Molecular genetics of schizophrenia: a review of the recent literature

Douglas F. Levinson

Purpose of review

The recent literature on the molecular genetics of schizophrenia is reviewed, to familiarize the reader with several important developments as well as a broad range of research efforts in a rapidly progressing field.

Recent findings

New genome scan projects, seen in the light of previous scans, provide support for schizophrenia candidate regions on chromosomes 1q, 2q, 5q, 6p, 6q, 8p, 10p, 13q, 15q and 22q. Linkage disequilibrium mapping studies of several of these regions have produced evidence from relatively large samples supporting the association of schizophrenia to neuregulin-1 (*NRG1*, 8p21–p12), dysbindin (*DTNBP1*, 6p22.3), proline dehydrogenase (*PRODH2*, 22q11.21), *G72* (13q34) with weaker evidence implicating its interacting gene D-amino acid oxidase (*DAAO*, 12q24), and catechol-*O*-methyltransferase (*COMT*, 22q11.21). Other reports have described including the application of microarray techniques to schizophrenia post-mortem tissue, candidate gene studies in diverse regions, efforts to develop quantitative phenotypes (e.g. neuroimaging and neuropsychological variables) and proposed models of schizophrenia pathogenesis.

Summary

Schizophrenia linkage findings are beginning to converge on a number of chromosomal regions. Linkage disequilibrium mapping studies are beginning to produce findings of great interest in some of these regions, and additional findings should be expected. Enlarged linkage and association samples, combined with rapidly evolving technologies, hold out the promise that in the next 5–10 years, the role of some specific schizophrenia susceptibility genes will be confirmed resulting in an initial understanding of the pathogenesis of schizophrenia.

Keywords

schizophrenia, genetics, genetic linkage, genetic association, candidate genes

Curr Opin Psychiatry 16:157–170. © 2003 Lippincott Williams & Wilkins.

Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA 19104-3309, USA

Correspondence to Douglas F. Levinson, MD, Department of Psychiatry, University of Pennsylvania School of Medicine, 3535 Market Street, Room 4006, Philadelphia, PA 19104-3309, USA
Tel: +1 215 746 5151; fax: +1 215 746 5155; e-mail: dfl@mail.med.upenn.edu

Current Opinion in Psychiatry 2003, 16:157–170

Abbreviations

ASP	affected sibling pair
LD	linkage disequilibrium
NIMH	National Institute of Mental Health
NMDA	*N*-methyl-D-aspartate
SNP	single-nucleotide polymorphism
UTR	untranslated region
VCFS	velo-cardio facial syndrome

0951-7367

Introduction

This article will review new literature relevant to the molecular genetics of schizophrenia from approximately the middle of 2001. Remarkable progress has been made in the 15 years since serious investigation began in this field. The past year alone witnessed the publication of eight new genome scans [1••–6••,7•,8••] and a meta-analysis of published genome scans [9••], with evidence that genome scan data are starting to converge on a set of chromosomal regions; five reports of substantial evidence for the association of schizophrenia with specific genes in positional candidate regions [10••–14••], and two reports of the use of microarray technology to screen for genes showing differential expression in the brains of schizophrenia patients [15•,16••], one of which detected a gene for which evidence for genetic association was also observed [17••]. It appears likely that positional cloning, microarray and other technologies will soon produce replicable findings that will begin to elucidate the pathophysiology of this severe common disease.

Progress in finding genes through positional cloning methods

Positional cloning is the primary strategy available for finding susceptibility genes for disorders with no known pathophysiology. The strategy is summarized in Table 1.

Multiply affected families are screened with a DNA marker map of all chromosomes (genome scan). Statistical analyses consider whether ill relatives have inherited the same marker alleles, indicating the proximity of a disease susceptibility gene. For complex disorders (such as schizophrenia) that probably have multiple interacting susceptibility genes, genome scans can only locate genes within 10 000 000–30 000 000 base pair (bp) regions.

In these candidate regions, additional markers are genotyped 1–2 cM apart, which sometimes narrows the candidate region.

