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# A Systematic Genomewide Linkage Study in 353 Sib Pairs with Schizophrenia

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**We undertook a genomewide linkage study in a total of 353 affected sib pairs (ASPs) with schizophrenia. Our sample consisted of 179 ASPs from the United Kingdom, 134 from Sweden, and 40 from the United States. We typed 372 microsatellite markers at ~10-cM intervals. Our strongest finding was a LOD score of 3.87 on chromosome 10q25.3-q26.3, with positive results being contributed by all three samples and a LOD-1 interval of 15 cM. This finding achieved genomewide significance ($P < .05$), on the basis of simulation studies. We also found two regions, 17p11.2-q25.1 (maximum LOD score [MLS] = 3.35) and 22q11 (MLS = 2.29), in which the evidence for linkage was highly suggestive. Linkage to all of these regions has been supported by other studies. Moreover, we found strong evidence for linkage (genomewide $P < .02$) to 17p11.2-q25.1 in a single pedigree with schizophrenia. In our view, the evidence is now sufficiently compelling to undertake detailed mapping studies of these three regions.**

## Introduction

Schizophrenia (MIM 181500) is a common disorder with a lifetime morbid risk of 1% (or more, if spectrum disorders are included) (Gottesman 1991). It is a major cause of morbidity and consumes a great deal of long-term medical and social care. Pathophysiological theories have been dominated for many years by the hypothesis that the disorder reflects a disturbance of dopaminergic neurotransmission. More recently, this has been extended to include serotonergic, glutamatergic, and GABAergic dysfunction (Bray and Owen 2001). However, strong evidence for a primary neurochemical abnormality has not been established, and schizophrenia is increasingly thought of as a neurodevelopmental disorder (Weinberger 1987; Murray and Lewis 1988) characterized by abnormal synaptic connectivity (Harrison 1999). A number of risk factors have been implicated by epidemiological studies (Murray et al. 2003). However, the direction of causation is often unclear; the findings rarely suggest particular pathological mechanisms; and relative risks tend to be small compared with those conferred by a history of illness in a close relative (Owen et al. 2002).

A large number of family, twin, and adoption studies show that individual differences in liability are predominantly genetic, with heritability estimates of ~80% (Owen et al. 2002). The most common mode of transmission are probably oligogenic, polygenic, and a mixture of the two with a threshold effect (Owen et al. 2002). However, the number of susceptibility loci, the disease risk conferred by each locus, the extent of genetic heterogeneity, and the degree of interaction among loci all remain unknown. Risch (1990) has calculated that the data for recurrence risks in the relatives of probands with schizophrenia are incompatible with the existence of a single locus conferring a relative risk in siblings ($\lambda s$) of >3, and, unless extreme epistasis exists, models with two or three loci of $\lambda s \leqslant 2$ are more plausible. It should be emphasized that these calculations are based on the assumption of homogeneity and refer to populationwide $\lambda s$. It is quite possible that alleles of larger effect are operating in some groups of patients—for example, families chosen for having a high density of illness. However, such families would also be expected to occur even under polygenic inheritance, and their existence does not force the conclusion that alleles of large effect exist (McGue and Gottesman 1988). As for other common genetic disorders, the moderate to

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weak effect at any given locus makes the task of identifying susceptibility genes difficult. It implies the need for large sample sizes for initial findings and even more so for replication (Owen et al. 2000). Further difficulties arise from the fact that the phenotype is mostly syndromic, as well as from the absence of compelling intermediate phenotypes that are easy to test in large populations. Nevertheless, given the evidence for substantial heritability, the difficulties inherent in studying the brain directly, and the lack of strong epidemiological clues to pathophysiology, the case for pursuing the genetics of schizophrenia is persuasive.

The results of linkage studies of schizophrenia have seemed to some to be disappointing, with positive studies often falling short of being compelling and failures to replicate being abundant. However—as >20 genomewide studies have been reported and as sample sizes and, hence, power have increased—positive, replicated linkages to several chromosomal regions have accumulated. The details of these studies have been comprehensively reviewed elsewhere (Williams et al. 2002; O'Donovan et al. 2003). Three of the best-supported regions are 6p24-22 (MIM 600511), 1q21-22 (MIM 604906), and 13q32-34 (MIM 603176). In these cases, single studies achieved genomewide significance at $P < .05$ (Straub et al. 1995; Blouin et al. 1998; Brzustowicz et al. 2000), and, in each case, suggestive positive findings have also been reported in other samples (Moises et al. 1995; Schizophrenia Linkage Collaborative Group 1996; Maziade et al. 1997; Brzustowicz et al. 2000; Schwab et al. 2000; Gurling et al. 2001; Lindholm et al. 2001). Other promising regions in which positive findings have been obtained from more than one study include 8p21-22 (MIM 603013), 6q21-25 (MIM 603175), 22q11-12 (MIM 600850), 5q21-q33, 10p15-p11, and 1q42 (Williams et al. 2002; O'Donovan et al. 2003).

None of the above regions has consistently been replicated in the majority of genome scans, and it is likely that some represent false positives. However, we also expect true linkages to fail to replicate in complex disorders, because replication of loci with small populationwide effects requires larger samples than the original data set (Suarez et al. 1994), and power for replication is often even less than assumed since initial studies tend to overestimate effect sizes (Göring et al. 2001). These issues are likely to be pertinent to schizophrenia, because the sample sizes for most genome scans have been small, with typical samples of 20–100 families, while the largest to date included 294 small pedigrees (DeLisi et al. 2002). Our previous genome scan (Williams et al. 1999), which was until recently the largest published study, found no areas of linkage at genomewide significance and suggested that the genes for schizophrenia are likely to be of modest to small effect (populationwide $\lambda s \leqslant 2$). It is clear, therefore, that larger studies are needed.

