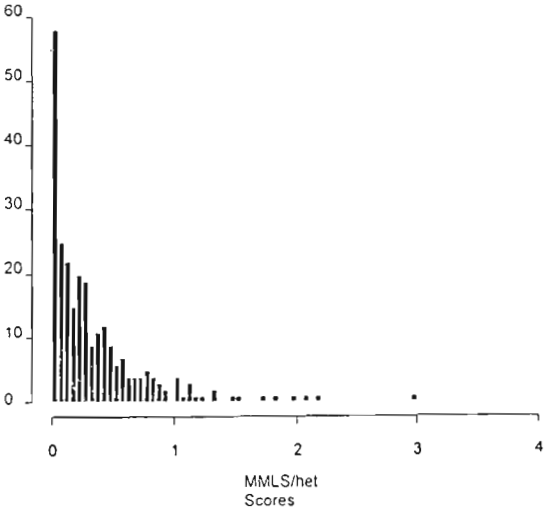

Fig. 2. Frequency distribution of multipoint MMLS/het scores.

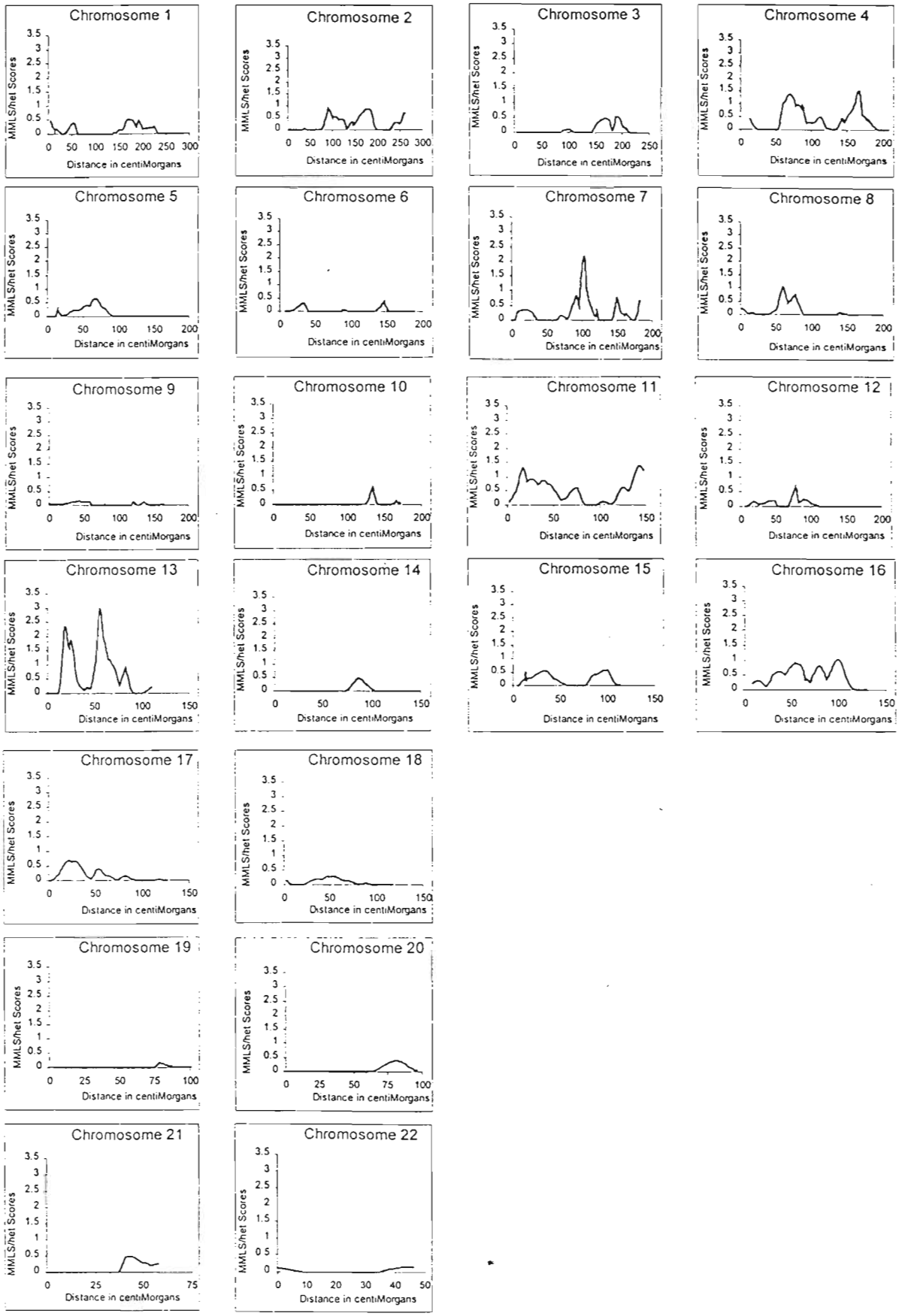

Fig. 3. Plot of MMLS/het scores across all autosomes. Note: scores are calculated at 416 markers and at 10 points between each pair of markers.

eter estimates even when the mechanism of inheritance is oligogenic [Greenberg and Berger, 1994].

RESULTS

Sample demographics are described in Table I. Two hundred and ninety-eight individuals from 75 families were genotyped for all chromosomes; one family was not genotyped on the even chromosomes. Among the individuals with autism, the ratio of males to females is 4.2:1, which is consistent with the fourfold increase in the prevalence of autism among males [American Psychiatric Association, 1994]. The ethnicity of the sample was predominately Caucasian (94.7%), probably because a large number of the families were from the Midwest (N = 51) and, in particular, from the Iowa site. Assuming those with an unknown IQ are in the lower IQ groups, 66% of the individuals with autism were in the mentally retarded IQ range. This proportion of autistic individuals with mental retardation is consistent with epidemiological reports in the literature [American Psychiatric Association, 1994].

Regions Identified for Follow-Up at Stage 2

Figure 1 shows the frequency distribution of Z_{ASP}, the maximum 2-point homogeneity LOD scores (ASP tests) for the 217/403 markers yielding a maximum LOD > 0.

A total of 60 Z_{ASP} scores, or 15% of the total 403 markers analyzed, exceeded the threshold (LOD = 0.36) for follow-up. These markers span roughly 27 regions on 16 chromosomes, including the region on chromosome 7 previously identified by the IMGSAC [IMGSAC, 1998a, 1998b], and the region of chromosome 15 identified by Pericak-Vance et al. [1997] and others [Cook et al., 1998; Schroer et al., 1998].

Evidence for Linkage in the Stage 1 Sample

Figure 2 shows the frequency distribution of the multipoint MMLS/het scores for the 259/416 markers with scores >0, including the 403 markers from the original screening set and thirteen additional follow up markers on chromosomes 7 and 13. As can be seen in Figure 2, three markers have MMLS/het scores >2; two of these are on chromosome 13, and the third is on chromosome 7.