DOI: 10.1097/01.yco.0000058617.61505.a5

Table 1. Stages of positional cloning studies

Stage	Clinical sample	Molecular strategy	Outcome
Genome scan	Multiply affected pedigrees	Genotype microsatellite DNA markers at 5 000 000–10 000 000 bp (5–10 cM) spacing, or denser SNP markers	Evidence for linkage in 10–30 cM candidate region(s)
Fine-mapping	Multiply affected pedigrees	Genotype microsatellite markers in candidate regions at 1–2 cM spacing (or denser SNPs)	Evidence for linkage in 2–10 cM candidate region(s)
LD mapping	Cases versus controls or case–parent trios	Genotype markers (primarily SNPs) at 10 000–50 000 bp (10–50 kb) spacing	Evidence for association of small sets of adjacent markers with disease, implicating one or two specific genes
Functional genomics	Animal models (e.g. 'knockout' mice), cases, postmortem tissue	Physiological studies to establish the role of the gene and protein, effects of mutations on physiology and behavior, and response to treatments for the disease	Plausible evidence that the gene plays a role in disease susceptibility; detection of other interacting genes and proteins

LD, Linkage disequilibrium; SNP, single nucleotide polymorphism.

Linkage disequilibrium (LD) mapping is based on a different principle: most of the genome's DNA sequence variations have arisen only once or a few times. Some 'unrelated' ill individuals may have inherited from a single ancient ancestor an identical DNA segment that increases the risk of disease. Each patient's complete DNA sequence cannot yet be sequenced cost-effectively, but one can study many variations (single-nucleotide polymorphisms; SNPs) 10 000–50 000 bp (10–50 kb) apart in the candidate region in 'unrelated' cases to look for 'haplotypes' (adjacent variations on the same chromosome) that are more common in ill individuals. It is believed that some (not all) susceptibility variants underlying common complex disorders can be identified in this way with larger samples, improved SNP maps and evolving molecular methods.

Functional studies can then be initiated to determine the gene's function, interactions and possible relationship to the disease.

Generally, two genome scan strategies have been employed. One is to study small samples of families with as many ill relatives as possible, in the hope that one or a few genes are conferring most of the risk of disease [18••,19••]. The other is to collect many families with at least an affected sibling pair (ASP), assuming that multiple interacting genes each confer a small proportion of risk [20], so that hundreds to thousands of families will be needed [21]. The complexities of this debate are beyond the scope of this paper. Existing data about familial patterns of schizophrenia tend to support the second view [20]. Small samples tend to exaggerate the genetic effects of some loci while missing others entirely [22,23]. However, some of the better-supported linkage findings in schizophrenia were initially detected in small samples [24,25].

New genome scans

Eight new scans and one partial scan were published this past year. Regarding the interpretation of scan results, 'genome-wide significance' usually refers to a result that is expected to occur by chance once in 20 scans, and 'suggestive significance' refers to a result that would occur once per scan on average [26]. However, for complex disorders, statistically significant linkage is not reliably observed at feasible sample sizes, and the pattern of results across studies may prove to be more important. In this discussion, 'narrow' diagnoses refer generally to schizophrenia and schizoaffective disorder, and 'broad' or 'spectrum' diagnoses refer to schizophrenia-related psychoses and personality disorders.

Straub *et al.* [1••] published scan results for 270 Irish pedigrees. They previously reported evidence for linkage on chromosome 6p21–24, which approached genome-wide significance depending on how one corrects for multiple tests [27], and suggestive evidence on 5q21–31 [28], 8p22–21 [29] and 10p15–p11 [30]. Results suggested at least two susceptibility loci on chromosome 6p, both of which have been supported by other studies (see below), but peaks this close together are difficult to prove with current methods. This relatively large sample was drawn from one ethnic population, which might improve the power to detect linkage [31]. But the scan was completed some years ago using three different, sparse (20–30 cM) maps in subsamples of 90 families. A range of diagnostic and genetic models were analysed to explore the data fully, but this also makes the findings more difficult to interpret.

