Article

Genetics of Recurrent Early-Onset Major Depression (GenRED): Final Genome Scan Report

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Objective: The authors carried out a genomewide linkage scan to identify chromosomal regions likely to contain genes that contribute to susceptibility to recurrent early-onset major depressive disorder, the form of the disorder with the greatest reported risk to relatives of index cases.

Method: Microsatellite DNA markers were studied in 656 families with two or more such cases (onset before age 31 in probands and age 41 in other relatives), including 1,494 informative "all possible" affected relative pairs (there were 894 independent affected sibling pairs). Analyses included a primary multipoint allele-

sharing analysis (with ALLEGRO) and a secondary logistic regression analysis taking the sex of each relative pair into account (male-male, male-female, female-female).

Results: Genomewide suggestive evidence for linkage was observed on chromosome 15q25-q26 (at 105.4 centimorgans [cM]). The authors previously reported genomewide significant linkage in this region in the first 297 families. In the secondary analysis, after empirical genomewide correction for multiple testing, suggestive linkage results were observed on chromosome 17p12 (28.0 cM, excess sharing in male-male and male-female pairs) and on chromosome 8p22-p21.3 (25.1 cM, excess sharing in male-male pairs).

Conclusions: These regions of chromosomes 15q, 17p, and 8p might contain genes that contribute to susceptibility to major depression and related disorders. Evidence for linkage has been reported independently in the same regions of chromosome 15q for major depression and of chromosome 8p for related personality traits.

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In a genomewide linkage scan, families with at least a pair of ill relatives (other than parent-child pairs) were recruited, and DNA markers on all chromosomes were assayed to search for locations where ill subjects have inherited the same sequence variants (within families) more often than expected by chance. These markers are likely to be close to genes that contribute to disease susceptibility, which can then be identified by using other methods. The Genetics of Recurrent Early-Onset Depression (GenRED) sample was recruited to carry out a large-scale genome scan. In a preliminary analysis of 297 families (wave 1), significant linkage (corrected for genomewide analyses) was observed on chromosome 15q (1) (see Primary Linkage Analysis, below, for details). We report here that in all 656 families (waves 1 and 2), genomewide suggestive linkage (a result expected by chance once per genome scan) was observed on chromosome 15q and also on chromosomes 17p and 8p in a planned second analysis accounting for the sex of each pair of relatives.

The lifetime prevalence of major depressive disorder is at least 10%, with women affected twice as often as men (2-4). Twin studies estimate heritability at 40%-50% (5-11) or as high as 70% with repeated assessments (6). Adoption studies also suggest genetic factors (12-14). The mode of inheritance is unclear (2, 15). The relative risk to first-degree relatives versus comparison relatives is 2-3 (16-18), but a further increase in relative risk is observed for probands with an age at onset in the 30s or earlier (15, 17, 19-24) or recurrent episodes (6, 22, 25-27). The relative risk for recurrent and early-onset major depressive disorder is probably at least 4-5 based on family studies (16, 22, 24, 28), although its prevalence in the general population is unknown. Because the power to detect a given gene is predicted by its effect on the relative risk (29), large-scale genetic studies of current early-onset major depressive disorder were proposed because it has the largest reported overall relative risk of any phenotype related to unipolar depression (30).

This article is featured in this month's *AJP Audio* and is discussed in an editorial by Dr. McGuffin and colleagues on p. 195.

TABLE 1. Numbers of Informative Affected Relative Pairs^a

Phenotype Number of Families (wave 1 or wave 2)	Sex	All Possible Informative Affected Relative Pairs							Independent Affected Sibling Pair
		Affected Sibling	Affected Half-Siblings	Avuncular (aunt or uncle with niece or nephew)	First Cousin	Grandparent-Grandchild	All Other Informative Affected Relatives	Total	
Recurrent early-onset major depressive disorder (656 families, 296 of 360)	All	1,199	39	204	34	12	6	1,494	894
	Female-female	773	28	122	12	6	1	942	
	Male-female	362	9	74	16	6	5	472	
	Male-male	64	2	8	6	0	0	80	
Recurrent early-onset major depressive disorder plus bipolar II disorder (676 families, 303 of 373)	All	1,262	41	217	37	12	8	1,577	934
	Female-female	808	30	129	13	6	1	987	
	Male-female	384	9	79	18	6	7	503	
	Male-male	70	2	9	6	0	0	87	
Recurrent early-onset major depressive disorder (European ancestry) (631 families, 284 of 347)	All	1,166	35	193	30	11	6	1,441	864
	Female-female	755	27	115	12	5	1	915	
	Male-female	351	7	70	12	6	5	451	
	Male-male	60	1	8	6	0	0	75	