Our region of greatest interest is on chromosome 13, where the peak multipoint MMLS/het score is 3.0 under the recessive model at marker D13S800 (55 cM; NPL p value = 0.008). We estimate that 35% of families in our data are linked to this locus. It is of interest to note that under the dominant model, the MMLS/het at this locus is 1.1. Greenberg and Berger [1994] have shown that a difference of two LOD units is strong evidence in favor of one mode of inheritance over the other when there really is linkage. Additionally, when we maximize the MMLS/het over disease allele frequency, the MMLS/het score is 3.4 at a disease allele frequency of ≤.002, with an estimated 30% of families linked. A second, smaller peak occurs around 19 cM, between markers D13S217 and D13S1229, with a MMLS/het = 2.3 under the recessive model (NPL p-value = 0.019). We estimate that 33% of families are linked to this locus. Our third highest peak (MMLS/het = 2.2 under the recessive model; NPL p-value = 0.022) occurs on chromosome 7 at marker D7S1813 around 104 cM, with 29% of families estimated to be linked to this locus. Figure 3 shows plots of the multipoint MMLS/het scores across all autosomes.

DISCUSSION

We examined 75 families with 416 markers. Our strongest result is an MMLS/het score of 3.0 on chromosome 13, at D13S800 (map position 55 cM). Assuming an autosomal recessive model we estimate that approximately 35% of families in our data set are linked to this locus. The one other published genomic screen in autism [IMGSAC, 1998a] reported an MLS of approximately 0.60, approximately 20 cM distal to our highest peak on chromosome 13. Studies of simulated data sets have shown that peaks around a true locus can vary by as much as 15 cM in either direction in different samples from the same population [Hauser et al., 1996]. Thus, two peaks even 30 cM apart may represent the same underlying locus, suggesting that the IMGSAC score might represent the same locus. Also of note, the IMGSAC analysis did not explicitly allow for locus heterogeneity. If indeed only a subset of families in their data set are linked to this locus, allowance for heterogeneity might increase their signal at that locus.