Some of the problems of power and replication can be addressed by meta-analysis, although this has limitations (Levinson et al. 2003). A recent such study included 20 schizophrenia genome scans (Lewis et al. 2003). The number of loci meeting aggregate criteria for significance was much greater than the number of loci expected by chance ($P < .001$), revealing greater consistency than had been previously recognized. The authors concluded that schizophrenia loci are highly likely to be present in some, perhaps even all, of the regions 2p, 2q, 5q, 3p, 11q, 6p, 1p, 1q, 22q11-12, 8p, 20p, and 14pter-q13. Other regions were also implicated, but the evidence was somewhat weaker. These were 16p-q, 18q, 10p, 15q, 6q, and 17q. Another meta-analysis (Badner and Gershon 2002) found significant results only on chromosomes 8p, 13q, and 22q. The two studies differed in many important respects, including the fundamental approach, but it seems reasonable that because it was based on a larger and more complete data set, the study by Lewis and colleagues (2003) identified additional significant regions.

Given that the results of our first sib-pair genome scan, supported by evidence from genetic epidemiology, suggested that the genes for common forms of schizophrenia are likely to be of modest to small effect ($\lambda s \leqslant 2$), we undertook a more highly powered genome scan. We typed markers at 10-cM intervals in a total of 353 affected sib pairs (ASPs). Our sample consisted of 179 ASPs from our original U.K. sample, 134 ASPs from Sweden, and 40 from the United States. It should be noted that, in our first sib-pair study, we adopted a two-stage strategy and undertook a genomewide screen in only 97 of our ASPs (Williams et al. 1999). Moreover, we only typed a relatively low density of markers (~20 cM) and did not type parents or unaffected siblings. In the present study, we typed the ASPs, together with parents and unaffected siblings, at a greater density (~10 cM), using the more informative ABI Prism Linkage Mapping Set, version 2 (Applied Biosystems), as well as substantially increasing the sample size by including ASPs from Sweden and the United States. The resulting sample of 353 ASPs is one of the largest studied to date. We report linkage of schizophrenia to chromosome 10q25.3-q26.3 (maximum LOD score [MLS] = 3.87), with a LOD-1 interval of 15 cM. This finding achieved genomewide significance ($P < .05$), on the basis of simulation studies. We have also identified highly suggestive evidence for linkage at two other regions, 17p11.2-q25.1 (MLS = 3.35) and 22q11 (MLS = 2.29). Linkage to all three regions has been supported by other studies.

## Materials and Methods

### *Patient Resources*

We report data from 353 ASPs (including 353 broad diagnoses and 287 narrow diagnoses) drawn from 272 families. For narrow diagnosis, both sibs had schizophrenia or schizoaffective disorder, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). The broad category included extra pairs in which one had a narrow diagnosis but the other had any nonorganic psychotic disorder or schizotypal personality disorder. Our sample consisted of 179 ASPs (170 narrow) from the United Kingdom, 134 ASPs from Sweden (79 narrow), and 40 from the United States (38 narrow). Within-family relationships were confirmed by examination of the degree of allele sharing across the genome, as described below.

Ascertainment and collection of the U.K. sample has been fully described elsewhere (Williams et al. 1999). ASPs were ascertained through mental health services and relatives' support groups in England, Wales, Scotland, and the Republic of Ireland. All individuals were white and had been born in the United Kingdom or the Republic of Ireland. All patients gave written, informed consent, as approved by the Multi-Centre Research Ethics Committee and the relevant local research ethics committee. In Sweden, families were ascertained through the Mental Health Inpatient Register and the Swedish Second Generation Register. Patients who had a register diagnosis of "ICD-10 schizophrenia" were included. All individuals were white and had been born in Sweden. All gave written, informed consent, as approved by the institutional review board of the Karolinska Institute. In Pittsburgh, recruitment occurred primarily at the university-affiliated tertiary care center, which also serves as a catchment-area hospital. Inpatients and outpatients were also sought at 35 university hospitals, nonacademic community centers, and hospitals and state facilities located within a 500-mile radius of Pittsburgh. All participants provided written, informed consent, as approved by the institutional review board of the University of Pittsburgh. All patients were white.

### *Diagnosis*

In the United Kingdom, consensus diagnoses were made by two independent, trained raters on the basis of all available clinical information, including a semistructured interview (PSE-9 [Wing et al. 1974] or SCAN [Wing et al. 1990]), case notes, and information from relatives and mental health professionals. All interviews were conducted by psychiatrists or psychologists. Vignettes were prepared on background, interview, and case-note data. Clinical information was collated using the Operational Criteria Checklist for Psychotic Illness (OPCRIT) (McGuffin et al. 1991), the Scales for the Assessment of Positive and Negative Symptoms (SAPS/SANS), and the Global Assessment Scale (GAS). The rating scales were completed by the interviewer, and individual members of pairs were rated by separate raters in 69.4% of cases. Each case was separately rated by two independent raters and a consensus diagnosis was reached. If there were any discrepancies, the case was brought to a full team meeting so consensus could be reached or the case was excluded. For each rater to obtain her/his kappa-score reliability, 40 cases were rated against the consensus diagnosis. Inter-rater reliability for diagnosis was excellent, with an average kappa score of 0.9 for all raters, for the duration of the study.