^a Shown are the numbers of informative affected relative pairs in each analysis broken down by sex, with inclusion of all possible pairs, as well as the number of statistically "independent" affected sibling pairs counting data supplement Table 1 (available online at <http://ajp.psychiatryonline.org>) pairs for a sibship with supplementary affected cases. The primary analysis considered all major depressive disorder pairs in 656 eligible families. The planned second analysis considered the same families, with the sex of the pair (male-male, male-female, female-female) entered as a covariate. Exploratory analyses considered the current early-onset major depressive disorder plus bipolar disorder II phenotype (676 families) and the current early-onset major depressive disorder phenotype in families of predominantly European ancestry only (631 families). Families were recruited at Columbia University (N=133), the University of Pittsburgh (N=119), the University of Pennsylvania (N=115), Rush University Hospital (N=113), Johns Hopkins University (N=98), and the University of Iowa (N=98). Self-reported ancestries were predominantly European (647 families), African American (N=17), Hispanic (N=8), Asian (N=3), and Sephardic Jewish (N=1).

Method

Subjects

Eligibility criteria, ascertainment, and assessment procedures have been previously described (1, 31). Briefly, all protocols were approved by local institutional review boards, and after complete description of the study to each subject, written informed consent was obtained. Probands were recruited through clinicians and by self-referrals in response to Internet, print, and broadcast announcements and screened by telephone to determine whether the proband and at least one sibling were likely to be eligible. Family members with possible mood disorders were interviewed by telephone or in person using the Diagnostic Interview for Genetic Studies (DIGS 3.0) (32) and the Family Interview for Genetic Studies (<http://zork.wustl.edu/nimh>). For each case, two research clinicians reviewed Diagnostic Interview for Genetic Studies and Family Interview for Genetic Studies data, an interview summary, and available psychiatric records and completed independent and consensus ratings of "best estimate" primary and secondary DSM-IV diagnoses (33), including age at onset and confidence levels; number of major depressive, manic, or hypomanic episodes; and ratings of severity, chronic versus remitting course, and temporal relationship to substance use.

Probands with current early-onset major depressive disorder had at least two lifetime major depressive episodes (persisting past age 18) or one episode lasting 3 or more years, with major role impairment, age of onset before age 31, and high diagnostic confidence. We recruited all available ill family members (connected by first-degree relationships to other ill members) who met the same criteria, except with age of onset before 41, because the risk of major depressive disorder increases through the 30s in relatives of early-onset probands (12). Exclusion criteria were having bipolar I disorder, schizophrenia, or schizoaffective diagnoses; having a parent or sibling with suspected bipolar I disorder; or having a likely medical basis for the mood disorder. Subjects with antisocial personality or somatization disorders (which both proved rare in ascertained subjects) were also excluded because of the difficulty of diagnosing major depressive disorder with confidence in these individuals. Individuals with substance dependence were included if major depressive disorder started first or recurred after 2 years without dependence (or 1 year for relatives). If the initial proband's consensus diagnosis was bipolar II disorder, the family was excluded, but bipolar II disorder relatives were recruited (but excluded from the primary analyses) because the relationship of major depressive disorder to bipolar II disorder remains unclear.

Blood specimens were obtained from interviewed subjects, available parents, and (if fewer than two parents were available)

TABLE 2. Relationships of Genotyped Individuals to Probands^a

Relation to Proband	Recurrent Early-Onset Cases of Major Depressive Disorder	"Diagnosis Unknown"
Proband	656	0
Sibling	856	142
Parent	102	238
Aunt or uncle	24	5
Child	47	11
Half-sibling	13	2
Other	50	30
Total	1,748	428

^a Shown are the biological relationships between probands and other genotyped individuals (total N=2,176) in 656 families that were eligible for the primary linkage analysis. Only individuals with recurrent early-onset major depressive disorder were designated as affected. The "diagnosis unknown" individuals in this analysis included 24 relatives of those with bipolar II disorder (16 siblings, two parents, and six others), while an additional 21 genotyped cases of bipolar II disorder, 25 recurrent early-onset cases, and five "diagnosis unknown" relatives were members of families that were only informative in the exploratory analysis that considered both recurrent early-onset major depressive disorder and bipolar II disorder cases as affected (see text).

up to two siblings without known major depressive disorder by the Family Interview for Genetic Studies report. Specimens were shipped by courier to a National Institute of Mental Health (NIMH) repository (<http://www.rucdr.org>) for creation and storage of lymphoblastic cell lines and DNA extraction.

