

FEATURE REVIEW

Excitement and confusion on chromosome 6q: the challenges of neuropsychiatric genetics in microcosm

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The search for genes that are implicated in the pathogenesis of schizophrenia (SCZ), bipolar disorder (BPD) and other complex neuropsychiatric phenotypes has yielded a plethora of positive findings, but has also engendered a substantial degree of confusion. Exciting findings include positive linkage results in a number of chromosomal regions and the identification of several genes that have been associated with SCZ and to a lesser extent with BPD. Confusing aspects include the difference between studies in localization of linkage peaks in the same chromosomal regions, raising the possibility that these regions may harbor more than one gene, the fact that positive linkage findings as well as associated genes appear in several cases to be shared by more than one disorder, and the failure to identify thus far the precise pathogenic variants in associated genes. Recent findings of linkage and association studies on chromosome 6q illustrate the current status of neuropsychiatric genetics in intriguing microcosm. Positive findings from linkage and association studies are reviewed in order to identify approaches that may help to settle apparent contradictions and allow an interpretation of the results that may prove useful in application to findings from other chromosomal regions. Not only SCZ and BPD but also other psychiatric and neurological phenotypes are considered. Taking a topographic approach, we identify five foci of positive findings on chromosome 6q and suggest that each may harbor gene(s) that confer susceptibility to SCZ or BPD or may modify their onset or clinical course. We further suggest that in searching for these genes the possibility that they may be implicated in more than one disorder should be taken into account. We also discuss the potential contribution of rare genetic variants identified in homogeneous, isolated populations to the subsequent identification of common variants in the same gene that contribute to disease susceptibility in outbred populations.

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The last three decades have seen considerable advances in the field of psychiatric genetics. First, family twin and adoption studies conclusively established that genes play a major role in the etiology of many psychiatric disorders. Then, an increasing number of groups embarked on linkage studies aiming at localizing these genes. With ever improving technology, whole genome scans became the standard vehicle for these endeavors. Studies became more and more sophisticated, involving larger samples of carefully characterized affected individuals, using denser maps of markers and employing increasingly powerful statistical tools. Over the years, linkage studies have repeatedly implicated several chromosomal regions as linked to major psychiatric disorders, particularly schizophrenia (SCZ) and bipolar disorder (BPD) (for reviews, see Riley and McGuffin,¹ Berrettini,²

Kohn and Lerer³ and Mathews and Reus⁴). Recent meta-analyses of linkage studies have established the significance of these findings as well as pointing to other linked regions unrecognized by individual studies.^{5–7} Subsequently, genes within these regions were studied and single-nucleotide polymorphisms (SNPs) within their sequence were found to be associated with SCZ and BPD.^{8–17}

Notwithstanding the excitement that these findings have aroused, significant confusion has also ensued. In most cases, linkage findings from different studies have not delineated the identical chromosomal region with peaks often separated by a substantial genetic distance, in some cases covering almost the entire chromosomal arm. For example, linkage to SCZ on chromosome 6p was demonstrated by many groups in a region spanning 25 Mb (6p24–6p21) before association with the dysbindin-encoding gene *DTNBP1* at 6p22 was identified.⁸ The same was true for chromosomal regions 8p and 13q before association with *NRG1* and *G72/DAAO*, respectively, was established (for a review of the linkage findings in these regions, see Brzustowicz *et al*¹⁸). Also, most of the SNPs found to be associated with SCZ or BPD have no clear

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functional significance in terms of affecting the structure or expression of the encoded proteins. Even though several associations were replicated by some (but not all) other groups, the newly associated SNPs were in some cases different from the those originally reported, or if they were the same, the other allele was found to be associated (for a review of the case of the dysbindin gene, see Kendler¹⁹). This conflicting pattern of findings raises the question whether the observed associations are true or are a spurious product of the many statistical tests involved in these studies. Another option is that these associations are a consequence of linkage disequilibrium with the true causative variant, which has not been identified yet. This is supported by findings of SNP associations within more than one gene in the same linked chromosomal region; for example, the dysbindin gene and *NOTCH4* on 6p^{8,16} and *COMT*, *ZDHC8*, *XBP1* and *PRODH2* on 22q.^{10,15,20,21} This pattern of findings might be a consequence of poor localization of linkage and association studies. Alternatively, it is possible that this reflects the presence of multiple predisposing genes within a cluster in the same region. More questions arise from findings of linkage in the same chromosomal regions in both SCZ and BPD (for a review, see Berrettini²²), and associations of SNPs within the same genes in both disorders.^{12,23} While these findings have stimulated discussion about the shared etiology of these disorders, their nonspecific nature poses a question regarding their validity.

Linkage and association findings on the long arm of chromosome 6 exemplify in microcosm the state of excitement and confusion that our field is experiencing. In this review, we aim to highlight these issues by critically summarizing major findings on 6q in SCZ, BPD and other neuropsychiatric disorders. We will make an effort to settle apparent contradictions and propose an interpretation of the results that may prove useful in the search for susceptibility genes on 6q and in application to findings from other chromosomal regions.