The methods used in Sweden were modeled closely on those used in the United Kingdom. Moreover, the Swedish raters were trained by members of the U.K. team. Specially trained research nurses performed a semistructured interview with each patient in her/his home, using SCAN, SAPS, and SANS. Patients' lifelong psychiatric records were also collected (average number of hospitalization records per patient = 10), and, in most cases, information from the relatives was also obtained. Vignettes were then prepared by collecting all the data. Once again, diagnoses were made independently by two clinicians on the basis of all available information, and consensus was sought in the case of disagreement. Inter-rater reliability for diagnosis was established, with an average kappa score of >0.9. In the United States, clinical information was obtained using the Diagnostic Interview for Genetic Studies (DIGS), as well as medical records and supplemental information from relatives, as appropriate (Nurnberger et al. 1994). Consensus diagnoses were established by two psychiatrists/psychologists using DSM-IV criteria. Those making the diagnoses were blind to family history. Inter-rater reliability was examined throughout the study (kappa >0.80). In addition, we assessed the inter-rater reliability between the U.K. and U.S. centers by the blind-rating of case histories (kappa >0.90).

### *Markers*

Included in this study were 372 microsatellite markers. Most ($n$ = 352) were selected from the ABI Phase Linkage Mapping Set, version 2, with a further 20 being added from the Marshfield genetic map (see the Web site for the Marshfield Center for Medical Genetics). This resulted in an average intermarker distance of 10.22 cM across the genome. The marker order and the distances between them were checked by referring to the high-resolution genetic map determined by Kong et al. (2002), where possible, and by using CRI-MAP (Lander and Green 1987).

### *Genotyping*

All DNA samples were extracted either from whole blood or from saline mouthwash samples, using standard procedures. PCR was performed in 12 $\mu$l volumes containing 24 ng of genomic DNA, 1.4 pmol of each primer, 400 $\mu$M dNTPs, 1.2 $\mu$l of 10 × PCR reaction buffer (Qiagen), and 0.3 U of HotStar*Taq* polymerase (Qiagen). All PCRs were performed on MJ Research Tetrad thermal cyclers, with an initial denaturation stage at 95°C for 15 min, followed by a touchdown procedure of 11 cycles (5 s at 94°C, 5 s at 60°C, 10 s at 72°C [−0.5°C/cycle]), which was then followed by 27 cycles of 5 s at 94°C, 5 s at 54°C, and 10 s at 72°C, and a final 10 min at 72°C. Reactions for each marker were prepared separately, with products multiplexed into size-specific sets prior to gel electrophoresis. All markers were genotyped on ABI Prism 3100 sequencers using the software GeneScan and Genotyper (Applied Biosystems).

### *Statistical Analysis*

Genetic relationships between family members were confirmed using marker data from across the genome and a suite of software packages: RELATIVE (Göring and Ott 1997), RelCheck (Boehnke and Cox 1997; Broman and Weber 1998), and PREST (McPeek and Sun 2000). In-house software and genotypic relative risk (GRR) (Abecasis et al. 2001) were employed to detect MZ twins and to ensure that no individual was typed in two different families. As a result of this extensive error-checking procedure, 62 individuals were excluded (half siblings, false paternity, MZ twins, unrelated individuals). A further 53 individuals were excluded because of an unacceptably high rate of PCR dropout. A total of 353 ASPs remained and were included in the linkage analysis. Non-Mendelian errors were detected using the software PedCheck (O'Connell and Weeks 1998). In all, 48 markers from the original ABI Phase Linkage Mapping Set, version 2, were excluded from the study and replaced on the grounds of having either a high PCR dropout rate or excessive (>12) non-Mendelian errors. Data from nine MZ twin pairs who were genotyped and one individual who was blindly genotyped in duplicate allowed us to estimate the genotyping error rate to be 0.2% (based on 3,033 duplicate genotypes).

Single-point LOD scores were computed using SPLINK under the "possible triangle" restrictions (Holmans and Clayton 1995). Multipoint analyses were performed using the MAPMAKER/SIBS package (Kruglyak and Lander 1995), which calculates the MLS at each point in the genome by estimating the maximum-likelihood–sharing probabilities (identity by descent [IBD]) for each ASP. When parental genotypes are not available, the degree of inferred allele sharing can be sensitive to misspecification of marker-allele frequencies, which can lead to false-positive results. We therefore estimated marker-allele frequencies by SPLINK directly from our data set, using maximum-likelihood methods. The analyses and simulations reported were determined for all possible pairs without weighting, whereby if there were $n$ affected individuals in one family, they would contribute $n(n-1)/2$ possible ASPs. We also undertook analyses of a single ASP chosen randomly from each family. With the exception of the linkage peak on chromosome 17, the results were similar to those for all possible pairs (data not shown).

We obtained empirical significance levels and the expected number of given LOD scores per genome screen by simulating replicates of the broad and narrow data sets under the null hypothesis of no linkage and then analyzing with MAPMAKER/SIBS. These simulations maintained the same marker-allele frequencies, marker locations, family structures, and individuals typed at each locus as in the observed data set.

The power of the study was estimated by a similar method. Replicate data sets were simulated, using markers with four equifrequent alleles every 10 cM. The family structures were once again identical to those actually genotyped. Disease loci were simulated, with a given $\lambda_s$ midway between markers. This was intended to represent the most unfavorable position for detection of linkage and therefore to give a conservative estimate of true power. Power to detect a particular LOD score was estimated as the proportion of replicates with at least that LOD score.