Genotyping

Genotyping was carried out at the Center for Inherited Disease Research with standard methods for fluorescently labeled microsatellite markers (<http://www.cidr.jhmi.edu>). Details of the multi-stage genotyping effort and the combining of genotypes across stages are available in the data supplement text (available online at <http://ajp.psychiatryonline.org>). Briefly, 418 markers were genotyped (392 of them in wave 1 families and 404 in wave 2) at mean 9 centimorgans (cM) spacing and mean marker heterozygosity of 0.77. There were 3.29% missing genotypes (of 956,220), with 0.04% genotypewise errors based on duplicated genotypes and 0.32% detected Mendelian inconsistencies, including pedigree or specimen errors.

Error Checking

Pedigree structure and sample swap errors were detected by PEDCHECK analysis of 15 markers (34) and then with RELCHECK analysis of all markers (35). Genotypes were excluded from analyses for family marker combinations with Mendelian inconsistencies or if SIBMED (36) estimated a 70% probability of error (N=72).

Primary Linkage Analysis

Additional details of statistical methods are available in the data supplement text. Briefly, multipoint allele-sharing analysis (ALLEGRO [37]) was carried out in 656 informative families with current early-onset major depressive disorder diagnoses and marker locations from the deCODE map (38) or by interpolation from Marshfield locations (<http://research.marshfieldclinic.org/genetics/>). Analyses considered all possible informative relative pairs, with a weighting function that is approximately midway between equal weighting for each pair versus for each family (39). We computed genomewide (corrected) significance levels by simulating 5,000 replicates, assuming no linkage and counting the number of "hits" per genome (at least 30 cM apart) that exceeded each observed Z likelihood ratio score statistic of Kong and Cox (Z_{LR}) (40). Significant linkage was defined as a result observed by

chance in 5% or fewer genome scans, and suggestive linkage, as a result, expected no more than once per genome scan (41). This study group has excellent power to detect a genetic locus responsible for an approximately 30% populationwide increase in risk to siblings of probands under several genetic models (31). For the three results that achieved genomewide suggestive significance (chromosome 15q in the primary analysis and chromosomes 1p and 17q in the secondary analysis, taking sex into account), linkage analyses were repeated with sex-specific marker locations from the deCODE map and with the option for sex-specific distances in ALLEGRO to recompute linkage scores for chromosome 15 and identical-by-descent sharing probabilities (for subsequent logistic regression analyses) for chromosome 8 and 17.

Secondary Analyses

We also carried out a planned secondary logistic regression analysis with a covariate encoding the sex of each informative pair (male-male, male-female or female-female) (1, 42, 43). Computational details are available in data supplement text. Briefly, the probability of each pair sharing each marker allele identical-by-descent was computed (with ALLEGRO) based on prior and posterior sharing probabilities (29, 44) and expressed as a logistic regression on two parameters: the divergence of identical-by-descent from the null without covariate effects and the three-level factor for sex of the pair. Two lod scores were computed: one for the *covariate effect* (allowing for linkage), by calculating the ratio of the likelihood maximized with respect to both parameters to that maximized in the absence of covariate effects, and the second for *linkage allowing for covariate effects*, by calculating the ratio of the likelihood maximized with respect to both parameters to that obtained in the absence of both overall linkage and covariate effects. Analysis of the X chromosome considered the maternally inherited chromosome for affected sibling pairs. Genomewide empirical significance levels were determined for *linkage allowing for covariate effects* with 5,000 simulations of genotypes for the group, assuming no linkage, with actual marker locations, allele frequencies, affected status, and sex. As a correction for carrying out a secondary analysis, we first determined the empirical significance of the largest peak on each chromosome, with allowance for covariate effects, and then counted the number of peaks observed in each simulated genome that achieved the same empirical significance level *either with or without* covariate effects modeled. We also computed empirical chromosomewide p values for the *covariate effect* by randomly permuting covariate values among affected individuals and determining the significance of the difference between the lod score *with* and *without* the sex covariate. Because this depends on evidence for linkage on the chromosome without allowance for the covariate, a genomewide p was estimated by dividing the p by the chromosome's proportion of genome length.