Our other strong region of interest is on chromosome 7 (MMLS/het = 2.2, at D7S1813, map position 104 cM, under the recessive model), where we estimate 29% of our families are linked. A second smaller peak on chromosome 7 (MMLS/het = 0.8) occurs at GATA32C12 at 150 cM. The IMGSAC [1998a] reported their highest LOD score (2.5 calculated using ASPEX) on chromosome 7 at map position 145 cM. Their follow up of this region with additional markers and families yielded a peak LOD of 3.6 near D7S530 at 135 cM. [IMGSAC, 1998b]. This locus falls between our primary and secondary peaks on this chromosome, suggesting the possibility that a single locus lies in this region. Given the strong evidence in the IMGSAC sample, our results lend further support to the importance of this region in autism. Also of note, Fisher et al. [1998] have mapped a locus for a specific speech and language disorder (SLI) gene (*SPCH1*) between D7S2459 and D7S643 (at 121–125 cM), and others have suggested that these two conditions, autism and SLI, may have overlapping genetic etiologies [Lord and Paul, 1997].

Another region of interest is at the proximal end of chromosome 15 (15q11-13), which has received substantial attention because of both cytogenetic abnormalities [Baker et al., 1994] and positive genetic linkage results that have been reported [Cook et al., 1998, Pericak-Vance et al., 1997]. Our maximum MMLS/het scores in this region are 0.51 and 0.54 at D15S975 (13 cM) and ACTC (32 cM), respectively. Thus, we are unable to confirm or deny the presence of a chromosome 15 susceptibility locus in our data.

The interpretation of linkage results based on multiple data sets is a particularly vexing problem for complex diseases, with failure to replicate appearing to be the rule rather than the exception. For example, four

genomic screens in MS [Ebers et al., 1996; Haines et al., 1996; Kuokkanen et al., 1997; Sawcer et al., 1996] reported a total of 77 different regions across all four studies, only 20 of which overlapped in at least two studies and only 2 of which overlapped all four studies.

However, this failure to replicate does not demonstrate that the initial findings were false positives. Suarez et al. [1994] have shown that replication of a true linkage may require substantially larger sample sizes than those required for initial detection. More recently, Wang et al. [In press] have confirmed an important corollary to this: that when similarly sized data sets are used, it is expected that true findings will be followed up by nonreplications as a matter of course. Thus, while the concordance between our findings and the IMGSAC findings on chromosome 7 are promising, the fact that the IMGSAC does not report a strong signal similar to the one we report on chromosome 13 (a likelihood ratio of 1000:1 in favor of linkage) cannot necessarily be interpreted as evidence that a true linkage does not exist in that region. In summary, we have identified evidence for linkage to a previously unreported region on chromosome 13, and obtained evidence in support of a previously implicated region on chromosome 7. We are currently undertaking the second stage of our project, which involves collecting an additional 100 families for follow-up analysis.

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NOTE ADDED IN PROOF

Since our manuscript was accepted, two additional genome screens of multiplex autism families have been published:

Philippe A, Martinez M, Guilloud-Bataille M, et al. 1999. Genome-wide scan for autism susceptibility genes Hum Mol Genet 8:805–812.

Risch N, Spiker D, Lotspeich L, et al. 1999. A genomic screen of autism: evidence for a multilocus etiology. Am J Hum Genet 65:493–507.

REFERENCES

American Psychiatric Association. 1994 Diagnostic and statistical manual of mental disorders, 4th ed. Washington, D.C.: American Psychiatric Association.

Anderson M, Gusella J. 1984. Use of cyclosporin A in establishing Epstein-Barr virus-transformed human lymphoblastoid cell lines. In Vitro 20: 856–858.

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(1):63–77.

Baker P, Piven J, Schwartz S, Patil S. 1994. Brief report: duplication of chromosome 15q11-13 in two individuals with autistic disorder. J Autism Dev Disord 24:529–535.

