# *Incorporation of molecular data and redefinition of phenotype: new approaches to genetic epidemiology of bipolar manic depressive illness and schizophrenia*

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*Considerable advances have been made in identifying specific genetic components of bipolar manic depressive illness (BP) and schizophrenia (SZ), despite their complex inheritance. Meta-analysis of all published whole-genome linkage scans reveals overall support for illness genes in several chromosomal regions. In two of these regions, on the long arm of chromosome 13 and on the long arm of chromosome 22, the combined studies of BP and SZ are consistent with a common susceptibility locus for the two disorders. This lends some plausibility to the hypothesis of some shared genetic predispositions for BP and SZ. Other linkages are supported by multiple studies of specific chromosomal regions, most notably two regions on chromosome 6 in SZ. The velocardiofacial syndrome is associated with deletions very close to the linkage region on chromosome 22, and with psychiatric manifestations of both BP and SZ. Endophenotypes of SZ, previously demonstrated to be heritable, have been found to have chromosomal linkage in at least one study. These include eye-tracking abnormalities linked to the short arm of chromosome 6, and abnormality of the P50 cortical evoked potential linked to chromosome 15. Variants in specific genes have been associated with susceptibility to illness, and other genes have been associated with susceptibility to side effects of pharmacological treatment. These genetic findings may eventually be part of an integrated genetic, environmental, and interactive-factor epidemiology of the major mental illnesses.*

## Molecular genetic epidemiology of bipolar manic depressive illness and schizophrenia

Beginning with the advent of DNA markers in 1978, and whole-genome genetic linkage marker maps in the late 1980s, research into the genetic epidemiology of bipolar manic depressive illness (BP) and schizophrenia (SZ) has been aimed at identifying gene variants that contribute to susceptibility to illness. This enterprise has not yet seen success, but there are reasons for optimism. Identification of susceptibility genes for complex inheritance psychiatric disorders has recently become feasible, due to advances in genomics and the analysis of complex inheritance disorders.

### Research strategies

Several alternative strategies for disease gene identification may reasonably be considered at this time in the development of genomics and the neuroscience of psychiatric disorders:

- Study of candidate genes based on neurobiology.
- Comparative analysis of gene expression in ill and well persons, followed by study of genes with differential expression in ill persons.

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## Selected abbreviations and acronyms

| | |
|---|---|
| ***BP*** | *bipolar manic depressive illness* |
| ***COMT*** | *catechol-O-methyltransferase* |
| ***MSP*** | *multiple scan probability* |
| ***SNP*** | *single nucleotide polymorphism* |
| ***SZ*** | *schizophrenia* |
| ***TNR*** | *trinucleotide repeat* |
| ***VCFS*** | *velocardiofacial syndrome* |

- Positional strategies:
  - whole-genome association (linkage disequilibrium) with densely spaced markers and/or/followed by mutational analysis;
  - positional cloning (detection of linkage, followed by association and mutational analysis of genes within the linkage region).

Positional approaches based on linkage are currently in some disfavor, yet the recent success in type 2 diabetes (see below), a common disease with similar inheritance to psychiatric disorders, belies the current disfavor. This review selectively focuses on a positional strategy, because such strategies exhaust all possibilities and thus have the capacity to uncover susceptibility genes that are surprises (ie, for which there is no prior hypothesis). Linkage followed by association (as opposed to genome-wide association) is currently a feasible positional strategic choice. This is not to suggest that other strategies might not, in the end, prove more successful in finding susceptibility mutations. The scientific advances supporting the positional strategy include the following.

*Completion of the finished sequence phase of the Human Genome Project*

The Human Genome Project has made enormous contributions to the various maps of the human genome, including genome-wide physical maps, very dense polymorphism maps, and integrated transcript maps. Sufficient single nucleotide polymorphisms (SNPs) for very dense mapping at almost all locations in the genome have also been developed. The genome project is now rapidly nearing its complete annotated sequence goal. This enables the genomic sequence of any gene to be examined in blood or other specimens from any individual. An ability to do mutational analysis of any gene or group of genes is a vast advance over what has been so often done in psychiatry until now—testing one or a few polymorphisms of a gene, and generalizing from that result.

*Recent scientific developments supporting the feasibility of cloning genes for complex disorders, based on initial linkage findings*

The discovery of susceptibility genes for the major psychiatric disorders, BP and SZ, is thought to include some of the most intractable current problems in human genetics.[1] The outlook for major advances based on genetic linkage and linkage disequilibrium has now greatly improved. The very recent availability of very dense SNP and other polymorphism maps has greatly improved the statistical power to detect linkage disequilibrium. Statistical methods developed in recent years for linkage and for combined linkage and linkage disequilibrium analyses, including haplotype-based analyses,[2-6] are capable of teasing apart subtle genetic components contributing to common diseases with complex inheritance.

*Detection of* NIDDM1*, a susceptibility gene for type 2 diabetes mellitus*

An instructive recent report of a near-certain causal connection between calpain 10 mutations and increased susceptibility to type 2 (non–insulin-dependent) diabetes mellitus[7] demonstrates the plausibility of applying currently available experimental, statistical, and computational tools to the successful identification of complex disease genes, starting with a linkage result. This discovery was made despite the usual complications of complex disease genetics: apparently inconsistent linkage results; study of an outbred population; and no obvious candidate genes in the linkage region. The keys to the discovery were innovative and meticulous analysis of disequilibrium in a sample of families with a positive linkage result, and thorough molecular scrutiny of the disequilibrium region.

Horikawa et al[7] found a strong statistical association of type 2 diabetes with a complex haplotype that produces an intronic polymorphism in the calpain 10 gene. The haplotype was found by detection of a small region (66 kb) that showed disequilibrium, followed by intensive examination of that region. The haplotype successfully partitioned the linkage evidence (it was associated

with nearly all the linkage evidence in the sample in which linkage was originally detected). In addition, the haplotype was associated with increased relative risk of illness in a Finnish population, and was found to alter expression of the calpain 10 gene.