Additional exploratory analyses included repeating the primary ALLEGRO analysis while considering both current early-onset major depressive disorder and bipolar II disorder cases as affected and repeating the ALLEGRO and sex covariate analyses for current early-onset major depressive disorder in families of predominantly European ancestry (by self-report of up to four ethnicities for each parent). Familial clustering of comorbid features was examined by computing odds ratios for each feature for occurrence in the first and second sibling in each sibship. Finally, several analyses were undertaken to explore possible factors that might account for the large difference in linkage results on chromosome 15 in waves 1 and 2, including differences in clinical symptoms and comorbid diagnoses between wave 1 and 2 families (t tests and chi-square tests) and examination of whether identical-by-descent sharing in affected relative pairs differed significantly across study sites (cross-site heterogeneity), with the

TABLE 3. Comorbid Disorders and Demographic and Clinical Characteristics of the Study Group^a

Variable	Characteristic		
	N		Percent
Comorbid disorders			
Panic disorder	442		25
Obsessive-compulsive disorder	165		09
Social anxiety disorder	250		14
Any anxiety diagnosis	686		39
Alcohol abuse	198		11
Alcohol dependence	215		12
Substance abuse	163		09
Substance dependence	191		11
Alcohol or substance abuse	316		18
Alcohol or substance dependence	403		23
Alcohol or substance abuse or dependence	589		34
Nicotine dependence	310		18
Clinical and demographic features			
	N		Percent
Sex (female/male)	1,392/356		80/20
Major depressive disorder with psychotic features	72		04
Chronic course ^b	520		30
Suicide attempt (>minimal intent)	284		16
	Mean	SD	Median
Age at onset (years at first major depressive episode)	19.0	7.3	18
Number of episodes	6.7	10.3	4
Longest episode (days)	723.5	1243.7	365
Age at interview (years)	42.0	12.5	42
Age at onset of major depressive disorder with psychotic features (years)	28.2	10.2	26
Number of eight major depressive disorder criteria met (worst episode)	6.7	1.2	7

^a Shown are the distributions of comorbid psychiatric disorders and demographic and clinical variables for cases of recurrent early-onset major depressive disorder in 656 families eligible for the primary linkage analysis.

^b Refers here to the consensus diagnosticians' global rating of lifetime course of depression (see text).

logistic methods described above for the analysis of sex effects but with site as the covariate.

Changes in the Data Set for Wave 1 Families

The results for wave 1 differ slightly from those published previously (1) because there were 26 additional subjects from 23 wave 1 families and 12 changes in diagnostic status from further data cleaning (three to affected and nine to unaffected status), which made one family uninformative (i.e., there were 297 wave 1 families previously versus 296 here). Details are available in the data supplement text. With or without these changes, chromosome 15q produced genomewide significant linkage in wave 1 families and suggestive linkage in the total group, and chromosomes 8p and 17p produced suggestive evidence for linkage in the secondary analysis.

Data Sharing

The NIMH Human Genetics Initiative web site (<http://zork.wustl.edu/nimh>) describes how scientists can obtain de-identified clinical information and marker genotypes from this study.

Results

Description of the Eligible Families

Table 1 shows the numbers of families and of affected relative pairs for the three sets of families used in the analyses (families that were informative with current early-onset major depressive disorder cases considered as affected, with bipolar II disorder cases added, or with current early-onset major depressive disorder only but restricted to European ancestry). All types of pairs were considered in the analyses. Three additional families were excluded (for identical or unrelated genotypes in the two siblings). The table note provides information about distribution of families by recruitment site and self-reported ethnicity. Our re-

cruitment concentrated on families from a single broad ethnic group (Europeans) to reduce genetic heterogeneity, but volunteers with other ancestries were accepted.

In the 656 families in the primary current early-onset major depressive disorder analysis, there were 1,748 affected, interviewed genotyped individuals, including 1,720 with recurrent major depressive disorder and 28 with one major depressive episode lasting 3 years or longer. The other 428 genotyped relatives were treated as "diagnosis unknown," including 24 with bipolar II disorder and 404 who provided only blood specimens or were interviewed and received ineligible diagnoses. Relationships of family members to probands are shown in Table 2. In the 20 families that were eligible only when the bipolar II disorder cases were added, 51 individuals were genotyped (25 current early-onset major depressive disorder cases, including 20 probands and five parents, 21 bipolar II disorder siblings, and four siblings and one parent with "diagnosis unknown"). Table 3 provides information on comorbid disorders and on clinical, demographic, and course-of-illness variables. Cross-site interrater reliability and agreement of clinical ratings have been previously described (31).