We conducted a systematic review of all published literature that appears on PubMed using the search words chromosome 6q, schizophrenia, bipolar and neuropsychiatric genetics, while screening for all genetic studies that reported positive findings on the long arm of chromosome 6 for any psychiatric disorder as well as for related neurological disorders. We did not limit the review to significant findings but included studies achieving suggestive and also lower levels of statistical significance, even if these were not the main findings of the study. On the other hand, we excluded studies that did not find any evidence for the involvement of chromosome 6q genes in neuropsychiatric disorders. In this manner of selecting studies to be reviewed, we were aiming to achieve a comprehensive survey without limiting ourselves to a specific diagnosis or to the significance of results. We also prevented studies with negative results (that might be relevant to a particular studied cohort but not for another) from undermining the potential

significance of this region demonstrated by other studies. For the same reason we did not conduct a meta-analysis of the reviewed studies (given also the very well-conducted meta-analyses that were recently reported⁵⁻⁷). Instead, we chose to use other criteria when integrating results from different studies, such as level of significance, the certainty of localization, support from other less significant studies and the convergence of studies of related phenotypes. This approach has clear limitations in that it allows inclusion of results that might be spurious and might bias our conclusions in that the weighting of studies is impressionistic and not corrected by statistical means. On the other hand, given the existence of comprehensive meta-analyses, the approach we have taken provides a different perspective and allows the identification of possible patterns that could not emerge with the application of rigorous statistical criteria. In particular, our review allows a better resolution and differentiation between the results of separate studies, which is not possible when summing up their results into one composite statistic. Thus, the identification of several loci of interest within the same region can be more evident from the results of our analysis, even if less supported by statistics. This approach permits the development of hypotheses that might otherwise not be evident, and these could be tested in future studies.

Positive linkage findings on 6q in SCZ (Table 1, Figure 1)

The first report of linkage findings on 6q in SCZ came from the National Institute of Mental Health (NIMH) in 1997.²⁴ A total of 81 affected sib pairs (ASP) diagnosed with either SCZ or schizoaffective disorder (SA) were studied for allele sharing of microsatellite markers across the genome. Excess sharing was found for many markers spanning a wide portion of chromosome 6q. The highest score (69% sharing, $P=0.00024$) was for D6S416 at 113 Mb. (As linkage maps are different from each other and continuously changing, we converted the reported location of markers to positions on the most updated physical map (UCSC Genome Browser, May 2004 freeze). When conversion was not possible, we left the specification of location in cM as reported.) In the same publication,²⁴ this group reported a study of 109 ASP diagnosed with SCZ or SA depressed type from a second cohort. A total of 13 microsatellite markers on 6q were studied in an attempt to replicate the findings from the genome scan sample. Positive results were obtained for most of the studied markers although the peak was more proximal compared to the genome scan findings: 64% sharing ($P=0.0004$) at D6S424 (96 Mb). The apparent gap of 17 Mb between the peak results in the two samples was explained as typical for the poor localization of linkage studies.

In 1999, a follow-up of these findings was reported.²⁵ In all, 66 ASP with a somewhat wider variety of SCZ and related disorders were identified

Table 1 6q linkage findings in schizophrenia

<i>Study</i>	<i>Diagnosis</i>	<i>Ethnicity</i>	<i>Sample</i>	<i>Markers</i>	<i>Best results (at 6q)</i>	<i>Comments</i>
Cao <i>et al</i> ²⁴	SCZ, SA (both types) (DSM-IIIIR)	Mixed US	81 ASP (<i>n</i> max)	41 MS (Chr 6) as part of a genome scan	AS $P=0.00024$, D6S416 (113 Mb) MLS(mp) = 3.06, $P=0.00018$, D6S278–D6S423/D6S454 (108–115 Mb)	Reduced significance after correction for weighting and multiple testing Large interval of positive results (104–162 Mb)
Cao <i>et al</i> ²⁴	SCZ, SA depressed type (DSM-IIIIR)	Mixed US	109 ASP (<i>n</i> max)	13 MS on 6q (72–125 Mb)	AS $P=0.0004$, D6S424 (96 Mb) MLS(mp) = 2.35, $P=0.00095$, D6S424 (96 Mb)	Reduced significance after correction for weighting Large interval of positive results (93–120 Mb)
Martinez <i>et al</i> ²⁵	SCZ, SA, delusional dis., atypical nonaffective psychosis (DSM-IIIIR)	Mixed US/Australia	66 ASP (<i>n</i> max)	12 MS on 6q (72–133 Mb)	AS $P=0.022$, D6S424 (96 Mb) NPL(mp) = 1.07, $P=0.013$, D6S424 (96 Mb) NPL(mp) = 3.82, $P=0.000014$ in combined replication at D6S424–D6S301 (96–104 Mb)	Large interval of positive results (96–104 Mb)
Kaufmann <i>et al</i> ²⁶	SCZ, SA depressed type (DSM-IIIIR)	African American	42 ASP (independent)	459 MS for a genome scan	NPL-Z(mp) = 1.89, $P=0.032$, D6S1009 (137 Mb) NPL-Z(mp) = 1.56, $P=0.062$, D6S1056 (94 Mb)	Large interval of positive results (83–142 Mb) with two peaks
Levinson <i>et al</i> ²⁷	SCZ, SA (both types) (DSM-IIIIR)	Mixed (eight samples combined including all of the above)	1003 ASP (<i>n</i> max) 1937 affected 734 pedigrees	8 MS for 6q (83–132 Mb)	MLS(mp) = 3.10 empirical, $P=0.0036$ distal to D6S424 (96 Mb) NPL-Z(mp) = 2.47, $P=0.0046$, (empirical $P<0.0002$ allowing for heterogeneity), HLOD = 2.47, AR, all within 3 cM of D6S424	Results come mainly from samples previously reported as linked ^{24–26}
Bailer <i>et al</i> ²⁸	SCZ, SA, schizotypal PD, schizophreniform dis. (DSM-IIIIR)	Austrian	16 affected 5 pedigrees	388 MS for a genome scan	NPL-Z(mp) = 2.24 ($P=0.02$), D6S1570 (91 Mb) NPL-Z(mp) = 2.20 ($P=0.02$), D6S290 (153 Mb)	
Lindholm <i>et al</i> ³⁰	SCZ, SA –(both types), Psychotic Dis NOS (DSM-IV)	Swedish	43 affected 1 pedigree	371 MS for a genome scan	MLS(tp) = 6.6 D6S253 (162 Mb) for SCZ and SA depressed type MLS(3p) = 7.7 D6S253–D6S297 (162–167 Mb)	Shared haplotype found in affected

Table 1 Continued.