## Results

A description of the families from which the 353 ASPs were drawn is presented in table 1. Simulation studies of our genome scan under the narrow (broad) diagnostic criteria suggested that we would have expected to have obtained, on average, one multipoint MLS of 2.00 (2.06) per genome scan, while an MLS of 3.82 (3.92) would have been expected to occur only once in every 20 genome scans in the absence of linkage. These therefore correspond to "suggestive" and "significant" thresholds for genomewide significance, as defined by Lander and Kruglyak (1995). In genotyping 372 markers spanning the genome at an average intermarker distance of 10.22 cM, we have extracted, on average, 65.8% of the IBD information available.

The results of multipoint ASP linkage analysis of all chromosomes using MAPMAKER/SIBS are presented in figure 1. Two regions were identified that had a maximum LOD score of >3.00; these were located on chromosome 10q25.3-q26.3 (MLS = 3.87; all samples, narrow diagnosis) and on chromosome 17p11.2-q25.1 (MLS = 3.35; U.K. samples only, broad diagnosis). The

**Table 1**

**Summary Description of the Sample Studied**

| Subject(s) | No. with Narrow Diagnosis (Broad Diagnosis) | | | |
|---|---|---|---|---|
| | United Kingdom | Sweden | United States | Total |
| Families | 137 | 97 | 38 | 272 |
| Sibling pairs | 125 (122) | 55 (86) | 35 (37) | 215 (245) |
| Sibling trios | 10 (14) | 3 (9) | 1 (1) | 14 (24) |
| Sibling quartets/quintets/sextets | 1 (1) | 1 (2) | 0 (0) | 2 (3) |
| Total no. of ASPs | 170 (179) | 79 (134) | 38 (40) | 287 (353) |
| Families with one parent typed | 41 | 41 | 0 | 82 |
| Families with both parents typed | 21 | 38 | 0 | 59 |
| Individuals: | | | | |
| Affected offspring | 286 (292) | 125 (209) | 73 (77) | 482 (578) |
| Unaffected offspring typed | 43 (37) | 143 (81) | 4 (0) | 190 (118) |

linkage on chromosome 10 achieved genomewide significance ($P < .05$), on the basis of simulation studies, whereas that on chromosome 17 failed to achieve this stringent criterion and can only be regarded as suggestive. It is interesting that the MLS at 10q consisted of positive contributions from all three of our combined sample groups (U.K. MLS = 1.44, Swedish MLS = 3.00, and U.S. MLS = 1.63), whereas the MLS on chromosome 17 was a result of linkage in the U.K. sample only.

Closer inspection of the data revealed that the linkage signal on chromosome 17 was, for the most part, the result of a single pedigree (named C702) containing six affected siblings, all of whom met our narrow diagnostic criteria. When family C702 was excluded from our analysis, the narrow MLS on chromosome 17 dropped to 0.89 at 68 cM. Multipoint linkage analysis using MAPMAKER/SIBS of family C702 alone identified a MLS of 8.32 at 17q (77 cM). Simulations suggested that a LOD score of 8.32 in family C702 has a genomewide significance of $P = .02$.

We also obtained evidence that was suggestive of linkage to 22q11 (LOD 2.29 at 4 cM). Notable results were also obtained on chromosomes 12q24 (LOD 1.43 in the full sample at 127 cM); 20q12 (LOD 1.54 in the U.K. sample at 57 cM), using our narrow diagnostic criteria; and 6q15 (LOD 1.46 in the U.K. sample at 88 cM), using our broad diagnostic criteria.

Simulations suggested that this study had a power of >0.95 (0.98), 0.61 (0.72), 0.20 (0.24), and 0.03 (0.034) to detect a susceptibility locus of $\lambda s = 3$, 2, 1.5, and 1.25, respectively, for the narrow (broad) model with a genomewide significance of $P = .05$.

## Discussion

We report here the results of the second-largest genomewide linkage scan of schizophrenia to date. We have obtained LOD scores of >3 in two regions, both of which have received support from other genome scans. Our strongest finding was a LOD score of 3.87 on chromosome 10q25.3-q26.3 (140–172 cM; 115.8–135.5 Mb in the UCSC human genome reference sequence [April 2003 freeze]), with positive results being contributed by all three samples and a LOD-1 interval of 15 cM (155–170 cM; 128.1–135.2 Mb in the UCSC human genome reference sequence [April 2003 freeze]). This finding achieved genomewide significance ($P < .05$) according to stringent criteria (Lander and Kruglyak 1995), on the basis of simulation studies. The region identified on chromosome 10 (140–172 cM) is close to a region that has been implicated in several studies. Levinson et al. (1998) reported a genome scan using 48 pedigrees (126 affected) from Australia and the United States. One of the most significant findings was at D10s1239 (130 cM), with a nonparametric linkage (NPL) score of 2.02 ($P = .01$). The positive linkage signal spanned a region defined by D10s677 (117 cM) to D10s1230 (143 cM). This study was subsequently followed up by Mowry et al. (2000), who studied the region spanning positions 122 cM to 172 cM with a greater marker density (5 cM) in an extended sample (the original pedigrees plus an extra 23 pedigrees [73 affected individuals]). This was the only region from the original genome screen for which further supportive evidence for linkage could be obtained. The analysis identified a peak defined by D10s1239 (125 cM) to D10s1237 (135 cM) with the MLS of 2.08 ($P = .01$), occurring at D10s168 (131 cM). Lerer et al. (2003) recently reported data from a genome scan of 21 large families (155 affected individuals) from Israel. They found suggestive evidence for linkage in a region spanning D10s543 (129 cM) to D10s587 (148 cM) ($P = .0008$). Positive findings from this region have also been reported by Shaw et al. (1998) and Ewald et al. (2002).