Primary Linkage Analysis

Figure 1 illustrates genomewide Z_{LR} for the primary linkage analysis. Table 4 shows the maximum scores on each chromosome. Genomewide suggestive linkage (a score expected by chance once or less per genome scan) was observed on chromosome 15q25-q26 at 105.43 cM, between markers D15S652 (99.9 cM, 90.247 megabase)

FIGURE 1. Genome Scan Results of Recurrent Early-Onset Major Depressive Disorder^a

^a Shown are Z likelihood ratio score statistics of Kong and Cox (40) across the genome for the primary multipoint linkage analysis (with ALLEGRO) with recurrent early-onset major depressive disorder cases considered affected.

and D15S816 (110.9 cM, 92.750 megabase). The genetic map is substantially different for men and women in this region, but similar results were observed when the analysis was repeated with sex-specific map distances ($Z_{LR}=3.04$, $\text{lod}=2.0$). Results are shown in Figure 2 for 15q analyses for wave 1, wave 2, all families, and European families, and details are shown in data supplement Table 1 and Table 2. We previously reported a wave 1 Z_{LR} of 4.14 at 103.2 cM on 15q (1). Here, with the group changes described above and in data supplement text, the Z_{LR} was 3.93 at 105.4 cM (0.049 expected genomewide false positive peaks). No nominally significant evidence for linkage was observed on 15q in wave 2. The analysis of all families was considered primarily a priori. Interpretation of this result must await linkage fine mapping. No other region produced genomewide significant or suggestive evidence for linkage. Linkage information content with ALLEGRO's exponential measure averaged 0.699 across the genome (evaluating 10 points per interval) and 0.712 under the 15q peak (30 cM).

Linkage Analysis With Sex of the Pair as a Covariate

Table 4 and Figure 3 summarize these results. For the primary outcome ("Linkage With Sex Effect"), the number of expected genomewide peaks of the observed size after correction for multiple testing was <1 for chromosomes 17p12 (28.04 cM near marker D17S974), which came very close to the genomewide 0.05 level, and 8p22-p21.3 (25.09 cM, near D8S1106). As shown in the last column of Table 5, increased identical-by-descent sharing was observed on 8p only in the small number of male-male pairs, while on 17p, it was observed in male-male and male-female pairs. Results on 8p and 17q were similar when sex-specific map distances were used to combine identical-by-descent sharing probabilities; with sex-averaged versus sex-spe-

cific maps, the difference between the lod's allowing and not allowing for sex was 3.54 versus 3.47 for 17q and 2.12 versus 2.03 for 8p with almost identical identical-by-descent sharing probabilities. Without covariates, the lod score on chromosome 15 was suggestive, consistent with the primary analysis.

Estimated empirical significance is also shown for the covariate effect (how often one would observe by chance a given increase in lod score). Chromosome 6p (31.19 cM) produced a suggestive result with identical-by-descent sharing increased in male-male pairs and decreased below 50% in male-female pairs. This finding might be less plausible biologically, although in theory it could occur if an allele increased the risk of major depressive disorder in men and decreased it in women or if two or more loci in one region had different sex effects.

Exploratory Analyses

When bipolar II disorder cases were added, maximum scores for the primary analysis (data supplement Table 3) and secondary analysis (data not shown) were similar but slightly lower. For example, the maximum Z_{LR} on chromosome 15q was reduced from 3.05 to 2.80. Note that only a few families had more than one case of bipolar II disorder, so separate linkage analyses of this disorder were not feasible.

Because allele frequency estimates can affect linkage scores when parental genotypes are unavailable (45-49), inclusion of families from several ethnic backgrounds with different frequencies could bias the results. Thus, European families were analyzed separately. Scores were similar in most regions and were higher on 15q: for wave 1, the Z_{LR} was 4.31 in European families (105.43 cM, genomewide expected peaks=0.014) versus 3.93 for all ethnicities; in all 631 European families, the Z_{LR} was 3.43 (106.53 cM, genomewide expected peaks=0.27) versus