Study	Diagnosis	Ethnicity	Sample	Markers	Best results (at 6q)	Comments
Williams <i>et al</i> ²⁹	SCZ, SA, nonorganic psychosis, schizotypal PD (DSM-IV)	Caucasians (UK, Sweden, US)	353 ASPs (179 from UK) (<i>n</i> max)	372 MS for a genome scan	MLS(mp) = 1.46 for the UK subsample at 6q15 (88 cM), broad model	Other more significant results in the same study
Lerer <i>et al</i> ³¹ Levi <i>et al</i> ³²	SCZ, SA –(both types), others (mainly nonaffective) psychotic dis.) (RDC, DSM-IV)	Israeli Arab	75 Affected 21 pedigrees	347 MS for a genome scan 42 MS for fine (uneven) mapping of 6q (99–190 cM)	<p><i>Genome scan:</i> NPL(mp) = 4.6, <i>P</i> = 0.000004 D6S292 (136 Mb), broad model LOD(mp) = 4.16 D6S292 (136 Mb), AD, core model</p> <p><i>Fine mapping:</i> NPL(mp) = 4.98, <i>P</i> = 0.00000058 D6S1626 (136 Mb), broad model LOD(mp) = 4.63 D6S292–D6S1626 (136 Mb), AD, core model</p>	

SCZ = schizophrenia; SA = schizoaffective disorder; DSM = Diagnostic and Statistical Manual; PD = personality disorder; RDC = Research Diagnostic Criteria; ASP = affected sibpairs, *n* max (for ASP) = maximal number of possible pairs [$n(n-1)/2$]; MS = microsatellite markers; AS = affected sharing; MLS = maximum likelihood score; mp = multipoint; NPL = nonparametric LOD; Z = Z score; tp = two point; 3p = three point; AD = autosomal dominant.

in a newly recruited sample of pedigrees from the US and Australia. A total of 12 microsatellite markers on 6q were studied and compared to the two samples previously reported.²⁴ Evidence for linkage in the new replication sample was exactly at the same location as for the first replication sample (D6S424 at 96 Mb), even if rather weak; 62% sharing (*P* = 0.022). The multipoint NPL increased to 3.82 (*P* = 0.000014) when the two replication samples were combined, although the linked interval remained quite wide between D6S424 and D6S301 (96–104 Mb).

A year earlier Kaufmann *et al*²⁶ reported whole genome scan results in a sample of 42 African-American ASP diagnosed with SCZ or SA depressed type. There were two peaks within the broad signal of weak positive results on 6q; one at D6S1056 (94 Mb), very close to the proximal peak reported by Cao *et al*²⁴ and Martinez *et al*,²⁵ and the other more distally at D6S1009 (137 Mb).

In 2000, a collaborative effort resulted in combining eight SCZ samples from different groups around the world in order to study linkage in several candidate regions.²⁷ These samples included all those mentioned above. The best multipoint MLS was 3.10 (empirical *P* = 0.0036), slightly distal to D6S424 (96 Mb). Contribution to these results came from five out of the eight subsamples, and mainly from the three that were previously reported (Cao *et al*,²⁴ Martinez *et al*²⁵ and Kaufmann *et al*²⁶). Still, the results were significant after the exclusion from analysis of the first sample that showed linkage to 6q (the genome scan sample from Cao *et al*²⁴). Between the two subsamples that showed new evidence of linkage to 6q, one supported the more proximal peak at 96 Mb, while the other peaked more distally and close to the peak of the genome scan sample from Cao *et al*²⁴ at 113 Mb.

Bailer *et al*²⁸ studied 16 individuals affected with SCZ-related disorders from five Austrian pedigrees. A genome scan was conducted, and several weak positive NPL scores were obtained. Among them were two on chromosome 6q: a multipoint NPL Z score of 2.24 (*P* = 0.02) for D6S1570 at 91 Mb, and a multipoint NPL Z score of 2.2 (*P* = 0.02) for D6S290 at 153 Mb. The locus at 6q15 (which includes the markers at 91 Mb) is also weakly supported by a study of 179 ASPs from the UK²⁹ diagnosed with SCZ spectrum disorders. Although significant and suggestive results were found in other regions in this study, a multipoint nonparametric LOD score of 1.46 at 6q15 (88 cM) under the broad diagnostic model was shown.

In 2001, Lindholm *et al*³⁰ reported a genome scan in a very large extended pedigree from northern Sweden. A total of 43 pedigree members with a diagnosis of SCZ, SA (both subtypes) and psychotic disorder NOS were analyzed in an affected only design. The best result, a parametric LOD = 3.45 under a broad definition of the phenotype, was obtained for D6S264 (167 Mb). Fine mapping of another six microsatellite markers around this marker increased the LOD score to 6.6 at D6S253 (162 Mb) under a diagnostic model