Our second-strongest finding was a LOD score of 3.35 in the U.K. sample on chromosome 17p11.2-q25.1 (44–97 cM; 16.2–72.5 Mb in the UCSC human genome reference sequence [April 2003 freeze]), with a LOD-1 interval of 17 cM (57–74 cM; 26.6–58.7 Mb in the

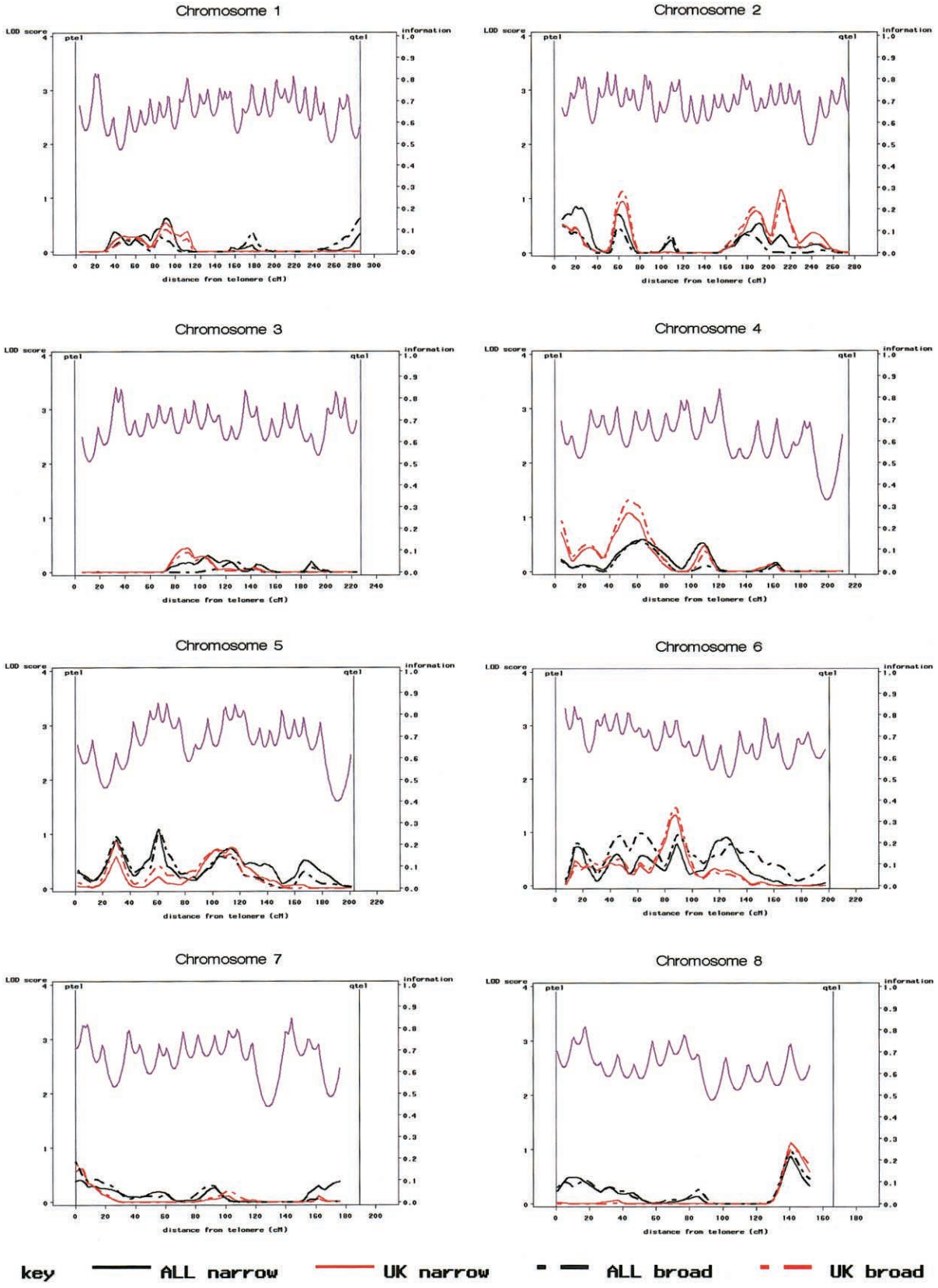
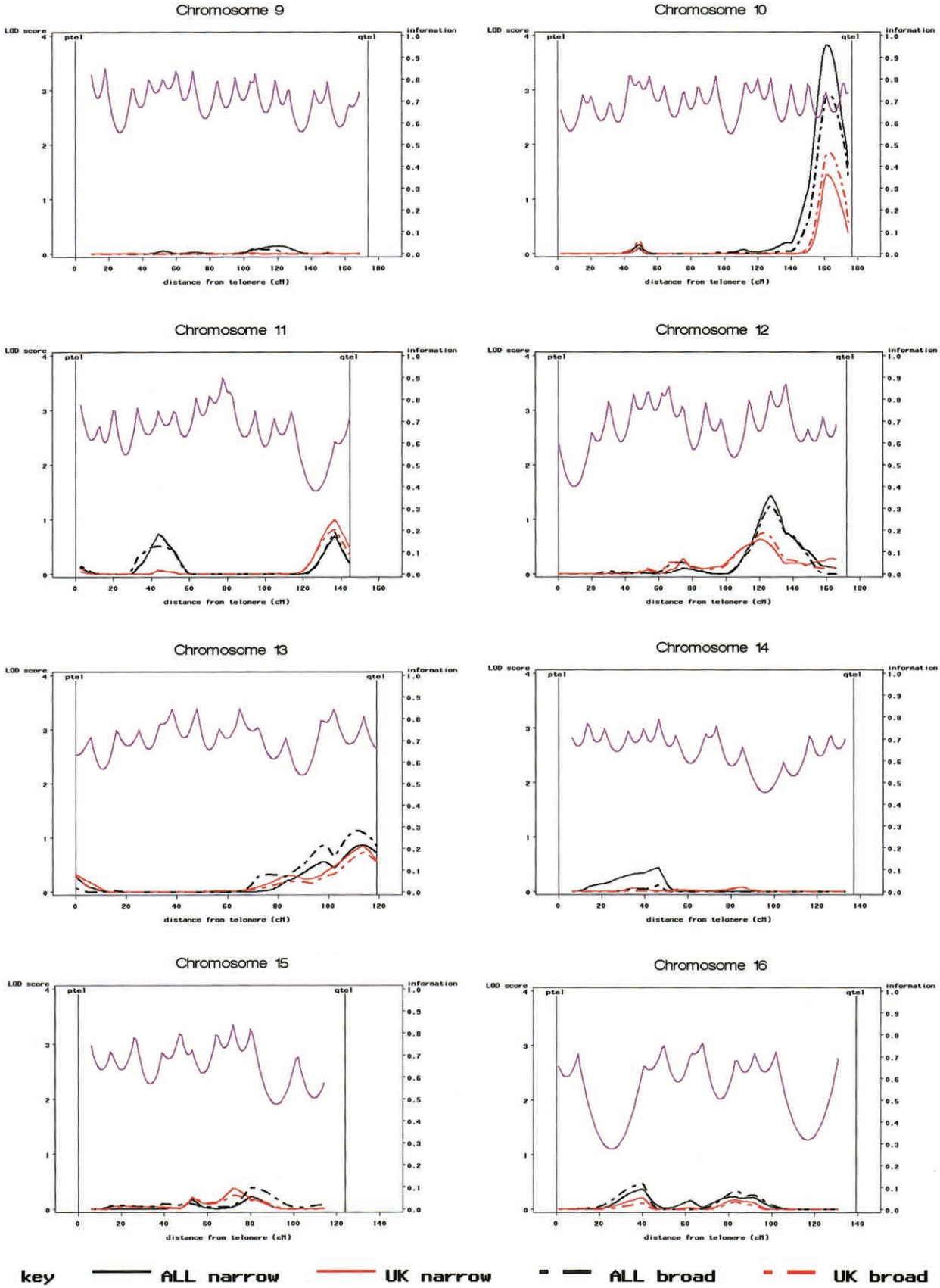