The sample studied by Horikawa et al is the only one known with significant linkage evidence for type 2 diabetes in this region of chromosome 2.[8] It is a sample from an outbred Mexican-American population, and one of four samples studied in that report. There exist two other major linkage reports: a report from a French sample, which does not reach significance, but provides modest nominal support for linkage (*P* values roughly 0.01 to 0.07), and a large multinational study, which is not at all positive.[9,10] Meta-analysis of all reports using Fisher's meta-analysis test[11] gives a *P* value for the linkage of $5.6\times10^{-5}$, which retrospectively supports the approach taken by the type 2 diabetes researchers (data not shown).

Calpain 10 had been a very unlikely candidate diabetes gene, judging from its putative function and expression pattern. The identification of calpain 10 relied exclusively on positional data (derived from linkage and linkage disequilibrium). This precedent underscores the utility of a "no-a-priori-assumption" approach to complex disease gene identification. Nonetheless, this approach is especially powerful, and perhaps even necessary, for the genetic dissection of complex diseases such as BP or SZ, for which little mechanistic knowledge is available to warrant educated guesses about their molecular etiology.

## Recent history and interpretation of linkage results in psychiatry and results of meta-analysis of all published genome scans

Following analysis by Risch in 1990,[12] it became apparent in SZ—and by implication in BP illness as well—that the observed genetic epidemiological prevalences of high concordance in monozygotic twins, and very much lower relative risks in more distant relatives, implied oligogenic inheritance. This, in turn, would require that models of analysis be employed which are cognizant of oligogenic inheritance. It also implies that linkage may be detectable at multiple locations, without the results contradicting each other.

The "modern" era of gene scans can be said to begin with the development of a reasonably dense genomic map of more informative linkage markers and efficient multilocus analyses. In recent years, observations of linkage have been reported to be consistent with small-effects genes, using nonparametric analyses, or parametric analyses with suitable parameters to "cover" oligogenic inheritance (analysis under both a dominant and a recessive model, allowance for phenocopies, and low penetrance).[13-16] There have been only intermittent replications of these observations, as summarized in published reviews,[17-19] but there is not a complete absence of credible replication, as was true earlier.

It is possible to intuitively reject data out of hand when not all studies are positive, but it has long been recognized that it is desirable to develop a systematic meta-analytic statistical approach to the total linkage data for a given disease. Fisher's method of meta-analysis involves taking the *P* values from individual studies and testing the null hypothesis that these *P* values fit a uniform distribution.[20] This method has been applied to linkage studies by using the same *P* values at the same point in the genome from each linkage study.[21] This information, however, is frequently not available in published studies, but information is generally available about the local minimum *P* value and its associated genome location. Allison and Heo,[11] and Badner and Gershon (unpublished data) applied Fisher's meta-analysis method to analyze common disease results. Badner and Gershon used a method of statistical analysis based on the *P* values observed in a chromosomal region, using the mathematical formula of Feingold.[22] This allows for the inherent variability of the observed peak, and for the use of different markers in different studies. The minimum *P* values and their locations reported in the several studies are "corrected" for the distance away from the location of the peak of the most significant study. (The corrected *P* value of a study is higher, and thus less significant, if its peak is at a distance from the most significant peak.) The test of Fisher is then applied. The significance of the Fisher statistic is termed the multiple scan probability (MSP). Badner and Gershon[23] performed simulations and determined that a genome-wide significance criterion is appropriate for this statistic (such as the affected-sib-pair criterion where $2.2\times10^{-5}$ is significant and $7\times10^{-4}$ is suggestive[24]). Passing the threshold is interpreted to mean that a significant deviation from the null hypothesis of no linkage is present in at least some of the data.

As with any method of meta-analysis, our analysis would be susceptible to publication biases, ie, linkage results being more likely to be published if they are

positive. However, this bias is much less likely if only the results of whole-genome scans are included in our analysis of psychiatric disorders. This is because whole-genome scans are likely not to remain unpublished, even if they lack a significant linkage. In omitting published evidence that are not from whole-genome scans, we are mindful that some true findings might be omitted from our analysis, such as the linkages to SZ reported separately on each arm of chromosome 6.[25-29]

Our simulations (not shown) indicate that results from different analytical methods can be combined so long as a particular result is not included on the basis of its significance. For the current study, we developed an objective hierarchy for choosing affection status model and analytical method, so that results of each scan were not preferentially considered according to their *P* values. For comparison purposes, we present a table of meta-analysis results for all chromosomes for which at least one published genome scan had a *P* value <0.01 *(Table I)*.[30-51] For chromosome regions where the MSP<0.001, we present a "replication" MSP, where an MSP is calculated for that region, excluding the most significant study. Simulations show that the empirical *P* value of this statistic is equivalent to the nominal P value, ie, a replication MSP of 0.05 occurs ~1/20 times. The replication MSP statistic indicates whether the results of the MSP for all the studies are primarily due to a single significant study or whether other studies are also contributing. For the analysis combining BP and SZ, the most significant BP study and the most significant SZ study are excluded from the replication MSP.

These meta-analysis results strongly suggest that a statistically promising susceptibility locus for BP and a similarly promising susceptibility locus for SZ resides on the 13q chromosomal region. If the evidence for BP and SZ is combined, the data are consistent with the same regions on two chromosomes (13 and 22) and leads to the speculation that the same genes are conferring susceptibility to both illnesses.[19,53-55] The data on chromosome 22, which are suggestive in themselves, are of increased interest because of deletions in the nearby chromosomal region that cause velocardiofacial syn-