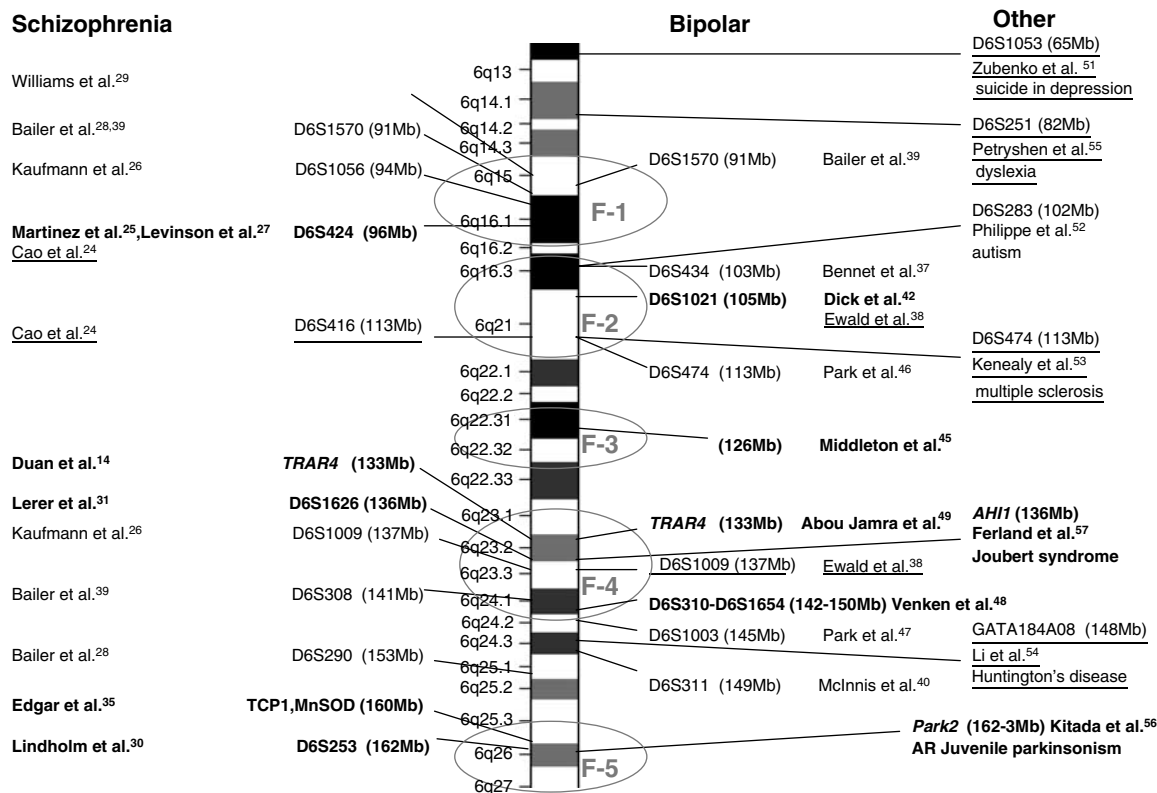


Figure 1 Schematic representation of positive linkage and association findings at 6q. Findings are arranged on an ideogram of this chromosomal arm from centromeric (up) to telomeric (down). Findings in SCZ are shown on the left side of the chromosome. On the right side are findings in bipolar disorder, and further to the right findings in other neuropsychiatric disorders (name of the disorder given near each finding). Findings are represented by the study citation, marker/gene (if available), location in Mb and an arrow pointing to the corresponding chromosomal region (last two are based on data from UCSC Genome Browser, May 2004 freeze). In bold: significant findings; underlined: suggestive findings; no marking: weak positive (as defined in Lander and Kruglyak⁵⁹).

including SCZ and SA depressed type. The multipoint MLS was 7.7 between D6S253 and D6S297 (162–167 Mb). Sharing of reconstructed ancestral haplotypes in this region was demonstrated for affected pedigree members.

Recently, our group reported a genome-wide linkage analysis in 21 pedigrees from a homogeneous inbred Arab population in Israel.³¹ In all, 75 pedigree members with either SCZ, SA (both types) or other psychotic disorders (mainly nonaffective) were studied. The best results across the genome were for chromosome 6q where the peak was a multipoint NPL of 4.6 ($P=0.000004$) at D6S292 (136 Mb) under a broad diagnostic model. The best parametric multipoint LOD was 4.16 at the same location under the core diagnostic model (SCZ, SA (both types) and unspecified functional psychosis). Subsequent fine mapping in the same sample³² increased the significance of the results to a multipoint NPL of 4.98 ($P=0.00000058$) at D6S1626 (136 Mb) under the broad model and a multipoint parametric LOD of 4.63 in the same location under the core model. Fine mapping also decreased the NPL-1 interval from 12 to 5 Mb, and the LOD-1 to 2 Mb around this peak.

The first gene to be associated with SCZ on 6q was the trace amine receptor gene 4 (*TRAR4*). Duan *et al*¹⁴ studied 31 SNPs to screen the region of 6q23.2 (average density 1 SNP/20 kb) in the samples that previously produced significant LOD scores on 6q.^{24,25} Interestingly, they chose to cover a region enriched with potential candidate genes, the *MOXD1-STX7-TRARs* at 133 Mb, even though it lies about 37 Mb from their most significant finding at 96 Mb. They found significant association with one SNP, rs4305745 within the *TRAR4* gene that remained significant after correction for multiple testing. Genotyping of other SNPs in its vicinity demonstrated association with two other SNPs, in perfect LD with rs4305745. Although these SNPs have no known functional significance, Duan *et al*¹⁴ suggested that they might affect expression of this gene. *TRAR4* is a good candidate gene for SCZ as it encodes a receptor that binds trace amines, endogenous compounds with a chemical structure similar to dopamine, serotonin and other classical biogenic amines. Association with *TRAR4* was not found in a very recently reported study of a large cohort of SCZ patients from Japan.³³ Our group was also not able to find association of the

same *TRAR4* SNPs with SCZ in the sample that yielded a very significant LOD score at this location (Amann *et al.*).³⁴

