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.
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 (i.e., 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. A n 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. 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, 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

A n instructive recent report of a near-certain causal connection between calpain 10 mutations and increased susceptibility to type 2 (non-insulin-dependent) diabetes mellitus 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.

H orikawa et al. 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. 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. M eta-analysis of all reports using Fisher’s meta-analysis test gives a P value for the linkage of 5.6×10^{-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 B P or S Z, 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, it became apparent in S Z— and by implication in B P 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). There have been only intermittent replications of these observations, as summarized in published reviews, 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. 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. 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. A llison and H eo, 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. 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 (M SP). B adner and Gershon performed simulations and determined that a genome-wide significance criterion is appropriate for this statistic (such as the affected-sib-pair criterion where 2.2×10^{-4} is significant and 7×10^{-5} is suggestive). 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.

A s 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 Loc (cM) | BP MSP | Rep MSP | SZ Loc (cM) | SZ MSP | Rep MSP | BP and SZ Loc (cM) | BP and SZ MSP | Rep MSP |
|------------|-------------|--------|--------|-------------|--------|--------|------------------|----------------|--------|
| 1          | 238         | 0.006  |        | 171         | 0.0009 | 0.4    | 171              | 0.01           |        |
| 2          | 116         | 7x10^{-5} | 0.08  | 124         | 0.1    |        |                  |                |        |
| 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^{-4} | 0.02 | 85          | 0.0008 | 0.1    | 85               | 4x10^{-4}      | 0.02   |
| 14         |             |        |        | 44          | 0.03   |        |                  |                |        |
| 18 (p arm) | 41          | 0.003  |        | 72          | 0.2    |        | 41               | 0.09           |        |
| 18 (q arm) | 105         | 0.008  |        | 47          | 0.07   |        | 32               | 0.0005         | 0.01   |
| 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 map52); \( MSP \), 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. 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.

**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. 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. Replications are awaited. A composite phenotype of the two characteristics has been linked to chromosome 22. The attentional group of endophenotypes also includes the P300 cortical evoked potential and other variables, on which there are not yet molecular associations.

**The cognitive group of variables**

There is evidence that the “deficit syndrome” in SZ is familial as well. There is a great deal of nonmolecular epidemiological evidence for the cognitive group of variables, in which preschool schizophrenic 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.

**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.

**Age of onset**

Does prepubertal onset of BP or SZ imply a genetically distinct disease from older-onset illness? Work by Badner and Gershon 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. Papalos et al observed that BP illness associated with VCFS usually has childhood onset, suggesting a separate entity; replication is awaited.

A mong 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, 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**

A nticipation 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. A t 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. There have been some claims of expanding repeats associated with major psychiatric illness, including an association with childhood-onset SZ, but nearly all of these repeats have subsequently been shown to be common polymorphisms not associated with disease, as reviewed elsewhere. However, there remains some possibly disease-associated TNRs that merit further investigation.

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. 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, but other studies do not find any evidence for association in SZ or in BP.

Sex-of-parent-specific transmission

BP has been reported to have excess maternal transmission, and some linkages appear to be specific to paternal or maternal history. There has not been great consistency in these observations, but there are repeated findings to consider mechanisms that might be implicated. A mitochondrial variant has not appeared consistently. 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. Periodic catatonia, a form of SZ, had a paternal parent-of-origin effect associated with early onset in one series.

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, reelin, and neural cell adhesion molecule (NCAM), 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, 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. Other candidate genes, based on altered neurotransmission hypotheses of BP and SZ, have been reviewed elsewhere.

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 velo-cardio-facial 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 avances 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 métanalyse 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.
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