| Chromosome | BP | | | SZ | | | BP and SZ | | |
|---|---|---|---|---|---|---|---|---|---|
| | Loc (cM) | MSP | Rep MSP | Loc (cM) | MSP | Rep MSP | Loc (cM) | MSP | Rep MSP |
| 1 | 238 | 0.006 | | 171 | 0.0009 | 0.4 | 171 | 0.01 | |
| 2 | | | | 116 | $7x10^{-5}$ | 0.08 | | | |
| 3 | | | | 124 | 0.1 | | | | |
| 4 | 16 | 0.009 | | 61 | 0.01 | | 16 | 0.009 | |
| 5 | 78 | 0.2 | | 12 | 0.2 | | 78 | 0.5 | |
| 7 | 17 | 0.002 | | 114 | 0.001 | 0.03 | 114 | 0.01 | |
| 8 | 153 | 0.07 | | 50 | 0.001 | 0.06 | 50 | 0.003 | |
| 10 | 105 | 0.1 | | 46 | 0.2 | | 46 | 0.4 | |
| 11 | 38 | 0.0005 | | 76 | 0.02 | | 38 | 0.03 | |
| 12 | 64 | 0.1 | | 109 | 0.01 | | 109 | 0.06 | |
| 13 | 79 | $7x10^{-5}$ | 0.02 | 85 | 0.0008 | 0.1 | 85 | $4x10^{-6}$ | 0.02 |
| 14 | | | | 44 | 0.03 | | | | |
| 18 (p arm) | 41 | 0.003 | | 72 | 0.2 | | 41 | 0.09 | |
| 18 (q arm) | 105 | 0.008 | | | | | | | |
| 21 | 31 | 0.002 | | | | | | | |
| 22 | 30 | 0.003 | | 47 | 0.07 | | 32 | 0.0005 | 0.01 |
| X | | | | 40 | 0.3 | | | | |

Table I. Meta-analysis of linkage data in published whole-genome scans (as of October 2000). BP, bipolar manic depressive illness; SZ, schizophrenia; Loc, location (in cM) of the locus with the most significant result from a single study in this region (location estimates are obtained from the Marshfield map[52]); MSP, multiple scan probability; Rep MSP, "replication" probability, which omits most significant result of MSP (for the BP and SZ combined analysis, it omits two such results). Chromosomes are included if at least one study reported *P*<0.01.

drome (VCFS), which includes a high frequency of BP and SZ in the persons affected, as discussed below.
Additional positional strategies, such as linkage and association in population isolates, are also being employed in common disease inheritance, including psychiatric illnesses, but for reasons of space they could not be discussed here.

## Phenotype redefinition

The concept of endophenotype refers to biological aspects of illness that may have overlapping inheritance with an illness within families, represent a component of the genetic susceptibility, and be more amenable to linkage and mutation analysis than the related illness.[56] We may describe three major classes of putative endophenotypes in SZ: attentional, cognitive/communicative, and central nervous system (CNS) structural. In BP, there has not been a corresponding effort at endophenotype definition, although therapeutic drug response, particularly to lithium, has been investigated as a potential basis for genetic subtypes.[57]

### Eye-tracking findings

The eye-tracking findings of Holzman in schizophrenic families were the first attentional and neurophysiological variables to stimulate the suggestion that there were endophenotypes, and that separate genes might be found for them.[58,59] Two major attention-related measures, the P50 evoked potential and abnormal saccadic eye movements, have been reported to be linked to discrete chromosomal regions, on chromosomes 6 and 15.[60,61] Replications are awaited. A composite phenotype of the two characteristics has been linked to chromosome 22.[62] The attentional group of endophenotypes also includes the P300 cortical evoked potential and other variables, on which there are not yet molecular associations.[63,64]

### The cognitive group of variables

There is a great deal of nonmolecular epidemiological evidence for the cognitive group of variables,[65-69] ie, variables in which preschizophrenic children and children of schizophrenic parents show deficits, and in which there are deficits in relatives as well, include verbal working memory, negative symptoms, communication disturbances (including speech and language impairments), and "soft neurologic" and neurobehavioral measures. There is evidence that the "deficit syndrome" in SZ is familial as well.[70]

### Neuroanatomical variables

The third class, neuroanatomical variables, has had several familial investigations, but none have reported associated genetic markers. An interesting finding observed repeatedly is increased ventricular volume in SZ patients vs well siblings, with both groups having greater volume than controls.[71-73]

### Age of onset

Does prepubertal onset of BP or SZ imply a genetically distinct disease from older-onset illness? Work by Badner and Gershon[22] concluded that the cross-prevalence of adult illness in families of child probands does not support a separate disease entity, but that separate molecular and cytogenetic investigation of families with childhood-onset has barely begun. Papolos et al[74] observed that BP illness associated with VCFS usually has childhood onset, suggesting a separate entity; replication is awaited.
Among postpubertal onset BP and SZ (the vast majority of cases), there is conflicting evidence on whether early-onset is associated with increased morbid risk of illness,[75-78] and there is no molecular or cytogenetic evidence implying a separate inheritance in early- vs later-onset postpubertal BP or SZ.

## Alternative mechanisms of genetic transmission

### Anticipation

Anticipation is present in genetic diseases when successive generations have earlier onset of illness, greater severity, and/or greater likelihood of being affected. Once the mechanism of expanding trinucleotide repeats (TNRs) was discovered in fragile-X mental retardation, and then in a succession of other neuropsychiatric diseases, including Huntington's disease and several spinocerebellar atrophies, investigators began a scrutiny of BP and SZ for anticipation and for expanding TNRs.[79] At present, observations consistent with anticipation are being repeatedly reported, although there is some question as to whether this is a birth-cohort effect or ascer-

tainment artifact, as reviewed elsewhere.[80-83] There have been some claims of expanding repeats associated with major psychiatric illness, including an association with childhood-onset SZ,[84] but nearly all of these repeats have subsequently been shown to be common polymorphisms not associated with disease, as reviewed elsewhere.[85] However, there remains some possibly disease-associated TNRs that merit further investigation.[86]

**Aneuploidal events**

VCFS is associated with deletions in a region on the q arm of chromosome 22, including microdeletions, and with psychiatric manifestations of BP and SZ.[85-87] Many other aneuploidal events have been found in isolated cases or families with BP or SZ, but the finding on chromosome 22 is the most frequent. The region of reported linkage to these disorders on the q arm of chromosome 22 is consistent with the finding of microdeletions. The gene for catechol-*O*-methyltransferase (COMT) is within the deletion region for VCFS. Modest evidence for an association of COMT with SZ has been reported,[90-92] but other studies do not find any evidence for association in SZ[93,94] or in BP.[95]