Bassam B, Caetano-Anolles G, Gresshoff P. 1991. Fast and sensitive silver staining of DNA in polyacrylamide gels. Anal Biochem 196:80–83.

Blackwelder WC, Elston RC. 1985. A comparison of sib-pair linkage tests for disease susceptibility loci. Genet Epidemiol 2:85–97. [Published erratum appears in Genet Epidemiol 1986; 3:379.]

Cook EHJ, Courchesne R, Lord C, Cox NJ, Yan S, Lincoln A, Haas R, Courchesne E, Leventhal, BL. 1997. Evidence of linkage between the serotonin transporter and autistic disorder. Mol Psychiatry 2:247–250.

Cook EHJ, Courchesne RY, Cox NJ, Lord C, Gonen D, Guter SJ, Lincoln A, Nix K, Haas R, Leventhal BL, Courchesne E. 1998. Linkage-disequilibrium mapping of autistic disorder, with 15q11-13 markers. Am J Hum Genet 62:1077–1083.

Durner M, Vieland VJ, Greenberg DA. 1999. Further evidence for the increased power of LOD scores compared with nonparametric methods. Am J Hum Genet 64:281–289.

Ebers GC, Kukay K, Bulman DE, Sadovnick AD, Rice G, Anderson C, Armstrong H, Cousin K, Bell RB, Hader W, Paty DW, Hashimoto S, Oger J, Duquette P, Warren S, Gray T, P OC, Nath A, Auty A, Metz L, Francis G, Paulseth JE, Murray TJ, Pryse-Phillips W, Risch N, et al. 1996. A full genome search in multiple sclerosis. Nat Genet 13:472–476.

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

Greenberg DA. 1989. Inferring mode of inheritance by comparison of LOD scores. Am J Hum Genet 34:480–486.

Greenberg DA, Berger B. 1994. Using LOD-score differences to determine mode of inheritance: a simple, robust method even in the presence of heterogeneity and reduced penetrance. Am J Hum Genet 55:834–840.

Haines JL, Ter-Minassian M, Bazyk A, Gusella JF, Kim DJ, Terwedow H, Pericak-Vance MA, Rimmler JB, Haynes CS, Roses AD, Lee A, Shaner B, Menold M, Seboun E, Fitoussi RP, Gartioux C, Reyes C, Ribierre F, Gyapay G, Weissenbach J, Hauser SL, Goodkin DE, Lincoln R, Usuku K, Oksenberg JR, et al. 1996. A complete genomic screen for multiple sclerosis underscores a role for the major histocompatability complex. Nat Genet 13:469–471.

Haynes C, Speer MC, Peedin M, Roses AD, Haines JL, Vance JM, Pericak-Vance MA. 1995. PEDIGENE: a comprehensive data management system to facilitate efficient and rapid disease gene mapping. Am J Hum Genet 57:A193.

Hauser ER, Boehnke M, Guo SW, Risch N. 1996. Affected-sib-pair interval mapping and exclusion for complex genetic traits: sampling considerations. Genet Epidemiol 13:117–137.

Hodge SE, Abreu PC, Greenberg DA. 1997. Magnitude of type I error when single-locus linkage analysis is maximized over models: a simulation study. Am J Hum Genet 60:217–227.

Hodge SE, Elston RC. 1994. Lods, wrods, and mods: the interpretation of lod scores calculated under different models. Genet Epidemiol 11:329–342.

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

International Molecular Genetic Study of Autism Consortium (IMGSAC). 1998b. Linkage disequilibrium mapping and candidate gene analysis of autism. Am J Hum Genet 63(suppl):A298. Abstract 1723.

Klauck SM, Poustka F, Benner A, Lesch KP, Poustka A. 1997. Serotonin transporter (5-HTT) gene variants associated with autism? Hum Mol Genet 6:2233–2238.

Knapp M, Seuchter SA, Baur MP. 1994. Linkage analysis in nuclear families. 2: relationship between affected sib-pair tests and lod score analysis. Hum Hered 44:44–51.

Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES. 1996. Parametric and nonparametric linkage analysis: a unified multipoint approach. Am J Hum Genet 58:1347–1363.

Kuokkanen S, Gschewend M, Rioux JD, Daly MJ, Terwilliger JD, Tienari PJ, Wilstrom J, Palo J, Stein LD, Hudson TJ, Landers ES, Peltonen L. 1997. Genome-wide scan of multiple sclerosis in Finnish multiplex families. Am J Hum Genet 61:1379–1387.