TABLE 4. Results of Primary and Secondary Analyses (all chromosomes)^a

Chromosome	Primary Analysis		Secondary Analysis (accounting for sex of pair)					
	Z Likelihood Ratio Score Statistic of Kong and Cox (Z _{LR})	cM	Linkage (no covariate)		Linkage With Sex Effect			
			Maximum Lod	cM	Maximum Lod	cM	Genomewide Peaks Corrected (uncorrected)	Covariate Effect (genomewide peaks)
1	2.38 ^b	212.0	1.58	208.9	2.73	259.2		
2	1.39	77.5	0.39	110.1	1.33	3.0		
3	1.40	117.3	0.46	117.3	1.36	71.3		
4	-0.19	113.7	0.00	12.5	1.54	56.3		
5	2.37 ^b	190.8	0.77	190.8	1.13	29.9		
6	0.94	0.0	0.24	0.0	2.28	31.2		0.666
7	1.72 ^b	106.3	0.69	106.3	1.24	24.6		0.58/0.45/0.52
8	2.06 ^b	38.3	1.37	38.0	3.49	25.1	0.504 (0.304)	0.284
9	1.25	74.4	0.87	124.8	1.10	124.8		0.64/0.49/0.53
10	1.77 ^b	177.2	0.69	174.0	1.57	74.9		
11	0.99	73.0	0.22	137.7	1.43	137.7		
12	1.48	99.1	0.94	100.4	2.18	165.8		
13	1.78 ^b	101.3	0.93	100.8	1.54	115.3		
14	1.68	107.5	1.04	100.1	1.97	100.1		
15	3.05 ^c	105.4	2.06	104.3	2.72	106.5		
16	0.39	29.5	0.04	3.9	0.56	127.6		
17	1.74 ^b	28.0	1.23	28.0	4.77	28.0	0.052 (0.030)	<0.025
18	1.79 ^b	74.7	0.52	74.7	1.38	74.7		0.58/0.57/0.50
19	0.63	83.4	0.28	83.4	0.61	83.4		
20	1.05	2.5	0.18	2.5	1.86	60.7		
21	1.63	11.4	0.69	8.6	1.17	8.6		
22	0.80	4.6	0.10	3.0	0.95	68.8		
X	0.95	14.4	0.71	1.9	1.90	92.9		

^a For the primary analysis, the maximum Z_{LR} on each chromosome is shown along with its location in centiMorgans. For the secondary analysis, the maximum lod score on the chromosome is shown for the logistic regression analysis with no covariate and with a three-level covariate for sex effect (male-male, male-female, and female-female affected relative pair). For linkage with sex effect, the expected number of genomewide peaks is shown for chromosomes with a genomewide suggestive result after correction for a second genomewide analysis (uncorrected result shown in parentheses). The estimated expected number of genomewide peaks is also shown for the covariate effect (difference between lod scores with and without covariate effect) for chromosomes with genomewide suggestive results and the identical-by-descent sharing proportions for each pair type. In bold text are results that would be expected less than once per genome scan by chance (suggestive linkage).

^b Nominal (uncorrected) pointwise $p < 0.05$ (with ALLEGRO). The Z_{LR} threshold for $p < 0.05$ was 1.64, and for $p < 0.01$, it was 2.33.

^c Genomewide suggestive linkage in the primary analysis (0.81 genomewide expected peaks).

3.05 (expected peaks=0.81) for all ethnicities. Similar increases were seen in secondary analyses (data supplement text and Table 4 and Table 5).

We also examined linkage with sex covariate effects on chromosome 12q, where significant linkage to mood disorders was reported in men at 110 cM (50). Here, identical-by-descent sharing was increased in male-male (0.59) versus male-female (0.52) and female-female (0.53) pairs from 100 cM to 113 cM, but this effect did not reach suggestive genomewide significance. Note, however, that in the 62 families that were informative for linkage when only male cases were considered affected, nominally significant evidence for linkage (i.e., without genomewide correction) was observed in the previously reported region, with the peak score at 97.84 cM (lod=0.86, $p < 0.03$).

Clinical differences were observed between wave 1 and 2 families. Wave 1 cases had earlier age at onset ($t = 2.18$, $df = 1713.7$, $p = 0.03$), more major depressive episodes ($t = 4.39$, $df = 1769.5$, $p = 0.00001$), and more panic attacks ($t = 2.72$, $df = 1673.3$, $p < 0.007$), whereas wave 2 cases were more likely to be rated as having a chronic course ($\chi^2 = 11.26$, $df = 1$, $p = 0.0008$), although the two sets

of cases did not differ in substance dependence, abuse, or gender. However, these differences did not appear to predict chromosome 15q linkage. For example, when families from each site were analyzed separately, the Philadelphia and Pittsburgh sites produced the greatest evidence for linkage in wave 1, but for both sites, wave 1 cases had slightly older ages at onset ($0.05 < p < 0.10$ for each site), whereas all of the other variables mentioned were not significantly different except for more episodes occurring in wave 1 families for Pittsburgh but not Philadelphia. Comorbid diagnoses aggregated in families as expected in analyses of sibling-sibling concordance in independent affected sibling pairs, with significant odds ratios observed for panic disorder (odds ratio=2.16, 95% CI [95% confidence interval]=1.5–3.1); panic with agoraphobia (odds ratio=4.51, 95% CI=2.43–8.37); alcohol dependence (odds ratio=3.15, 95% CI=1.86–5.35); substance dependence (odds ratio=2.54, 95% CI=1.43–5.41); obsessive-compulsive disorder (odds ratio=2.66, 95% CI=1.21–4.22); nicotine dependence (odds ratio=2.46, 95% CI=1.59–3.82), and nicotine persistence (odds ratio=4.37, 95% CI=3.05–6.26).