**Sex-of-parent–specific transmission**

BP has been reported to have excess maternal transmission,[96,97] and some linkages appear to be specific to paternal or maternal history.[96-98] There has not been great consistency in these observations,[99,100] but there are enough repeated findings to consider mechanisms that might be implicated. An associated mitochondrial variant has not appeared consistently.[101,102] Imprinting has not been sufficiently investigated for comment. Malaspina has presented data showing that sporadic cases of SZ are associated with increased paternal age, but not increased maternal age, implying that new mutations may be playing a role.[103] Periodic catatonia, a form of SZ, had a paternal parent-of-origin effect associated with early onset in one series.[104]

## Candidate genes

In contrast to linkage, associations do not yet have an agreed-upon criterion for genome-wide significance. A plausible case can be made for each of a great many genes that it is an a priori candidate, and that therefore nominal significance of $P<0.05$ is adequate to provide supportive evidence. However, as has been noted by others, there are so many such genes that any one result has to be looked at cautiously, even when it is highly significant.

The neurodevelopmental hypothesis of SZ, supported by the association of the illness with in utero infections and obstetric complications, has generated genetic hypotheses. Developmental genes known from lower species are important in mammalian CNS development. Reduced expression in SZ brain has been reported for several of these, such as the genes encoding for Wnt-1,[105] reelin,[106] and neural cell adhesion molecule (NCAM),[107] although association of molecular variants of these genes with SZ has not been demonstrated. *NOTCH4*, on the other hand, has been reported to have a very significant association with SZ,[108] and replication is awaited.

It had been suggested that Wolfram syndrome is associated with a large proportion of BP and SZ illness, but now that the gene (wolframin) has been cloned, association of BP with variants or markers of the gene has not been observed.[109,110]

Other candidate genes, based on altered neurotransmission hypotheses of BP and SZ, have been reviewed elsewhere.[111-113]

## Conclusions

Eventually, the genetic epidemiology of BP and SZ will include knowledge of genetic variants that increase susceptibility to illness, as well as susceptibility to specific components of the illness and to side effects of certain treatments. With such knowledge, an integrated epidemiology becomes achievable, in which interaction of these genetic susceptibilities with environmental events (such as exposure to infectious agents, drugs, and various stressors) leads to useful predictions on premorbid characteristics, onset of illness, course, and response to treatment. The current knowledge on genetic linkages, endophenotypes, and associations of specific gene variants with illness and with side effects of treatment may represent the beginnings of the genetic component of a comprehensive epidemiology of these mental disorders. ❑

## Incorporación de información molecular y redefinición del fenotipo: nuevas aproximaciones a la epidemiología genética de la enfermedad bipolar maníaco-depresiva y de la esquizofrenia

Se han realizado avances significativos en la identificación de componentes genéticos específicos de la enfermedad bipolar maníaco-depresiva (BP) y de la esquizofrenia (EQZ) a pesar de su compleja herencia. El meta-análisis de todos los mapeos de enlaces del genoma completo publicados revela una fuerte base para genes enfermos en regiones de algunos cromosomas. En dos de estas regiones, en el brazo largo del cromosoma 13 y en el brazo largo el cromosoma 22, los estudios combinados de BP y EQZ son consistentes con un locus de susceptibilidad común para los dos trastornos. Esto proporciona alguna credibilidad a la hipótesis de cierta predisposición genética compartida para BP y EQZ. Otros enlaces están sustentados por múltiples estudios de regiones cromosómicas específicas, más notablemente dos regiones en el cromosoma 6 en la EQZ. El síndrome velocardiofacial está asociado con supresiones muy cercanas a la región de enlace en el cromosoma 22 y con manifestaciones psiquiátricas tanto de BP como de EQZ. Endofenotipos de EQZ, que previamente demostraron ser heredados, al menos en un estudio se ha encontrado que tienen ligazón cromosómica. Estos incluyen anormalidades del seguimiento ocular, el cual está ligado al brazo corto del cromosoma 6 y anormalidades del potencial evocado cortical P50 ligado al cromosoma 15. Se han asociado variantes en genes específicos con la susceptibilidad para la enfermedad, y otros genes se han vinculado con susceptibilidad a los efectos colaterales del tratamiento farmacológico. Estos hallazgos genéticos pueden ser parte, eventualmente, de una integración genética, ambiental y de un factor epidemiológico interactivo en las principales enfermedades mentales.

## Prise en compte des données moléculaires et redéfinition du phénotype : avancées dans le domaine de l'épidémiologie génétique de la maladie bipolaire maniacodépressive et de la schizophrénie

Des avancées très importantes ont été réalisées dans l'identification des composants génétiques spécifiques porteurs de la psychose maniacodépressive (PMD) et de la schizophrénie (SZ) malgré l'hérédité complexe de ces deux maladies. Une métaanalyse de la carte des liaisons génétiques publiées sur l'ensemble du génome révèle un consensus général sur l'atteinte des gènes dans plusieurs régions chromosomiques. Dans deux de ces régions, sur le bras long du chromosome 13 et celui du chromosome 22, les résultats des études combinées sur la PMD et la SZ sont concordants et incriminent un gène commun de susceptibilité pour les deux maladies. L'hypothèse de prédispositions génétiques communes à la PMD et à la SZ se trouve donc confortée. D'autres régions chromosomiques spécifiques, surtout deux régions sur le chromosome 6 dans la SZ, ont fait l'objet de multiples études qui ont mis en évidence d'autres liaisons. Le syndrome vélo-cardio-facial est associé à des délétions très proches du groupe de liaison sur le chromosome 22 et à des manifestations psychiatriques identiques à celles de la PMD et à la SZ. Une étude au moins a mis en évidence des liaisons chromosomiques avec les endophénotypes de la SZ, connus comme étant héréditaires. Ces liaisons concernent les anomalies de la poursuite oculaire liées au bras court du chromosome 6 et une anomalie du potentiel évoqué cortical P50 liée au chromosome 15. Des variantes de gènes spécifiques ont été associées à une prédisposition à la maladie et d'autres gènes à une susceptibilité aux effets secondaires du traitement. Ces données génétiques pourraient un jour trouver leur place dans le cadre d'une définition épidémiologique des principales maladies psychiatriques intégrant les aspects génétiques et environnementaux ainsi que les facteurs interactifs.