A pioneer work in proteomics has also pointed to the role of genes on chromosome 6q in SCZ. Edgar *et al.*³⁵ performed a comparative proteome analysis of the hippocampus in post-mortem brains from schizophrenics vs controls. Four out of 18 proteins with an altered concentration in schizophrenic brains were characterized. Two out of them (corrected from three in the original publication following a comment by Sanders and Gejman³⁶) were encoded by genes on 6q25—T-complex protein 1 (TCP1) and manganese superoxide dismutase (MnSOD), both at 160 Mb. The probability of two genes that encode two proteins with altered concentration in this analysis to reside on the same chromosomal segment was calculated to be highly unlikely by chance. This is extremely interesting in relation to the possibility that more than one gene on 6q is associated with SCZ. However, the genes that were identified by this analysis are extremely close to each other and may be under the regulation of the same genetic variant that is associated with SCZ.

Positive linkage findings on 6q in bipolar disorder (Table 2, Figure 1)

In 2002, Bennett *et al.*³⁷ reported the results of the first stage of the Wellcome Trust UK–Irish bipolar affective disorder sibling-pair genome scan. In 154 ASP with narrowly defined BPD, a multipoint MLS of 0.78 (nominal *P*-value of *P*<0.05) was demonstrated on 6q near D6S434 (103 Mb). In the same year, Ewald *et al.*³⁸ reported a parametric LOD score of 2.59 at D6S1021 (105 Mb) and a multipoint parametric LOD of 2.52 at D6S1009 (137 Mb) in the context of a genome scan study of two BPD Danish pedigrees. Also in 2002, Bailer *et al.*³⁹ reported a genome scan linkage analysis for psychosis in eight Austrian pedigrees. In three out of these pedigrees, patients had diagnoses of BPD spectrum disorders. These were combined with five pedigrees, in which patients had diagnoses of SCZ spectrum disorders that were reported previously.²⁸ Weak evidence for linkage was demonstrated at D6S1570 (91 Mb) and D6S308 (141 Mb). The signal at D6S1570 (91 Mb) seemed to come from both subsets of pedigrees, while the more distal peak D6S308 (141 Mb) was attributed to the SCZ pedigrees.

In 2003, two reports from the NIMH Genetic Initiative for bipolar disorder appeared. McInnis *et al.*⁴⁰ reported the results of a genome scan in 641 individuals affected with BPD, SA-bipolar type or recurrent major depression. The maximum multipoint NPL on 6q was 2.5 (*P*=0.008) at D6S311 (149 Mb) for a broad model. This peak narrowed down a region of interest on 6q that was previously reported in this sample.⁴¹ At about the same time, Dick *et al.*⁴² reported a genome scan in a separate sample of 250 newly recruited pedigrees. Initially, a peak multipoint nonparametric LOD score of 3.61

(empirical *P*<0.05) near D6S1021 (105 Mb) was found. Subsequently the results were corrected to 2.2 in an erratum of this paper. Nevertheless, in this erratum, the authors stated that combining the two samples from the NIMH Genetics Initiative yielded an LOD score of 3.8 in this location. In a subsequent analysis of these data,⁴³ a possible maternal parent-of-origin effect and an interaction with a locus on 6p22 were demonstrated for this locus on 6q.

In a study of pedigrees from the Portuguese islands and mainland,^{44,45} 25 pedigrees were genotyped with both a dense map of microsatellite markers and SNPs. The best multipoint NPL (4.2, empirical *P*<0.05) and LOD (3.56) were on 6q at 126 Mb.

Park *et al.*⁴⁶ studied psychotic BPD or recurrent major depressive disorder with psychotic symptoms in 36 pedigrees. A parametric two-point LOD of 1.81 was obtained at D6S474 (113 Mb) under the narrow model of affection. In a subsequent study of non-psychotic patients with the same diagnoses, these authors have found weak evidence for linkage to a more distal locus of 6q, at D6S1003 (145 Mb).⁴⁷

Very recently, Venken *et al.*⁴⁸ found significant (according to their simulations) linkage to BPD at 6q24–25 in a genome scan of pedigrees from a genetically isolated population in Northern Sweden. The peak multipoint LOD score was 3.25, and the LOD-1 interval was between D6S301 and D6S1654 (142–150 Mb).

Another very recent study has shown association between rs8192624, a coding SNP in the sequence of the *TRAR4* gene at 6q23, and BPD.⁴⁹ This group followed their previous finding of some evidence for linkage in BPD at this locus.⁵⁰ This study replicates in BPD the association found by Duan *et al.* in SCZ.¹⁴ Still, the interpretation of these results is limited by the fact that in each study a different SNP was associated. Also, this coding SNP causes a conservative amino-acid change, which is not expected to have functional significance.

Findings in other neuropsychiatric disorders

Zubenko *et al.*⁵¹ have found evidence for linkage of suicide risk in depression with D6S1053 (65 Mb) at 6q12. Weak evidence for linkage on 6q in autism was found in a multicenter study of 51 multiplex families.⁵² The maximum multipoint MLS was 2.23 (*P*=0.0013) at D6S283 (102 Mb), 3 Mb proximal to the significant linkage with BPD that was found by Dick *et al.*⁴² Suggestive evidence for linkage on 6q with multiple sclerosis was found in a subset of pedigrees at D6S474 (113 Mb).⁵³ This is the marker that gave weak positive results in a linkage study of psychosis in BPD.⁴⁶ Li *et al.*⁵⁴ found suggestive evidence for a modifier gene for age of onset in Huntington's disease at 6q24 with an LOD score of 2.28 at 148 Mb. Suggestive linkage for phonological coding dyslexia was found for several markers at 6q,⁵⁵ spanning the interval between D6S965 and D6S251 (70–82 Mb).