**Figure 1** The results of multipoint ASP linkage analysis of all chromosomes, performed using MAPMAKER/SIBS. LOD scores (*left axis*) are shown for all ASPs ($n = 353$) in black, and U.K.-only ASPs in red ($n = 179$). Solid and dotted lines refer to narrow and broad diagnostic criteria, respectively. Information content (*right axis*) at each locus is shown in purple.


Chromosome 9
Chromosome 10
Chromosome 11
Chromosome 12
Chromosome 13
Chromosome 14
Chromosome 15
Chromosome 16
LOD score
information
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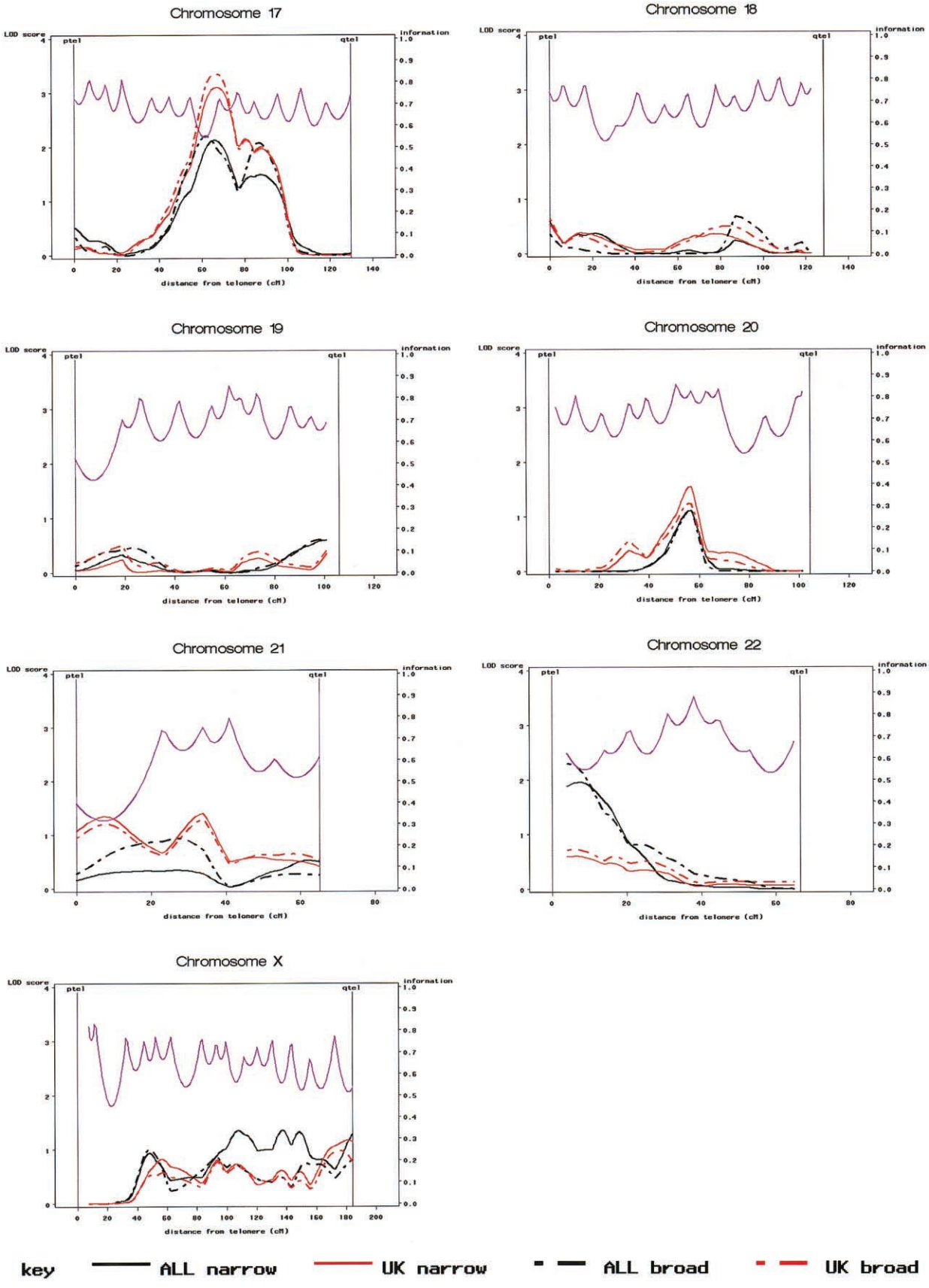
qtel
distance from telomere (cM)
key
ALL narrow
UK narrow
ALL broad
UK broad