## REFERENCES


1. Risch N, Botstein D. A manic depressive history [news]. *Nat Genet.* 1996;12:351-353.
2. Cox NJ, Frigge M, Nicolae DL, et al. Loci on chromosomes 2 (NIDDM1) and 15 interact to increase susceptibility to diabetes in Mexican Americans. *Nat Genet.* 1999;21:213-215.
3. Hauser ER, Boehnke M, Guo SW, Risch N. Affected-sib-pair interval mapping and exclusion for complex genetic traits: sampling considerations. *Genet Epidemiol.* 1996;13:117-137.
4. Kong A, Cox NJ. Allele-sharing models: LOD scores and accurate linkage tests. *Am J Hum Genet.* 1997;61:1179-1188.
5. Spielman RS, McGinnis RE, Ewens WJ. Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes mellitus (IDDM). *Am J Hum Genet.* 1993;52:506-516.
6. Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES. Parametric and nonparametric linkage analysis: a unified multipoint approach. *Am J Hum Genet.* 1996;58:1347-1363.
7. Horikawa Y, Oda N, Cox NJ, et al. Genetic variation in the gene encoding calpain-10 (*CAPN10*) is associated with type 2 diabetes mellitus. *Nat Genet.* 2000;26:163-175.
8. Hanis CL, Boerwinkle E, Chakraborty R, et al. A genome-wide search for human non–insulin-dependent (type 2) diabetes genes reveals a major susceptibility locus on chromosome 2 [see comments]. *Nat Genet.* 1996;13:161-166.
9. Ghosh S, Hauser ER, Magnuson VL, et al. A large sample of Finnish diabetic sib-pairs reveals no evidence for a non–insulin-dependent diabetes mellitus susceptibility locus at 2qter. *J Clin Invest.* 1998;102:704-709.
10. Hani EH, Hager J, Philippi A, Demenais F, Froguel P, Vionnet N. Mapping NIDDM susceptibility loci in French families: studies with markers in the region of *NIDDM1* on chromosome 2q. *Diabetes.* 1997;46:1225-1226.
11. Allison DB, Heo M. Meta-analysis of linkage data under worst-case conditions: a demonstration using the human OB region. *Genetics.* 1998;148:859-865.
12. Risch N. Linkage strategies for genetically complex traits. I. Multilocus models. *Am J Hum Genet.* 1990;46:222-228.
13. Abreu PC, Greenberg DA, Hodge SE. Direct power comparisons between simple LOD scores and NPL scores for linkage analysis in complex diseases. *Am J Hum Genet.* 1999;65:847-857.
14. Durner M, Vieland VJ, Greenberg DA. Further evidence for the increased power of LOD scores compared with nonparametric methods. *Am J Hum Genet.* 1999;64:281-289.
15. Greenberg DA, Abreu P, Hodge SE. The power to detect linkage in complex disease by means of simple LOD-score analyses. *Am J Hum Genet.* 1998;63:870-879.
16. Vieland VJ, Greenberg DA, Hodge SE. Adequacy of single-locus approximations for linkage analyses of oligogenic traits: extension to multigenerational pedigree structures. *Hum Hered.* 1993;43:329-336.
17. Sanders AR, Detera-Wadleigh SD, Gershon ES. Molecular genetics of mood disorders. In: Charney DS, Neufeld K, Bunney BS, eds. *Neurobiology of Mental Illness.* New York, NY: Oxford University Press; 1999:299-316.
18. Gershon ES, Badner JA, Goldin LR, Sanders AR, Cravchik A, Detera-Wadleigh SD. Closing in on genes for manic-depressive illness and schizophrenia. *Neuropsychopharmacology.* 1998;18:233-242.
19. Gershon ES. Bipolar illness and schizophrenia as oligogenic diseases: implications for the future. *Biol Psychiatry.* 2000;47:240-244.
20. Hedges LV, Olkin I. *Statistical Methods for Meta-Analysis.* San Diego, Calif: Academic Press; 1985.
21. Guerra R, Etzel CJ, Goldstein DR, Sain SR. Meta-analysis by combining P values: simulated linkage studies. *Genet Epidemiol.* 1999;17(suppl 1):S605-S609.
22. Feingold E, Brown PO, Siegmund D. Gaussian models for genetic linkage analysis using complete high-resolution maps of identity by descent. *Am J Hum Genet.* 1993;53:234-251.
23. Badner JA, Gershon ES. Regional meta-analysis of published data supports linkage of autism with markers on chromosome 7. *Mol Psychiatry.* 2001. In press.
24. Lander E, Kruglyak L. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results [see comments]. *Nat Genet.* 1995;11:241-247.
25. Levinson DF, Holmans P, Straub RE, et al. Multicenter linkage study of schizophrenia candidate regions on chromosomes 5q, 6q, 10p, and 13q: schizophrenia linkage collaborative group III [In Process Citation]. *Am J Hum Genet.* 2000;67:652-663.
26. Straub RE, MacLean CJ, O'Neill FA, et al. A potential vulnerability locus for schizophrenia on chromosome 6p24-22: evidence for genetic heterogeneity. *Nat Genet.* 1995;11:287-293.
27. Kendler KS, Myers JM, O'Neill FA, et al. Clinical features of schizophrenia and linkage to chromosomes 5q, 6p, 8p, and 10p in the Irish Study of High-Density Schizophrenia Families. *Am J Psychiatry.* 2000;157:402-408.
28. Schwab SG, Albus M, Hallmayer J, et al. Evidence for susceptibility gene for schizophrenia on chromosome 6p by multipoint affected-sib-pair linkage analysis. *Nat Genet.* 1995;11:325-327.
29. Straub RE, Lehner T, Luo Y, et al. A potential vulnerability locus for bipolar affective disorder on chromosome 21q22.3. *Nat Genet.* 1994;8:291-296.