DeLisi *et al.* [2••] published two scans. The largest schizophrenia scan to date was of 294 families (333 independent ASPs). Two suggestive findings were

observed, on chromosomes 10p and 2 (centromeric region), with more modest evidence on 22q. The second scan was of 99 families from the Central Valley region of Costa Rica (62 ASPs by a narrow diagnostic model, 102 by a spectrum model) [3••]. The maximum evidence for linkage (falling short of the suggestive level, as has been the case for a number of scans) was observed in chromosome 5q34.

Paunio *et al.* [4••] analysed scan data for two subsamples; 163 Finnish general population families (191 ASPs), and 47 nuclear families (60 ASPs) from an isolated and inbred region. This group had previously reported suggestive evidence for linkage in two different regions of distal chromosome 1q, one in the national and the other in the isolate sample [32]. The scan produced significant findings on distal 2q (isolate sample) and on 5q31 (national sample).

Gurling *et al.* [5••] studied 13 British and Icelandic pedigrees. Suggestive linkage was observed on chromosomes 1q32.2, 5q33.2, 8p21–22, 11q23.2–q24 and 20q12.1–11.23.

Camp *et al.* [6••] studied seven extended pedigrees from the isolated island nation of Palau. Significant linkage was observed on chromosomes 2p13–14 (as reported previously [33]) and 13q12–22, and suggestive linkage on 5q22-qter.

Garver *et al.* [7•] studied 30 US pedigrees. No suggestive results were observed. The most positive scores were on chromosomes 1p, 5p, 20q and 8p.

Lindholm *et al.* [8••] studied a set of pedigrees from northern Sweden (39 narrow and four broad cases) that were inter-related going back 12 generations. Significant linkage was observed on chromosome 6q25. A six-marker haplotype segregated was observed in most ill relatives. Additional peaks included chromosomes 3p25, 20p11.2, 6p24 and 8p21–22.

Maziade *et al.* [34••] reported a partial scan (denser in candidate regions) in 19 Quebecoise pedigrees with schizophrenia or bipolar disorder. Suggestive linkage to schizophrenia was observed on chromosomes 6p22–24 and 18q.

Although most scans to not replicate each other, there is in fact substantial convergence in the results across all studies. Previous linkage findings have been reviewed recently by Waterwort *et al.* [18••] and Baron [19••], and will not be thoroughly reviewed here, but there is support from several studies for (at least) regions of chromosomes 1q, 2q, 5q, 6p, 6q, 8p, 10p, 13q, 15q and 22q. A meta-analysis of published schizophrenia linkage reports (including some but not all of the above data) reported P values <0.001 in candidate regions of chromosomes 1q, 2q, 8p, 13q and 22q [9••]. (A larger meta-analysis is being carried out by a collaboration of investigators and should be available soon.) Power analyses suggest that replicable linkage would require multiple samples of 500–1000 ASPs or more. Two samples of 500 and 900 ASPs are currently being collected for the National Institute of Mental Health (NIMH) cell repository. A series of multicenter collaborations in which samples of 500–800 pedigrees were genotyped produced evidence supporting linkage on chromosomes 6p [35], 6q [36], 10p [36] and 8p [35], although not 1q [37•], 5q [36] or 13q [36]. It is likely that that some or perhaps many of these candidate regions contain schizophrenia susceptibility loci, each contributing to a small increase in population-wide risk (although some loci could have larger effects in individual families).

Candidate genes in positional candidate regions

For the first time, LD mapping studies of positional candidate regions have implicated specific genes in schizophrenia susceptibility. Previously, no strong and replicable candidate genes had emerged from studies of genes involved in antipsychotic drug mechanisms (e.g. dopamine receptors) or in central nervous system processes that could be hypothetically related to schizophrenia. In the absence of evidence for linkage in a region, the prior probability for the association of a gene is so low that statistical proof becomes extremely difficult [38]. These new reports (Table 2) are therefore important new developments. Further replication will be needed before the validity of these associations can be evaluated.