Chromosome 17
Chromosome 18
Chromosome 19
Chromosome 20
Chromosome 21
Chromosome 22
Chromosome X
LOD score
information
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distance from telomere (cM)
key
ALL narrow
UK narrow
ALL broad
UK broad

UCSC human genome reference sequence [April 2003 freeze]). This finding fell just short of genomewide significance at the $P = .05$ level, a value that was set by our simulations and thus should be considered as suggestive (Lander and Kruglyak 1995). Much of the linkage signal at 17q was the result of a single pedigree (C702) containing six affected siblings, each of whom met our narrow diagnostic criteria for schizophrenia. Secondary analysis has allowed us to identify maternal and paternal haplotypes spanning markers D17S1852 to D17S785 and D17S1857 to D17S949, respectively, which cosegregate with each affected member of this family. When family C702 was excluded from analysis, the narrow MLS at chromosome 17q dropped to 0.89 at 68 cM. However, multipoint linkage analysis using MAPMAKER/SIBS of family C702 alone identified a MLS of 8.68 at 17q (77 cM, genomewide $P < .02$). The region on chromosome 17 (44–97 cM) overlaps bin 17.3 that showed significant evidence for linkage in the meta-analysis of Lewis et al. (2003). It is interesting that this bin had high scores in five of the larger genome scans from this meta-analysis. It should be noted that this meta-analysis does not include the data presented here, but it does include the results of previous genotyping of 97 of the U.K. ASPs.

In our genotyping to date, we have extracted 0.67 and 0.63 of the possible IBD information from the linked regions of chromosomes 10 and 17, respectively, with the LOD-1 regions spanning 13 cM and 18 cM, respectively. We are currently aiming to increase the marker density for both regions in an attempt to reduce the LOD-1 regions substantially. In parallel to this purely positional approach, we have also identified several candidate genes from the linked regions in which we are seeking disease-associated variants; these include *SLC6A4* (MIM 182138), *CNP1* (MIM 123830), and *ERBB2* (MIM 164870) from chromosome 17 and *CALCYON* (MIM 604647) and *GPR10* (MIM 600895) from chromosome 10.

We also obtained suggestive evidence for linkage on chromosomes 22q11 (LOD 2.29 at 4 cM). A linkage to this region has received support from a number of studies, and the region is one of only two to have been implicated in both meta-analyses of schizophrenia genome scans (Badner and Gershon 2002; Lewis et al. 2003). Our linkage peak also coincides with the region deleted in velocardiofacial syndrome (VCFS [MIM 192430]). VCFS, also known as "DiGeorge" or "Shprintzen" syndrome (MIM 188400), is associated with small interstitial deletions of chromosome 22q11. The phenotype of VCFS is variable, but, in addition to characteristic core features of dysmorphology, abnormalities of the palate, and congenital heart disease, there is strong evidence that individuals with VCFS have a substantial increase in the risk of psychosis, especially schizophrenia (Shprintzen et al. 1992; Pulver et al. 1994; Papolos et al. 1996; Murphy et al. 1999). The largest study (50 adult cases) found that 30% of patients met diagnostic criteria for psychosis, with 24% meeting DSM-IV criteria for schizophrenia (Murphy et al. 1999). Clearly, with an estimated prevalence of 1 in 4,000 live births, VCFS cannot be responsible for more than a small fraction (~1%) of cases of schizophrenia, and this estimate is in keeping with empirical data (Karayiorgou et al. 1995; Ivanov et al. 2003). However, the markedly increased risk of schizophrenia in VCFS, together with the linkage findings, suggests that variation in this region of the genome is of relevance to schizophrenia more generally.