30. Brzustowicz LM, Hodgkinson KA, Chow EW, Honer WG, Bassett AS. Location of a major susceptibility locus for familial schizophrenia on chromosome 1q21-q22. *Science.* 2000;288:678-682.
31. Ekelund J, Lichtermann D, Hovatta I, et al. Genome-wide scan for schizophrenia in the Finnish population: evidence for a locus on chromosome 7q22. *Hum Mol Genet.* 2000;9:1049-1057.
32. Williams NM, Rees MI, Holmans P, et al. A two-stage genome scan for schizophrenia susceptibility genes in 196 affected sibling pairs. *Hum Mol Genet.* 1999;8:1729-1739.
33. Rees MI, Fenton I, Williams NM, et al. Autosome search for schizophrenia susceptibility genes in multiply affected families. *Mol Psychiatry.* 1999;4:353-359.
34. Levinson DF, Mahtani MM, Nancarrow DJ, et al. Genome scan of schizophrenia. *Am J Psychiatry.* 1998;155:741-750.
35. Blouin JL, Dombroski BA, Nath SK, et al. Schizophrenia susceptibility loci on chromosomes 13q32 and 8p21. *Nat Genet.* 1998;20:70-73.
36. Shaw SH, Kelly M, Smith AB, et al. A genome-wide search for schizophrenia susceptibility genes. *Am J Med Genet.* 1998;81:364-376.
37. Faraone SV, Matise T, Svrakic D, et al. Genome scan of European-American schizophrenia pedigrees: results of the NIMH Genetics Initiative and Millennium Consortium. *Am J Med Genet.* 1998;81:290-295.
38. Kaufmann CA, Suarez B, Malaspina D, et al. NIMH Genetics Initiative Millennium Schizophrenia Consortium: linkage analysis of African-American pedigrees. *Am J Med Genet.* 1998;81:282-289.
39. Moises HW, Yang L, Kristbjarnarson H, et al. An international two-stage genome-wide search for schizophrenia susceptibility genes. *Nat Genet.* 1995;11:321-324.
40. Coon H, Jensen S, Holik J, et al. Genomic scan for genes predisposing to schizophrenia. *Am J Med Genet.* 1994;54:59-71.
41. Barr CL, Kennedy JL, Pakstis AJ, et al. Progress in a genome scan for linkage in schizophrenia in a large Swedish kindred. *Am J Med Genet.* 1994;54:51-58.
42. Friddle C, Koskela R, Ranade K, et al. Full-genome scan for linkage in 50 families segregating the bipolar affective disease phenotype. *Am J Hum Genet.* 2000;66:205-215.
43. Detera-Wadleigh SD, Badner JA, Berrettini WH, et al. A high-density genome scan detects evidence for a bipolar-disorder susceptibility locus on 13q32 and other potential loci on 1q32 and 18p11.2. *Proc Natl Acad Sci U S A.* 1999;96:5604-5609.
44. Morissette J, Villeneuve A, Bordeleau L, et al. Genome-wide search for linkage of bipolar affective disorders in a very large pedigree derived from a homogeneous population in Quebec points to a locus of major effect on chromosome 12q23-q24. *Am J Med Genet.* 1999;88:567-587.
45. Stine OC, McMahon FJ, Chen L, et al. Initial genome screen for bipolar disorder in the NIMH genetics initiative pedigrees: chromosomes 2, 11, 13, 14, and X. *Am J Med Genet.* 1997;74:263-269.
46. Detera-Wadleigh SD, Badner JA, Yoshikawa T, et al. Initial genome scan of the NIMH genetics initiative bipolar pedigrees: chromosomes 4, 7, 9, 18, 19, 20, and 21q. *Am J Med Genet.* 1997;74:254-262.
47. Rice JP, Goate A, Williams JT, et al. Initial genome scan of the NIMH genetics initiative bipolar pedigrees: chromosomes 1, 6, 8, 10, and 12. *Am J Med Genet.* 1997;74:247-253.
48. McInnes LA, Escamilla MA, Service SK, et al. A complete genome screen for genes predisposing to severe bipolar disorder in two Costa Rican pedigrees. *Proc Natl Acad Sci U S A.* 1996;93:13060-13065.
49. Ginns EI, Ott J, Egeland JA, et al. A genome-wide search for chromosomal loci linked to bipolar affective disorder in the Old Order Amish. *Nat Genet.* 1996;12:431-435.
50. Blackwood DH, He L, Morris SW, et al. A locus for bipolar affective disorder on chromosome 4p. *Nat Genet.* 1996;12:427-430.
51. Coon H, Jensen S, Hoff M, et al. A genome-wide search for genes predisposing to manic-depression, assuming autosomal dominant inheritance. *Am J Hum Genet.* 1993;52:1234-1249.
52. Broman KW, Murray JC, Sheffield VC, White RL, Weber JL. Comprehensive human genetic maps: individual and sex-specific variation in recombination. *Am J Hum Genet.* 1998;63:861-869.
53. Berrettini WH. Genetics of psychiatric disease. *Annu Rev Med.* 2000;51:465-479.
54. Berrettini WH. Susceptibility loci for bipolar disorder: overlap with inherited vulnerability to schizophrenia. *Biol Psychiatry.* 2000;47:245-251.
55. Wildenauer DB, Schwab SG, Maier W, Detera-Wadleigh SD. Do schizophrenia and affective disorder share susceptibility genes? *Schizophr Res.* 1999;39:107-111.
56. Freedman R, Adler LE, Leonard S. Alternative phenotypes for the complex genetics of schizophrenia. *Biol Psychiatry.* 1999;45:551-558.
57. Alda M, Grof P, Grof E, Zvolsky P, Walsh M. Mode of inheritance in families of patients with lithium-responsive affective disorders. *Acta Psychiatr Scand.* 1994;90:304-310.
58. Holzman PS. Behavioral markers of schizophrenia useful for genetic studies. *J Psychiatr Res.* 1992;26:427-445.
59. Matthysse S, Levy DL, Kinney D, et al. Gene expression in mental illness: a nav-