NRG1

A genome scan in 33 Icelandic pedigrees with 105 cases of schizophrenia produced suggestive evidence for linkage on chromosome 8p [10••], near where suggestive linkage has been reported by others [18••,19••]. LD mapping studies in cases and controls suggested the association of individual SNPs and SNP haplotypes in *NRG1* (neuregulin-1, 8p21–p12). The 'core' haplotype was observed in 15.4% of 478 affected cases and 7.5% of 394 controls, with $P=0.000087$ for cases not known to be related. *NRG1* is a glycoprotein with a variety of isoforms that bind to the ErbB family of tyrosine kinase transmembrane receptors. *NRG1* and ErbB4 heterozygous mutant mice demonstrated hyperactivity that was reduced by very low doses of clozapine, slightly deficient pre-pulse inhibition, and a small reduction in functional *N*-methyl-D-aspartate (NMDA) receptors. Note that *NRG1* lies 9–25 cM towards the centromere from previously reported 8p linkage peaks, and it is possible that another gene in

Table 2. Schizophrenia candidate genes in positional candidate regions

Gene(s)	Location	Study population(s)	Comments
Neuregulin 1 (*NRG1*) [10••]	8p12–21	Icelandic. Linkage: 33 pedigrees. Association: 478 cases versus 394 controls	*NRG1* lies outside the 8p region where positive linkage evidence has been reported, and might not explain those reports.
Dysbindin (*DTNBP1*) [11••]	6p22	Irish. Linkage: 270 pedigrees. Association: same (family-based method)	The gene product is part of the dystrophin protein complex involved in muscular dystrophy, but may also be involved in signal transduction and receptor gene expression.
Proline dehydrogenase (*PRODH2*)	22q11	107 US triads (adult schizophrenia); 29 US childhood schizophrenia triads; 75 Afrikaner cases and 109 controls	Association was observed in early-onset cases. Sample sizes were small and *P* values were modest ($\approx$ 0.001), but positive evidence was observed in three samples.
G72 (D-amino acid oxidase; *DAAO*) [13••]	13q34 (12q24)	213 French Canadian cases and 241 controls; 183 Russian cases and 183 controls	*G72* was identified through LD mapping of linkage regions from other reports. Yeast two-hybrid experiments identified *DAAO* as interacting with *G72*; modest association was observed for *DAAO*.
Catechol-*O*-methyltransferase (*COMT*) [14••]	22q11	Ashkenazi. Association: 714–724 cases and 2849–4899 controls	*COMT* is in the VCFS deletion region. It degrades catecholamines including dopamine.

LD, Linkage disequilibrium; VCFS, velo-cardio facial syndrome.

that region, rather than a variation in *NRG1*, will prove to explain those findings.

DTNBP1

Straub *et al.* [11••] reported the association of schizophrenia to SNPs and SNP haplotypes on chromosome 6p22.3, implicating the *DTNBP1* (dysbindin) gene, in the linkage region from their and others' genome scans [18••,19••,27]. Dysbindin binds to dystrobrevin, part of the protein complex involved in the pathogenesis of muscular dystrophy. These proteins have diverse functions related to neurotransmitter signal transduction. Evidence supporting this association has recently been reported in two German samples [39].

PRODH2

Individuals with velo-cardio facial syndrome (VCFS) are at a substantially increased risk of schizophrenia [40–42], so that the identification of the relevant genes in the 22q11 microdeletion region is an important task. Liu *et al.* [12••] reported the association of schizophrenia to SNPs in *PRODH2* (proline dehydrogenase, 22q11.21), particularly in childhood cases and in adults with age at onset below the age of 18 years. Evidence for association was modest, but was observed in three separate small samples. Proline dehydrogenase is a mitochrondrial enzyme involved in transferring redox potential across the mitochondrial membrane.

G72 and DAAO

Chumakov *et al.* [13••] initiated LD mapping studies of chromosome 13q34 in the region where significant linkage was reported in two samples [25,43]. Strong association was observed in one French Canadian sample between schizophrenia and SNPs in a novel gene, *G72*, with weaker association in a Russian sample. Yeast two-hybrid experiments and subsequent studies demonstrated that *G72* activates D-amino acid oxidase (*DAAO*, 12q24), an enzyme that oxidizes D-serine, an activator of NMDA receptors. Weak association was observed between schizophrenia and DAAO.