Recently, two genes in the VCFS region have been implicated in schizophrenia, *PRODH* (MIM 606810) (Liu et al. 2002) and *COMT* (MIM 116790) (Shifman et al. 2002). *COMT* has long been considered a good candidate gene for schizophrenia because it encodes a key dopamine catabolic enzyme. There have been several studies that have examined a valine-to-methionine polymorphism that encodes high- and low-activity forms of *COMT*, respectively. Prior to the study by Shifman and colleagues, the evidence for association between *COMT* and schizophrenia was weak and not supported by meta-analysis (Lohmueller et al. 2003), although the valine allele has been more reliably associated with reduced performance in tests of frontal lobe function (Egan et al. 2001; Malhotra et al. 2002), providing a possible mechanism by which *COMT* might act as a susceptibility or modifying locus for schizophrenia.

The study by Shifman and colleagues reported highly statistically significant evidence for association between *COMT* and schizophrenia, but this was not attributable to the Val/Met polymorphism. Instead, the evidence for association required inclusion of a marker in intron 1 and/or a marker in the 3′ flanking region. We have recently shown that this haplotype is associated with low *COMT* expression, a finding that is consistent with the association between VCFS and schizophrenia and also the classic hypothesis that schizophrenia results from excess dopamine (Bray et al. 2003). However, we have not been able to confirm association between either the *COMT* (unpublished data) or the *PRODH* (Williams et al. 2003*a*) haplotypes. Since there are, as yet, no published replication data, it is premature to conclude that the reported associations at these loci explain either the evidence for linkage in this region or the relationship between VCFS and psychosis. Replication of the specific *COMT* findings, in particular, may prove difficult, as the study of Shifman and colleagues was performed on a sample of Ashkenazi Jews on the premise that they are relatively homogeneous for genetic (and environmental) risk factors.

We also obtained interesting evidence for linkage on 6q15 (LOD 1.46 at 88 cM), 12q24 (LOD 1.43 at 127 cM), and 20q12 (LOD 1.54 at 57 cM). Our signal on 6q is close to the original reports of suggestive linkage at 100–125 cM on 6q21-23.2 (Cao et al. 1997; Martinez et al. 1999; Levinson et al. 2000) and is also adjacent to bin 6.4, which showed some evidence for linkage in the meta-analysis of Lewis et al. (2003). However, it lies some distance centromeric to the highly significant findings in Arab-Israeli families (Lerer et al. 2003) and in extended kindred from northern Sweden (Lindholm et al. 2001), which were at 140 cM and 180 cM, respectively. Our data, therefore, add further weight to the view that there may be more than one susceptibility locus on 6q.

The region giving positive LOD scores on chromosome 20 is close to the region of suggestive linkage reported by Moises and colleagues (1995) in a two-stage international study and overlaps with bin 20.2, which gave suggestive evidence for linkage in a recent meta-analysis (Lewis et al. 2003). There are no previous reports of linkage to 12q24 in schizophrenia. However, it is notable that the gene encoding the D-amino acid oxidase (*DAAO* [MIM 124050]) is located at 118 cM, 9 cM away from the peak in this study. Recently, Chumakov and colleagues (2002) reported evidence that DAO may be a susceptibility locus for schizophrenia, although, as yet, this finding is unconfirmed in an independent sample.

Simulation studies suggested that this study had a power of >0.95 (0.98) to detect a susceptibility locus of $\lambda s = 3$ for the narrow (broad) model with a genomewide significance of $P = .05$. However, even with 353 ASPs, our power to detect effect sizes of $\lambda s$ 2, 1.5, and 1.25 was only 0.61 (0.72), 0.20 (0.24), and 0.03 (0.034), respectively. This is likely to explain why we were unable to detect evidence for the relatively well-established linkages to 6p24-22, 1q21-22, 13q32-34, and 8p12-22, which were reported elsewhere (see above). Indeed, we have found association between schizophrenia and both *NRG1* (MIM 142445) on 8p12 and *DTNBP1* (MIM 607145) on 6p22.3 in our U.K. sample, which includes members of the sibships from the present study (Williams et al. 2003*b*; Williams et al., unpublished data). Larger samples—of, say, 600–800 nuclear families—will be required to detect reliably the susceptibility genes of moderate-effect size; such studies may also allow detection of interactions between loci, relationships between allele sharing at particular loci, and aspects of the phenotype and loci of smaller effect.

In conclusion, we present data from one the largest systematic genomewide linkage studies for schizophrenia yet reported. We have found one region, 10q25.3-q26.3, that satisfies genomewide criteria ($P < .05$) for linkage and two that are highly suggestive, 17p11.2-q25.1 and 22q11. Linkage to all of these regions has been supported by other studies. Moreover, we found strong evidence for linkage to 17q in a single pedigree with schizophrenia. In our view, the evidence is now sufficiently compelling to undertake detailed mapping studies of these regions. Indeed, such studies in other regions, for which there is comparable evidence for linkage, are beginning to bear fruit, with evidence being reported for susceptibility genes on 6p (Straub et al. 2002; Schwab et al. 2003), 8p (Stefansson et al. 2002, 2003; Williams et al. 2003*b*), and 13q (Chumakov et al. 2002).

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## Electronic-Database Information

The URLs for data presented herein are as follows:

Marshfield Center for Medical Genetics, http://www.marshfieldclinic.org/research/genetics/

Online Mendelian Inheritence in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for schizophrenia, 6p24-22, 1q21-22, 13q32-34, 8p21-22, 6q21-25, 22q11-12, *SLC6A4*, *CNP1*, *ERBB2*, *CALCYON*, *GPR10*, VCFS, DiGeorge or Shprintzen syndrome, *PRODH*, *COMT*, *DAAO*, *NRG1*, and *DTNBP1*)

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