igation chart to future progress. *J Psychiatr Res.* 1992;26:461-473.
60. Arolt V, Lencer R, Nolte A, et al. Eye tracking dysfunction is a putative phenotypic susceptibility marker of schizophrenia and maps to a locus on chromosome 6p in families with multiple occurrence of the disease. *Am J Med Genet.* 1996;67:564-579.
61. Freedman R, Coon H, Myles-Worsley M, et al. Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. *Proc Natl Acad Sci U S A.* 1997;94:587-592.
62. Myles-Worsley M, Coon H, McDowell J, et al. Linkage of a composite inhibitory phenotype to a chromosome 22q locus in eight Utah families. *Am J Med Genet.* 1999;88:544-550.
63. Blackwood D. P300, a state and a trait marker in schizophrenia. *Lancet.* 2000;355:771-772.
64. Cornblatt B, Obuchowski M, Roberts S, Pollack S, Erlenmeyer-Kimling L. Cognitive and behavioral precursors of schizophrenia. *Dev Psychopathol.* 1999;11:487-508.
65. Erlenmeyer-Kimling L, Rock D, Roberts SA, et al. Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York High-Risk Project. *Am J Psychiatry.* 2000;157:1416-1422.
66. Faraone SV, Meyer J, Matise T, et al. Suggestive linkage of chromosome 10p to schizophrenia is not due to transmission ratio distortion. *Am J Med Genet.* 1999;88:607-608.
67. Faraone SV, Seidman LJ, Kremen WS, Toomey R, Pepple JR, Tsuang MT. Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: a 4-year follow-up study. *J Abnorm Psychol.* 1999;108:176-181.
68. Hans SL, Marcus J, Nuechterlein KH, Asarnow RF, Styr B, Auerbach JG. Neurobehavioral deficits at adolescence in children at risk for schizophrenia: The Jerusalem Infant Development Study. *Arch Gen Psychiatry.* 1999;56:741-748.
69. Kinney DK, Yurgelun-Todd DA, Woods BT. Neurologic signs of cerebellar and cortical sensory dysfunction in schizophrenics and their relatives. *Schizophr Res.* 1999;35:99-104.
70. Kirkpatrick B, Ross DE, Walsh D, Karkowski L, Kendler KS. Family characteristics of deficit and nondeficit schizophrenia in the Roscommon Family Study. *Schizophr Res.* 2000;45:57-64.
71. Dauphinais ID, DeLisi LE, Crow TJ, et al. Reduction in temporal lobe size in siblings with schizophrenia: a magnetic resonance imaging study. *Psychiatry Res.* 1990;35:137-147.
72. Silverman JM, Smith CJ, Guo SL, Mohs RC, Siever LJ, Davis KL. Lateral ventricular enlargement in schizophrenic probands and their siblings with schizophrenia-related disorders. *Biol Psychiatry.* 1998;43:97-106.
73. Staal WG, Hulshoff Pol HE, Schnack HG, Hoogendoorn ML, Jellema K, Kahn RS. Structural brain abnormalities in patients with schizophrenia and their healthy siblings. *Am J Psychiatry.* 2000;157:416-421.
74. Papolos DF, Faedda GL, Veit S, et al. Bipolar spectrum disorders in patients diagnosed with velo-cardio-facial syndrome: does a hemizygous deletion of chromosome 22q11 result in bipolar affective disorder? *Am J Psychiatry.* 1996;153:1541-1547.
75. Suvisaari JM, Haukka J, Tanskanen A, Lonnqvist JK. Age at onset and outcome in schizophrenia are related to the degree of familial loading. *Br J Psychiatry.* 1998;173:494-500.
76. Grigoroiu-Serbanescu M, Wickramaratne PJ, Hodge SE, Milea S, Mihailescu R. Genetic anticipation and imprinting in bipolar I illness. *Br J Psychiatry.* 1997;170:162-166.
77. Kendler KS, Karkowski-Shuman L, Walsh D. Age at onset in schizophrenia and risk of illness in relatives. Results from the Roscommon Family Study. *Br J Psychiatry.* 1996;169:213-218.
78. Gershon ES, Hamovit J, Guroff JJ, et al. A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. *Arch Gen Psychiatry.* 1982;39:1157-1167.
79. Ross CA, McInnis MG, Margolis RL, Li SH . Genes with triplet repeats: candidate mediators of neuropsychiatric disorders. *Trends Neurosci.* 1993;16:254-260.
80. McInnis MG, McMahon FJ, Crow T, Ross CA, DeLisi LE. Anticipation in schizophrenia: a review and reconsideration. *Am J Med Genet.* 1999;88:686-693.
81. Heiden A, Willinger U, Scharfetter J, Meszaros K, Kasper S, Aschauer HN. Anticipation in schizophrenia. *Schizophr Res.* 1999;35:25-32.
82. Borrmann-Hassenbach MB, Albus M, Scherer J, Dreikorn B. Age at onset anticipation in familial schizophrenia. Does the phenomenon even exist? *Schizophr Res.* 1999;40:55-65.
83. Margolis RL, McInnis MG, Rosenblatt A, Ross CA. Trinucleotide repeat expansion and neuropsychiatric disease. *Arch Gen Psychiatry.* 1999;56:1019-1031.
84. Burgess CE, Lindblad K, Sidransky E, et al. Large CAG/CTG repeats are associated with childhood-onset schizophrenia. *Mol Psychiatry.* 1998;3:321-327.
85. Vincent JB, Paterson AD, Strong E, Petronis A, Kennedy JL. The unstable trinucleotide repeat story of major psychosis. *Am J Med Genet.* 2000;97:77-97.