COMT

Catechol-*O*-methyltransferase (*COMT*, 22q11.21, in the VCFS region) is one of the major degradative pathways for catecholamines including dopamine. Association with schizophrenia has been inconsistent for a Val/Met polymorphism [18••], with several recent additional negative reports [44•–46•,47,48•], although two of the studies reported modest associations for symptom severity [44•] or age at onset [46•]. Recently, Shifman *et al.* [14••] screened new *COMT* SNPs with pooled genotyping in more than 700 Ashkenazi Jewish cases and 3000–5000 controls, with individual genotyping confirming strong associations for two SNPs ($P = 0.00016$–0.00003). Weinberger *et al.* [49•] proposed that *COMT* sequence variation modifies cognition through effects on dopaminergic transmission in prefrontal cortex.

Such reports usher in a new era in schizophrenia genetics. One might expect more such reports to appear over the next 3–5 years, with increasingly large samples supporting the association of schizophrenia

with plausible candidate genes in linkage candidate regions, or genes identified by large-scale expression studies. Initial reports may be difficult to interpret: many tests must be performed on SNPs and haplotypes, and there is no definitive threshold for a significant finding. Data mining techniques are evolving in this field, and replication is likely to be the cornerstone of data interpretation. The author would predict that, despite these difficulties, the pattern of replication studies and physiological findings will ultimately become clear and convincing for at least some of the new candidate genes. Through this process, the first real clues to the pathophysiology of schizophrenia are likely to emerge.

Other studies of candidate regions and genes

Other noteworthy reports include applications of microarray technology and studies of candidate genes in pharmacologically-relevant neurotransmitter systems and in positional candidate regions.

Probing the genome with microarrays

Several studies demonstrated the emerging potential of microarray methods to probe the genome or proteome for candidate pathways. The decreased expression of *RGS4* (regulator of G-protein signalling 4, 1q21–q22) had been observed in a complementary DNA microarray study of brains from schizophrenia and control individuals [15•]. SNPs were identified in the region, and haplotype analysis revealed four SNPs with a modest association to schizophrenia in two independent samples, with a trend in a third sample [17••]. The gene is located in a linkage candidate region [5••,24]. In a second study, Hemby *et al.* [16••] probed 18 000 messenger RNAs in case and control brains and demonstrated significant differences in the expression for a number of genes. A further example is discussed for chromosome 22q (below).

Genes related to dopaminergic neurotransmission

Schizophrenia has not been convincingly associated with polymorphisms in genes related to dopaminergic function, although meta-analyses have suggested a small but significant association for homozygosity at a polymorphism in *DRD3* (3q13.3) [50]. There are two recent reports of slightly positive evidence for an association at *DRD2* (11q22–q23) [51•,52•], and one report [53•] was negative. There was a report of the association ($P = 0.0001$–0.05) between measures of eye-tracking dysfunction in schizophrenia patients and *DRD3* [54•], as well as a negative study of *DRD3* homozygosity and of several new polymorphisms in alternative promoter and 5′ untranslated regions (UTRs) in the gene [55•]. A further report found a modest association between schizophrenia and two markers in or near *DRD5* (4p16) [56•].

Genes related to serotonergic neurotransmission

A modest but significant association between schizophrenia and a polymorphism in the serotonin-2A receptor gene (*HTR2A*, 13q14–q21) was reported in a large multicenter analysis [57] and a meta-analysis [18••,19••,58]. There are two new negative reports [59,60]. Association had been reported in Han Chinese individuals for the serotonin transporter gene (*SLC6A*, formerly *5HTT*, 17q11.1–q12) [61], and a very modest replication ($P = 0.043$) was reported in the same population [62•]. Negative studies of *5HTR1B* (6q13) [63] and *5HTR3A* (11q23.1–q23.2) [64] have been published.