Table 2 6q linkage findings in bipolar disorder

<i>Study</i>	<i>Diagnosis</i>	<i>Ethnicity</i>	<i>Sample</i>	<i>Markers</i>	<i>Best results (at 6q)</i>	<i>Comments</i>
Bennett <i>et al</i> ³⁷	BPD (I,II), SA-bipolar type, rec MDD (DSM-IV)	UK, Ireland (Caucasian)	258 ASP broad 154 ASP narrow (<i>n</i> max)	398 MS for a genome scan	MLS(mp) = 0.78 (<0.05) near D6S434 (103 Mb), narrow model	First stage of a genome scan
Ewald <i>et al</i> ³⁸	BPD, SA-bipolar type, recurrent depression (DSM-IV, ICD-10)	Danish (Caucasian)	23 affected 2 pedigrees	613 MS for a genome scan and fine mapping	LOD(tp) = 2.59, D6S1021 (105 Mb) LOD(3p) = 2.52, D6S1009 (137 Mb)	Many positive LOD scores
Bailer <i>et al</i> ³⁹	SCZ, Schizophreniform dis., SA-bipolar type, BPD, rec MDD (DSM-III-R)	Austrian	27 affected 8 pedigrees	388 MS for a genome scan	NPL(mp) = 2.74 (<i>P</i> = 0.0063), D6S1570 (91 Mb) NPL(mp) = 1.95 (<i>P</i> = 0.0321) D6S308 (141 Mb)	D6S1570 (91 Mb) from both D6S308 (141 Mb) from SCZ
Dick <i>et al</i> ⁴²	BPD, SA-bipolar type, unipolar depression recurrent (DSM-III-R, RDC)	US (mostly Caucasian)	737 affected (609 pairs)	391 MS for a genome scan	NPL(mp) = 3.61 empirical, <i>P</i> < 0.05 near D6S1021 (105 Mb), broad model	Corrected in erratum to NPL = 2.2 Combined NIMH NPL = 3.8 at the same location
McInnis <i>et al</i> ⁴⁰	BPD, SA-bipolar type, unipolar depression recurrent (DSM-III-R, RDC)	US (mostly Caucasian)	641 affected (909 pairs, <i>n</i> max)	513 (298 in all) MS for a genome scan	NPL(mp) = 2.5, <i>P</i> = 0.008, D6S311, broad model (149 Mb)	
Schultze <i>et al</i> ⁴³	BPD, SA-bipolar type, unipolar depression recurrent. (DSM-IV, RDC)	US (mostly Caucasian)	740 affected	18 MS on chromosome 6	NPL(mp) 2.26, D6S1021–D6S474 (105–113 Mb) LOD(mp) = 3.05, D6S1021 (105 Mb)	Data overlap with Dick <i>et al</i> ⁴⁰ Evidence for interaction with a 6p22 locus and for maternal parent of origin effect
Pato <i>et al</i> ⁴⁴ Middleton <i>et al</i> ⁴⁵	BPD, SCZ-bipolar type (DSM-IV)	Portugal	75 in affected 25 pedigrees	> 10 000 SNPs for a genome scan	NPL(mp) = 4.2 (<i>P</i> < 0.05 empirical) at 126 Mb LOD(mp) = 3.56 at 126 Mb	
Park <i>et al</i> ⁴⁶	BPD, rec MDD (all psychotic) (RDC)	US/Israel (Caucasian)	79 affected 36 pedigrees	343 MS for a genome scan	LOD(tp) = 1.81, D6S474 (113 Mb), AR, narrow model	Many positive scores in other regions

Table 2 Continued.

Study	Diagnosis	Ethnicity	Sample	Markers	Best results (at 6q)	Comments
Park <i>et al</i> ⁴⁷	BPD, rec. MDD (all nonpsychotic) (RDC)	US/Israel (Caucasian)	228 affected 40 pedigrees	343 MS for a genome scan	LOD(tp) = 1.78, 5 cM from D6S1003 (145 Mb), AD, narrow model LOD(mp) = 1.79 at D6S1003 (145 Mb), AD, narrow model	
Venken <i>et al</i> (2005) ⁴⁸	BPD, SA-bipolar type, unipolar depression recurrent.	Northern Sweden	46 affected 9 pedigrees	380 MS for a genome scan 19 MS for fine mapping of 6q	LOD(mp) = 3.25, LOD-1 between DS301-D6S1654 (142–150 Mb), AR, broad model	One of three candidate regions identified in this study

BPD = bipolar disorder; SA = schizoaffective disorder; rec MDD = recurrent major depressive disorder; DSM = Diagnostic and Statistical Manual; ICD = International Classification of Diseases; SCZ = schizophrenia; RDC = Research Diagnostic Criteria; ASP = affected sibpairs; *n* max (for ASP) = maximal number of possible pairs [$n(n-1)/2$]; MS = microsatellite markers; SNP = single-nucleotide polymorphism; MLS = maximum likelihood score; mp = multipoint; tp = two point; 3p = three point; NPL = nonparametric LOD; AR = autosomal recessive; AD = autosomal dominant.