Lathrop GM, Lalouel JM, Julier C, Ott J. 1985. Multilocus linkage analysis in humans: detection of linkage and estimation of recombination. Am J Med Genet 46:482–253.

Lord C, Paul R. 1997. Language and communication in autism. In: Cohen DJ, Volkmar FR, editors. Handbook of autism and pervasive developmental disorders, 2nd ed. New York: John Wiley & Sons. p 195–225.

Lord C, Rutter M, Goode S, Heemsbergen J, Jordan H, Mawhood L, Schopler E. 1989. Autism diagnostic observation schedule: a standardized

observation of communicative and social behavior. J Autism Dev Disord 19:185–212.

Lord C, Rutter M, LeCouteur A. 1994. Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord 24:659–685.

Pericak-Vance M, Wolpert C, Menold M, Bass M, DeLong G, Beaty L, Zimmerman A, Potter N, Gilbert J, Vance J, Wright H, Abransom R, Cuccaro M. 1997. Linkage evidence supports the involvement of chromosome 15 in autistic disorder. Am J Hum Genet 61(suppl):S40. Abstract 208.

Raven J. 1956. The coloured progressive matrices. London: H.K. Lewis.

Ritvo ER, Jorde LB, Mason-Brothers A, Freeman BJ, Pingree C, Jones MB, McMahon WM, Petersen PB, Jenson WR, Mo A. 1989. The UCLA-University of Utah epidemiologic survey of autism: recurrence risk estimates and genetic counseling. Am J Psychiatry 146:1032–1036.

Santangelo SL, Folstein SE. 1999. Autism: a genetic perspective. In: Tager-Flusberg H, editor. Neurodevelopmental disorders: contributions to a new framework from the cognitive neurosciences. Boston: MIT Press. p 431–448.

Sawcer S, Jones HB, Feakes R, Gray J, Smaldon N, Chataway J, Robertson N, Clayton D, Goodfellow PN, Compston A. 1996. A genome screen in multiple sclerosis reveals susceptibility loci on chromosome 6p21 and 17q22. Nat Genet 13:464–468.

Scheetz TE, Braun TA, Munn KJ, Stone EM, Sheffield VC, Casavant TL. 1998. GenoMap; a distributed system for unifying genotyping and genetic linkage analysis. J Parallel Computing.

Schroer RJ, Phelan MC, Michaelis RC, Crawford EC, Skinner SA, Cuccaro M, Simensen RJ, Bishop J, Skinner C, Fender D, Stevenson RE. 1998. Autism and maternally derived aberrations of chromosome 15q. Am J Med Genet 76:327–336.

Sheffield VC, Weber JL, Buetow KH, Murray JC, Even DA, Wiles K, Gastier JM, Pulido JC, Yandava C, Sunden SL, et al. 1995. A collection of tri- and tetranucleotide repeat markers used to generate high quality, high resolution human genome-wide linkage maps. Hum Mol Genet 4:1837–1844.

Smith CAB. 1963. Testing for heterogeneity of the recombination fraction values in human genetics. Ann Hum Genet 27:175–182.

Sparrow SS Cicchetti DV. 1985. Diagnostic uses of the Vineland Adaptive Behavior Scales. J Pediatr Psychol 10:215–225.

Suarez B, Hampe C, Van Eerdewegh P. 1994. Problems of replicating linkage claims in psychiatry. In: Gershon E, Cloninger C, editors. Genetic approaches to mental disorders. Washington, DC: American Psychiatric Press. p 23–46.

Vieland VJ, Hodge SE. 1996. The problem of ascertainment for linkage analysis. Am J Hum Genet 58:1072–1084.

Vieland VJ, Hodge SE, Greenberg DA. 1992. Adequacy of single-locus approximations for linkage analyses of oligogenic traits. Genet Epidemiol 9:45–59.

Wang K, Vieland VJ, Huang J. In press. A Bayesian approach to replication of linkage studies. In: Goldin L, Amos CI, Chase GA, Goldstein AM, Jarvik GP, Martinez MM, Suarez BK, Weeks DW, Wijsman EM, and MacCluer JW. Genetic Analysis Workshop 11. Analysis of Genetic and Environmental Factors in Common Diseases. Genetic Epidemiology.