FIGURE 2. Chromosome 15 Linkage Results^a

^a Z likelihood ratio score statistics of Kong and Cox (Z_{LR}) for all families are shown in Table 4 (see data supplement Table 1 and Table 2 for details for wave 1, wave 2, and European families). For European families, the maximum Z_{LR} of 3.43 was observed at 106.53 cM.

FIGURE 3. Logistic Regression Analyses With and Without Sex of the Pair as a Covariate^a

^a Shown for chromosomes 8 and 17 are lod scores from logistic regression allele-sharing analyses of all possible informative affected relative pairs, with and without a covariate coding the sex of the pair (male-male, male-female, female-female). Significance levels are shown in Table 4.

More detailed logistic regression analyses of the effects of clinical covariates on linkage results will be presented elsewhere.

No significant cross-site heterogeneity was observed for identical-by-descent sharing in affected relative pairs on chromosome 15q (maximum lod score assuming homogeneity=2.06 at 98.51 cM, identical-by-descent=0.537; maximum lod score assuming site heterogeneity=3.87 at 98.51 cM, $p=0.41$).

Discussion

In this genome scan analysis of families with multiple cases of recurrent early-onset major depressive disorder,

genomewide suggestive linkage was observed on chromosome 15q in the primary analysis and on chromosomes 17p and 8p in the secondary analysis after we accounted for the sex of the affected pair. The results suggest that no genetic locus makes a large contribution to the overall risk of major depressive disorder, that multiple loci (including some in these regions) may contribute to risk, and that the contribution of some loci may be sex dependent.

With use of a 9-cM microsatellite marker map, evidence for linkage was significant in wave 1, did not achieve nominal significance in wave 2, and was suggestive in the total group. There are several possible explanations (1). The initial 15q finding could have been a false positive result (2). There might be differences in the genetic susceptibilities

TABLE 5. Overlapping Results in Linkage Studies of Major Depression and Related Personality Traits^a

Study	Number of Families	Comments	Overlap With Present Results ^b	Other Overlap ^c
Linkage studies of major depressive disorder and related diagnoses				
Zubenko et al. (53)	81	Five phenotypic models from recurrent early-onset major depressive disorder to all mood disorders ± covariates, including sex		11q, 18q
Camp et al. (55)	87	Same families as reference 49 but restricted to recurrent early-onset major depressive disorder (onset before 31); ± anxiety disorders as affected; separate analyses of men and women	15q: highest lod (2.88, 121 cM), men	3q, 4q, 18q
Abkevich et al. (50)	110	Multiple cases of recurrent major depressive disorder; counted bipolar I and II disorder relatives as affected; separate analyses of men and women		12q (men)
McGuffin et al. (56)	417	Recurrent early-onset major depressive disorder; no age-at-onset restriction (but average age at onset was in the early 20s)	15q: fifth highest lod (1.14, 88.2 cM)	12q
Present study	656	Recurrent early-onset major depressive disorder; secondary analysis with sex covariate	15q: suggestive (105.4 cM), all families; 17p: suggestive (28 cM), male-male, male-female pairs; 8p: suggestive (25.1 cM), male-male pairs; 6p: possible sex effect (31.2 cM), male-male pairs	
Linkage studies of depression-related personality measures				
Cloninger et al. (58)	105	Harm avoidance	8p: Highest lod (3.2, 23.5 cM)	
Neale et al. (60)	129	Neuroticism (nicotine-dependence study sample)		1q, 3q
Nash et al. (59)	283	Neuroticism; extremely concordant and discordant sibling pairs design	6p: Highest lod (2.7, 61 cM)	
Fullerton et al. (54)	561	Neuroticism; extremely concordant and discordant sibling pairs design	8p: Best result, men ($p < 0.002$, 15.2 cM) and seventh best, all families ($p < 0.002$)	1q, 4q, 11q, 12q (women)