86. Vincent JB, Neves-Pereira ML, Paterson AD, et al. An unstable trinucleotide-repeat region on chromosome 13 implicated in spinocerebellar ataxia: a common expansion locus. *Am J Hum Genet.* 2000;66:819-829.
87. Karayiorgou M, Morris MA, Morrow B, et al. Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. *Proc Natl Acad Sci U S A.* 1995;92:7612-7616.
88. Carlson C, Papolos D, Pandita RK, et al. Molecular analysis of velo-cardio-facial syndrome patients with psychiatric disorders. *Am J Hum Genet.* 1997;60:851-859.
89. Gothelf D, Frisch A, Munitz H, et al. Velocardiofacial manifestations and microdeletions in schizophrenic inpatients. *Am J Med Genet.* 1997;72:455-461.
90. de Chaldee M, Laurent C, Thibaut F, et al. Linkage disequilibrium on the *COMT* gene in French schizophrenics and controls. *Am J Med Genet.* 1999;88:452-457.
91. Kotler M, Barak P, Cohen H, et al. Homicidal behavior in schizophrenia associated with a genetic polymorphism determining low catechol-*O*-methyltransferase (COMT) activity. *Am J Med Genet.* 1999;88:628-633.
92. Ohmori O, Shinkai T, Kojima H, et al. Association study of a functional catechol-*O*-methyltransferase gene polymorphism in Japanese schizophrenics. *Neurosci Lett.* 1998;243:109-112.
93. Wei J, Hemmings GP. Lack of evidence for association between the COMT locus and schizophrenia. *Psychiatr Genet.* 1999;9:183-186.
94. Chen CH, Lee YR, Chung MY, et al. Systematic mutation analysis of the catechol-*O*-methyltransferase gene as a candidate gene for schizophrenia. *Am J Psychiatry.* 1999;156:1273-1275.
95. Kirov G, Jones I, McCandless F, Craddock N, Owen MJ. Family-based association studies of bipolar disorder with candidate genes involved in dopamine neurotransmission: *DBH*, *DAT1*, *COMT*, *DRD2*, *DRD3* and *DRD5*. *Mol Psychiatry.* 1999;4:558-565.
96. McMahon FJ, Stine OC, Meyers DA, Simpson SG, DePaulo JR. Patterns of maternal transmission in bipolar affective disorder. *Am J Hum Genet.* 1995;56:1277-1286.
97. Gershon ES, Badner JA, Detera-Wadleigh SD, Ferraro TN, Berrettini WH. Maternal inheritance and chromosome 18 allele sharing in unilineal bipolar illness pedigrees. *Am J Med Genet.* 1996;67:202-207.
98. Stine OC, Xu J, Koskela R, et al. Evidence for linkage of bipolar disorder to chromosome 18 with a parent of origin effect. *Am J Hum Genet.* 1995;57:1384-1394.
99. Kato T, Winokur G, Coryell W, Keller MB, Endicott J, Rice J. Parent-of-origin effect in transmission of bipolar disorder. *Am J Med Genet.* 1996;67:546-550.
100. Kato T, Winokur G, Coryell W, et al. Failure to demonstrate parent-of-origin effect in transmission of bipolar II disorder. *J Affect Disord.* 1998;50:135-141.
101. Kato T, Kunugi H, Nanko S, Kato N. Association of bipolar disorder with the 5178 polymorphism in mitochondrial DNA. *Am J Med Genet.* 2000;96:182-186.
102. McMahon FJ, Chen YS, Patel S, et al. Mitochondrial DNA sequence diversity in bipolar affective disorder. *Am J Psychiatry.* 2000;157:1058-1064.
103. Malaspina D, Harlap S, Fennig S, et al. Advancing paternal age and the risk of schizophrenia. *Arch Gen Psychiatry.* 2001;58:361-367.
104. Stober G, Jatzke S, Meyer J, et al. Short CAG repeats within the hSKCa3 gene associated with schizophrenia: results of a family-based study. *Neuroreport.* 1998;9:3595-3599.
105. Miyaoka T, Seno H, Ishino H. Increased expression of Wnt-1 in schizophrenic brains. *Schizophr Res.* 1999;38:1-6.
106. Impagnatiello F, Guidotti AR, Pesold C, et al. A decrease of reelin expression as a putative vulnerability factor in schizophrenia. *Proc Natl Acad Sci U S A.* 1998;95:15718-15723.
107. Vicente AM, Macciardi F, Verga M, et al. NCAM and schizophrenia: genetic studies. *Mol Psychiatry.* 1997;2:65-69.
108. Wei J, Hemmings GP. The *NOTCH4* locus is associated with susceptibility to schizophrenia. *Nat Genet.* 2000;25:376-377.
109. Furlong RA, Ho LW, Rubinsztein JS, et al. A rare coding variant within the wolframin gene in bipolar and unipolar affective disorder cases. *Neurosci Lett.* 1999;277:123-126.
110. Middle F, Jones I, McCandless F, et al. Bipolar disorder and variation at a common polymorphism (A1832G) within exon 8 of the Wolfram gene. *Am J Med Genet.* 2000;96:154-157.
111. Sanders AR, Detera-Wadleigh SD, Gershon ES. Molecular genetics of mood disorders. In: Charney DS, Nestler EJ, Bunney BS, eds. *Neurobiology of Mental Illness.* New York, NY: Oxford University Press; 1999:299-316.
112. O'Donovan MC, Owen MJ. Candidate-gene association studies of schizophrenia. *Am J Hum Genet.* 1999;65:587-592.
113. Badner JA, Detera-Wadleigh SD, Gershon ES. Genetics of early-onset manic-depressive illness and schizophrenia. In: Rapoport JL, ed. *Childhood Onset of "Adult" Psychopathology.* Washington, DC: American Psychiatric Press; 2000:3-26.