Mutated genes that cause rare forms of neuropsychiatric disorders were identified at two loci on 6q exactly where significant linkage with SCZ was demonstrated. *PARK2*, a gene that causes autosomal recessive juvenile parkinsonism, was identified at 162–163 Mb on 6q⁵⁶ where linkage to SCZ was found in a large Swedish pedigree.³⁰ Mutations in the gene *AHI1* at 6q23 (136 Mb) were found to be causative in Joubert syndrome, a severe autosomal recessive neurological disorder characterized by motor abnormalities, cognitive difficulties and autistic symptoms.^{57,58}

Discussion

As reviewed, many studies have shown linkage on the long arm of chromosome 6 in SCZ, BPD and other neuropsychiatric disorders (Tables 1 and 2, Figure 1). Meta-analyses that included many (but not all) of these studies have shown support for linkage in specific locations on 6q. Badner and Gershon⁵ found nominally significant evidence ($P < 0.05$) of the single analysis multiple scan probability (MSP) for BPD at 6q23(138 cM) and for SCZ at 6q25(179 cM). These results did not reach the well-accepted criteria of Lander and Kruglyak⁵⁹ of $P = 2.2 \times 10^{-5}$ and $P = 7 \times 10^{-4}$ for significant and suggestive allele sharing (respectively) in the context of a genome scan, and were also not the best ones achieved across the genome. Another type of analysis presented in this work, the best analysis MSP, showed higher significance level for the finding in SCZ at 179 cM ($P = 0.0001$), but this significance disappeared altogether when the analysis was carried out again without the study that contributed the most significant result (replication MSP). Nevertheless, these findings merit some discussion. The finding in 6q25 for SCZ is probably a product of the very significant score that was obtained in the study of one pedigree from Sweden.³⁰ The 6q23 finding in BPD cannot be attributed to a specific study as none reported significant findings in this exact location. It is noteworthy, however, that significant evidence for linkage in this location was found in Arab pedigrees from Israel^{31,32} under a broad diagnostic model that included some patients with affective symptoms (mainly SA disorder, both types).

The meta-analysis by Lewis *et al*⁶ used a different methodology—the rank-based Genome Scan Meta-Analysis. 6q15–23(99–131 cM) was identified as meeting one of the criteria for significance ($P_{ord} < 0.05$) but not the other ($P_{AvgRank} < 0.05$). The low level of significance and the large interval implicated do not help in interpreting the numerous reports of linkage in this region. The application of this method to linkage studies in BPD⁷ did not yield any significant results for this region or others. In this regard, it is important to note that several studies reviewed here were published after these three meta-analyses were conducted, and thus the significance of 6q as a region of linkage in SCZ and BPD might have been

minimized. Indeed, a more recent meta-analysis of linkage studies in BPD (McQueen *et al.*, 2005),⁶⁰ which included some of these later studies, found genome-wide significant linkage on 6q (115 cM).

Using more 'impressionistic' tools to evaluate the linkage findings on 6q, one might look for convergence of significant findings in narrow regions that are supported by weaker positive ones and findings from other disorders. In doing so, it can be argued that five foci of findings may be identified, three with findings for SCZ being predominant, and two with an emphasis on BPD. These are delineated in Figure 1.

The first focus (from proximal to distal) of interest on chromosome 6q (F-1) is centered at 96 Mb with significant results for SCZ-related disorders demonstrated by two studies,^{25,27} and supported from findings in SCZ,^{24,26,28,30} and for both SCZ and BPD.³⁹

The second focus of findings (F-2) is at 105 Mb, mainly in BPD, with one significant study⁴² and several supporting studies,^{37,38,46} but also studies on SCZ,²⁴ autism⁵² and multiple sclerosis.⁵³

The third focus (F-3) is for BPD and is located at 126 Mb with a very significant finding from one study of Portuguese pedigrees.⁴⁵

The fourth focus (F-4) is centered at 136 Mb, with significant findings in SCZ-related disorders coming from one linkage study^{31,32} and one association study,¹⁴ and weak support from other studies in SCZ.^{26,39} Support for this focus also comes from linkage and association studies in BPD^{38,48,49} and from a meta-analysis of linkage studies in BPD⁵ as well as from the presence of *AHI1*, a gene causing a severe neuropsychiatric disorder (Joubert Syndrome) in this location. Weaker positive results in linkage studies of SCZ and BPD were also demonstrated distal to this focus^{28,40,47} and may represent poorer localization of the same locus. Suggestive evidence for linkage distal to F-4 was also demonstrated for a modifier gene in Huntington's disease.⁵⁴

The fifth focus (F-5) is at 162 Mb with the strongest evidence for linkage on 6q²⁹ in an SCZ pedigree. Although there are no other supporting linkage studies, altered levels have been shown in the hippocampus of schizophrenics for two proteins encoded by genes in this location (TCP1 and MnSOD). This is also the location of a gene for AR juvenile Parkinson's disease.

Is it possible that each one of the five foci of findings harbors a different gene for neuropsychiatric disorders? Hundreds of known genes lie on chromosome 6,⁶¹ and many of them are expressed in the brain. As many genes are thought to predispose to different neuropsychiatric disorders, it is possible that some of them will be found on the same chromosomal arm. In searching for candidate genes in the linked region in our sample, we identified at least 13 known candidate genes within the 5 Mb NPL-1 interval.³² The idea that each focus is the location of a separate gene is also supported by the fact that in three foci very significant and narrow peaks are found in well-defined homogenous populations^{30,31,45} and

may be the result of linkage to a gene specifically implicated in these populations. It is also possible that one or more of the five foci will be found to harbor several susceptibility genes for neuropsychiatric disorders. The phenomenon of functionally related genes located in the same chromosomal region and being under the same genetic control is well recognized (eg HLA genes or the beta-globin cluster). On the other hand, it is possible that at least some of the reports of positive findings represent spurious results or true results with poor localization. The answer for these questions will probably come with identification of variants within genes associated with disease. These associations will have to be replicated in different samples, and/or be of a clear functional significance. One assumes that the different groups who reported on linkage at 6q are currently pursuing this task. Before this task is achieved, we could address the question of whether this clustering is higher than expected by comparing it with the situation for potential SCZ and BPD loci on other chromosomal regions of similar size. We eagerly await the application of our review design in this manner by groups who focus on these regions.