Genes related to glutamatergic neurotransmission

A number of lines of evidence have suggested a role for glutamatergic dysfunction in the pathogenesis or pharmacology of schizophrenia [65•]. A modest association ($P = 0.0105$) was reported between schizophrenia and *GRIK3* (ionotropic glutamate receptor kainate 3, 1p34–33) in 99 cases and 116 controls [66•]; and an association ($P = 0.0022$) was reported for *GRM3* (metabatropic glutamate receptor 3, 7q21.1–q21.2) in 265 cases and 227 controls, which could not be replicated in an additional 288 cases or 128 trios [67•]. Negative association results were reported for *GRM4* (metabotropic glutamate receptor 4, 6p21.2) [68•], *GRIK1* (ionotropic glutamate receptor kainate 1, 21q22.11) [69•] and *GRM2* (metabotropic glutamate receptor 2, 3p12–p11) [70•].

Chromosome 1q

Significant linkage was reported on chromosome 1q21–q22 ($\approx$158 MB from pter on chromosome 1) in a 'Celtic' Canadian sample [24]; and suggestive linkage was reported on 1q21–q23 ($\approx$165 MB) in Icelandic and British pedigrees [5••], on 1q41–q42 ($\approx$208 MB) in families from a genetic isolate in Finland [5••,32], and on 1q42.1 ($\approx$230 MB) in a Finnish general population affected sib-pair sample [5••,32]. The latter region contains the breakpoint of a balanced (1;11) (q42.1; q14.3) translocation linked to psychotic and mood disorders in an extended Scottish pedigree, with maximum lod scores of 3.6 for schizophrenia, 4.5 for mood disorders and 7.1 for both [71]. The *DISC1* and *DISC2* genes are disrupted by this breakpoint [72••], but no variation associated with schizophrenia has yet been found in these genes [73•]. The genes in the 11q breakpoint region have also been identified [74•]. Linkage was not supported in a multicenter sample of 779 pedigrees using a 5 cM marker map of 1q21–q42 [37•], or in 1q21–q22 in extended French Canadian pedigrees [75•]. There have been mixed reports regarding the association with the CAG repeat polymorphism in *KCNN3* (1q21.2) [18••]. A new Japanese study was negative [76•]; but in Israelis, longer alleles were

associated with more severe negative and paranoid symptoms [77•].

Chromosome 6

Modest association was reported for SNPs in *TNF2A* (tumor necrosis factor alpha, 6p21.1–21.3) [78•]. A highly significant association had been reported in *NOTCH4* (6p21.3) in a small sample [79], but there have been many non-replications [80,81,82•,83•,84]. A suggestive linkage was reported in the adjacent HLA region (6p21.2) [85•]. However, although an immunological role in the pathogenesis of schizophrenia is plausible [18••,19••], no association was observed in recent reports on class I alleles in Japanese cases and controls [86•], in class II *DRB1*, *DQA1*, *DQB1* and *DPB1* alleles in Han Chinese trios [87•], or in *DQB1*, *DRB1*, *DQA1*, or *HLA-A* alleles or haplotypes in primarily European sib-pair families and trios [85•]. Reports on *DTNBP1* and on 6q linkage have been discussed above.

Chromosome 8p

No association with schizophrenia was observed for markers in three plausible candidate genes (*PNOC*, *CHRNA2* and *NAT1*) [88•] in the 8p21–22 linkage region discussed above.

Chromosome 15q

Freedman and colleagues [89] demonstrated the highly significant linkage of chromosome 15q13–q14 to deficient inhibition of the P50 auditory evoked potential (pre-pulse inhibition) in schizophrenia probands and their affected and unaffected relatives, and showed that the alpha-7 nicotinic receptor gene (*CHRNA7*) was involved in this deficit in animals and was a plausible candidate gene for schizophrenia [90–92]. However, evidence for linkage to schizophrenia in this region had been modest. Now, a re-analysis of the NIMH Schizophrenia Genetics Initiative genome scan using a dominant parametric lod score analysis produced significant evidence for linkage on 15q13–q14 [93••]. Suggestive evidence for linkage was also reported near *CHRNA7* in Taiwanese families [94•], with more modest support in two American samples [95•,96•]. An association was also observed ($P = 0.0004$) between markers at *CHRNA7* and schizophrenia in 31 pedigrees from the Azores [97•], but not in pedigrees with the periodic catatonia phenotype, which had shown linkage to this region [98•]. On the basis of these results, 15q13–q14 emerges as a stronger schizophrenia candidate region.