^a Published linkage studies of major depressive disorder or related personality traits are listed in order of group size.^b Shows the present results and possibly overlapping results in other studies.^c Lists other chromosomal regions that produced one of the most positive results in more than one study (see references for details).

of wave 1 and 2 families, although we have tried and (so far) failed to identify clinical differences between the two waves that predict 15q linkage (3). The wave 1 result could represent a true positive finding but with an overestimate of the genetic effect. For complex disorders, initial reports of significant linkage are often upwardly biased (51, 52) because the gene effects are small, so that thousands of families might be needed to estimate and then replicate each true effect. Smaller samples give more variable results: by analogy, in 10,000 coin flips, the proportion of heads will be 48.6%–51.4% (close to the true value) around 95% of the time, but in 50 flips, the range will be 36%–64% (i.e., large under- and overestimates will be common). Thus, the most significant observed result in a small group is often a true signal that will not reliably be replicated in other small samples but will emerge as a true but smaller effect in very large samples. Further evaluation of the 15q finding will require studying our group with more markers to increase informativeness and comparison or meta-analysis of results across multiple genome scans.

Two chromosomal regions (17p and 8p) produced suggestive evidence for linkage with a sex effect. Bierut et al. (5) reported greater heritability of major depressive disorder

in women than in men. Kendler et al. (7) supported this finding for broad but not narrow major depressive disorder criteria, concluding that major depressive disorder is probably more heritable in women, with a correlation of 0.5–0.6 for major depressive disorder genetic risk factors in men and women. Sex-specific evidence has been reported for linkage to major depressive disorder (50, 53) and to the related trait of neuroticism (54). Here the result on 17p is particularly interesting because it approached genomewide significance. It was attributable to increased allele sharing in male-male and male-female pairs, which might occur if a sequence variant increased risk more (but not exclusively) in men so that families with a male case would be more likely to be carrying the variant(s). Our findings on 17p and 8p could represent either false positives in a small male subgroup or important clues to sex-specific gene effects.

Table 5 summarized published linkage studies of major depressive disorder or related personality traits. In two studies of major depressive disorder (55–57), one of the highest lod scores was observed on chromosome 15q, whereas on 8p, a study of harm avoidance observed its highest score (58) and one of neuroticism observed its

Patient Perspective

Ms. F, age 50, felt nervous and had had insomnia as a child and lifelong social phobia. Since her first major depressive episode at 17, she had had a chronically depressed mood. Several times per year, she had episodes of increased appetite, insomnia with wakening at night, poor concentration, a lack of enjoyment in activities, a low energy level, slowed speech, and a restless and tense feeling. Changes in antidepressant medication sometimes led to periods of improvement. Three of Ms. F's relatives committed suicide, and she took overdoses of pills five times. Asked to describe depression, she said, "It's hard to explain, but I'd rather have a physical pain than that pain."

highest score in men (54). Another neuroticism scan (59) reported its highest lod on 6p, although it was somewhat far from the present result. Table 5 also lists regions where other studies reported overlapping results. Full assessment of the pattern of results across studies must await the appearance of more data, linkage fine mapping, and formal meta-analyses or combined analyses.

Some of these chromosomal regions have been of interest to investigators studying other psychiatric disorders. Evidence for linkage to schizophrenia has been reported in the same regions of chromosomes 6p and 8p (61), with our peaks occurring close to the schizophrenia candidate gene DTNBP1 on 6p but not to the candidate gene NRG1 on 8p (62). As noted, our study did produce some evidence to support the finding of linkage to major depressive disorder in men on chromosome 12q (50). However, we did not observe any evidence for linkage on chromosome 2q, where linkage was previously reported for several alternative major depressive disorder phenotypes in a smaller independent sample of families (53), or near several genes whose involvement in mood disorders is currently under intensive study, such as the genes encoding the serotonin transporter (SLC6A4 on more distal 17q), serotonin receptor 2A (13q), and brain-derived neurotrophic factor (11p) (63), or in previously reported significant linkage regions for bipolar disorder, such as those on chromosomes 6q and 8p (64). However, it is possible that major depressive disorder susceptibility genes will be discovered in some of these regions using genetic association methods that are more powerful than linkage analysis.

In conclusion, linkage analysis of 656 families demonstrated genomewide suggestive linkage on chromosome 15q and also on chromosomes 17p and 8p when the sex of the affected relative pair was taken into account. Further study of regions producing evidence for linkage in studies of major depressive disorder and related traits could lead

to the identification of genes contributing to susceptibility to severe depressive disorders.

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