Closely localized findings in different neuropsychiatric disorders are observed in 6q as in other chromosomal regions. This is especially the case for SCZ and BPD. Based on the influential work of Emil Kraepelin (reviewed in Angst and Marneros⁶²), these disorders are traditionally thought to be two distinct entities. Nevertheless, similarities in psychotic symptoms and response to the same medications led researchers over the years to question this dichotomous concept.⁶³ The existence of schizoaffective disorder as an 'in between' diagnostic category reflects the currently held consensus view that SCZ and BPD share at least some psychotic features. The identification of linkage for both disorders within the same chromosomal regions²² and association with the same candidate genes^{12,23} has renewed interest in possible shared etiological factors. On the other hand, there is currently an effort to narrow down the phenotype definition in linkage studies to more narrow diagnoses and to more homogenous endophenotypes to increase the power.⁶⁴ These measures could turn out to be counterproductive as they might preclude the identification of genes that predispose to a diverse range of psychiatric disorders. In extended multiplex pedigrees and in small isolated populations, genetic homogeneity might increase the chances of finding a common gene for different disorders. Indeed, very significant linkage results on 6q in two homogenous populations^{30,31} were found under a broad definition of the phenotype. Also, a study of one extended Scottish pedigree led to the identification of *DISC1*, a gene disrupted by a balanced 1:11 translocation that segregates with a variety of psychiatric disorders in this pedigree.^{65,66} An essential added value of isolated populations is apparent in the context of the common disease/common variant (CDCV) vs common disease/rare

variant CDRV debate.⁶⁷ Indeed, studying isolated populations, besides diminishing the underlying clinical, genetic and environmental heterogeneity, also offers the added value of approximating the CDCV situation by impacting allele frequency, which is more favorable to the uncovering of the etiologic factor. Whether the population attributable factor, which can be high in the isolated inbred cohorts, is or is not significant in the general population remains to be demonstrated. Yet, this information constitutes a valid starting point for further genetic and functional analyses.

In discussing the possibility of numerous genes of minor effect etiologically implicated in several neuropsychiatric disorders, one should consider the different roles that these genes may play. Fanous and Kendler⁶⁸ have recently suggested a framework for the study of such genes. They argue that five models of gene action could be predicted. The three main ones, 'S', 'M' and 'MS', represent, respectively, susceptibility genes that predispose to disease without affecting its clinical course, modifier genes that only affect the clinical course without increasing the risk of disease and genes of mixed action. The other two models (M_B and MS_B) are modifications of the M and MS models in which genes have a slightly different expression in unaffected relatives who carry the risk allele. Fanous and Kendler⁶⁸ argue that such a framework could become instrumental in linkage and association studies as it should help to increase power by inclusion and exclusion of family members from the study based on the presumed model of the gene that is being searched for. Application of these methods to the findings in the different foci on 6q could help to better localize the several genes with different etiological roles that presumably lie on this chromosomal arm.

Lessons from the study of other disorders with complex genetics can prove useful in leading us in the right direction to identify genes for psychiatric disorders. For example, Hirschsprung Disease (HSCR or congenital aganglionosis with megacolon) is a severe congenital disorder. It has been appreciated for a long time that for the more common short segment type of HSCR, etiology is multifactorial with a heritability of 80–95%.⁶⁹ Linkage studies in a region defined by chromosomal aberrations identified a locus on chromosome 10q that was subsequently narrowed down, until mutations in the gene *RET* were demonstrated.⁷⁰ Similarly other loci have been found, some in genetically isolated populations, and mutations in seven more genes were identified (for a review, see Stewart and von Allmen⁶⁹). Although nonsynonymous mutations in the coding domain of these genes are rare and explain only 0.1% of the variance in susceptibility, their identification has led to the study of more common variants in other patients. Recently, it has been shown that a common intronic variant in a *RET* enhancer is associated with HSCR susceptibility probably by reducing the enhancer activity.⁷¹ This common variant has low

penetrance and it explains only 1.1–2.6% of the variance in susceptibility. Thus, a combination of studies in outbred and inbred populations, rare Mendelian transmitted forms of the disease and chromosomal aberrations led to the identification of rare mutations in genes that later were found to be associated with more common forms of the disease. A similar phenomenon was demonstrated in osteoporosis, another complex disease, by Liu *et al.*⁷² The clear and more objective diagnosis of the phenotype is probably also related to the success of these studies.

Conclusions

Based on our observations, we suggest that further research, aimed at identifying genes for complex neuropsychiatric disorders on chromosome 6q, should take the following considerations into account:

- (1) Subject to the reservation that some of these findings may be spurious, there are five discernable foci of positive linkage findings on chromosome 6q, each of which may harbor gene(s) that are implicated in the pathogenesis of neuropsychiatric disorders.
- (2) These genes may confer susceptibility to SCZ, BPD and other neuropsychiatric disorders or may modify their onset or clinical course.
- (3) In searching for these genes, the possibility that they may be implicated in more than one psychiatric disorder should be taken into account.
- (4) Rare genetic variants with high penetrance identified in homogeneous, isolated populations may lead to the subsequent identification of common, low penetrance variants in the same gene that contribute to disease susceptibility in outbred populations.
- (5) Since genes associated with severe, neurological phenotypes have been identified in regions linked to common psychiatric disorders, the possibility that other variants in the same genes may be associated with the more common disorders should be considered.

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