Chromosome 22q

Microdeletions of 22q11.21 (VCFS) represent the only cytogenetic abnormality that is clearly associated with a substantial risk of chronic schizophrenia, suggesting that one or more genes in this region could play a role in schizophrenia in the absence of deletions. Although evidence for linkage has been modest, a meta-analysis suggested significant linkage [9••]. Evidence for *PRODH2* and *COMT* was discussed above. VCFS deletions were again found to be rare in schizophrenia – one in 300 Japanese cases [99•]. For genes in the deletion region, modest evidence for association was observed for two polymorphisms in promoter regions, including *UFD1L* (ubiquitin fusion degradation 1-like) in two small samples [100•], and *SNAP29* (synaptosomal-associated protein, 29 000 M_r) [101•]; and for SNPs in *ZNF74* (zinc finger protein 74) to age-at-onset but not schizophrenia in 300 Japanese cases and 300 controls [102•]. The latter age-at-onset finding was replicated in another 169 cases [102•]. Children with VCFS had similar behavioral and psychiatric disorders to children matched for the level of cognitive function, leading the authors to doubt the specific relationship between VCFS and schizophrenia [103•], but this conclusion ignores the 20% prevalence of schizophrenia symptoms among adults with VCFS [41]. Outside the deletion region, Meyer *et al.* [104•] described a putative potassium channel gene, *WKL1* (AF319633_1, 22q13.33), and reported that a missense mutation in this gene co-segregated with periodic catatonia in one extended pedigree. Three groups failed to find the mutation or association to other SNPs in the region in schizophrenia samples [105•,106•,107]. In periodic catatonia, an association was not observed for *CELSR1* (cadherin EGF (7 epidermal growth factor-like repeats) LAG (2 laminin AG-type repeats) seven-pass G-type receptor 1, 22q13.3) [108•]. Finally, Mimmack *et al.* [109•] carried out a cDNA microarray-based gene expression analysis of schizophrenia and control brains from two collections, and in both they found an increased expression of *APOL1*, *APOL2* and *APOL4* (apolipoproteins 1, 2 and 4, all in 22q12 outside the VCFS deletion region). These findings suggest a possible pathway in schizophrenia pathogenesis.

Other candidate genes

A role in schizophrenia has been hypothesized for cholecystokinin (*CCK*, (3p22–p21.3), which modulates dopaminergic neurotransmission [110•]. Recent reports include slightly positive evidence for the association of schizophrenia with a polymorphism in the promoter region in US cases [111•] and with polymorphisms in the promoter region of the *CCK-A* receptor gene (*CCKAR*, 4p15.1–p15.2) in Japanese cases and controls [110•], but not to a microsatellite in the *CCK-B* receptor gene (*CCKBR*, 11p15.4–p15.1) in Japanese cases and controls [112]. An association ($P = 0.031$–0.0001) was reported between schizophrenia and three SNPs in myo-inositol monophosphatase 2 (*IMPA2*, 18p11.2), in 302 Japanese schizophrenia cases versus 308 controls and 205 affective disorder cases [113•]. Modest evidence for association was reported for a SNP in *CTLA-4* (cytotoxic T-

lymphocyte antigen-4, 2q33) in 116 Korean cases and 149 controls ($P = 0.003$), as a result of fewer heterozygotes in the cases [114•]. Similarly, 268 Japanese cases showed increased homozygosity at linked SNPs in *GRIN2B* (the *NMDA-2B* receptor, 12p12) versus 337 controls ($P = 0.004$) [115•]. Maes *et al.* [116•] reviewed evidence for alterations in the acute phase inflammatory response in schizophrenia, and reported an association of polymorphic variation in haptoglobin (*HP*, 16q22.1) and haptoglobin plasma levels in 98 Italian cases versus established distributions in the local population. Finally, Hong *et al.* [117•] observed a modest association between schizophrenia and *TPH* (tryptophan hydroxylase, 11p14–p15.3) in 196 Han Chinese cases and 251 controls.

Additional negative association studies of candidate genes published during the review period will not be discussed in detail here [118–136].

Progress in identifying quantitative traits for genetic studies

There were several reports about schizophrenia-related quantitative traits that showed promise as phenotypes for genetic studies.

Neuropsychological measures

In 264 cases and relatives from a geographical isolate in Finland, measures of working memory showed strong heritability, possibly because of a small number of contributing loci [137•]. Measures of memory and IQ declined before the onset of psychosis in high-risk individuals in the Edinburgh high-risk project [138]. However, in the same project, attentional dysfunction did not differentiate the relatives of schizophrenic versus control subjects [139•].

Neuro-imaging measures

In a creative analysis from the Edinburgh project, a reduced volume of the amygdalohippocampal complex was observed in 'obligate carriers' (well individuals with a schizophrenic sibling and offspring) [140•]. In a study of monozygotic and dizygotic twins discordant for schizophrenia and control twins, an upward bowing of the corpus callosum was also suggested to be a marker of vulnerability [141•].

Neurological signs

Neurological signs were increased in the relatives of schizophrenia patients, but the low relative risk versus controls suggested that they might be poor genetic markers [142•]. A pattern of dysmorphic features was found to differentiate a subgroup of 18 schizophrenia cases from other clusters in a sample of 123 clinical schizophrenia cases and 36 cases referred for possible VCFS [143].

Clinical dimensions

Cardno *et al.* [144•] showed that 'first-rank' symptoms (such as delusions of being controlled or hearing voices conversing) were heritable in the Maudsley twin series, but less so than the category of schizophrenia. They also reported that genetic liability to schizophrenic, manic and depressive symptoms appeared to overlap substantially when rated non-hierarchically [145•]. Kendler [146•], in a commentary on the latter study, suggested that the data are better interpreted as showing that manic and depressive syndromes are somewhat heritable in individuals with schizophrenia, because no genetic overlap was shown between individuals with primary diagnoses of schizophrenic and mood disorders.

Models for genetic studies of schizophrenia

Several intriguing models have been proposed for conceptualizing genetic factors in schizophrenia.

Advancing paternal age and de-novo mutations

A re-analysis of data from a birth cohort study demonstrated that advancing paternal age slightly but significantly increased the risk of schizophrenia, after adjusting for possible confounding factors such as maternal age [147••]. In another study [148•], schizophrenia patients without a known family history of schizophrenia had significantly older fathers than those with a family history. Malaspina [149•] integrated these and other data into an intriguing hypothesis that de-novo germline mutations can increase the risk of schizophrenia, which suggests that novel strategies may be needed to identify these mutations [149•].

Neurodevelopmental hypotheses

Lewis and Levitt [150••] reviewed the evidence for a neurodevelopmental hypothesis of schizophrenia, suggesting a polygenic-multifactorial model whereby genetic predisposition alters development, gene–environment interactions influence or trigger genetic effects, and cumulative effects of altered development lead to a relatively stable and treatment-resistant state. Maynard *et al.* [151•] proposed a two-hit model requiring genetic or early environmental predisposing factors plus triggering factors closer to onset. Schiffman *et al.* [152••] reported that among 93 high-risk offspring, the number of physical anomalies at age 11–13 years predicted schizophrenia spectrum disorders at age 31–33 years. There were high rates of anomalies and of spectrum disorders in the samples. Bassett and colleagues [153•] reviewed evidence for neurodevelopmental hypotheses, focusing on physical anomalies and the implications of syndromes such as VCFS. DeLisi [154•] suggested that schizophrenic patients have language disorders that could be related to genes underlying the uniquely human characteristics of speech.

Conclusion

The pace of discovery is accelerating in the field of schizophrenia genetics. The most striking developments in the past year have included the apparent convergence of new and older linkage data on a number of chromosomal regions, and the first reports of LD mapping data supporting specific candidate genes in linkage candidate regions. *NRG1*, *DTNBP1*, *G72/DAAO* and *COMT* were all studied in 400 or more cases, more than in most previous candidate gene studies. However, inadequate power remains a problem in both linkage and LD mapping studies: ideally, it would be preferable to have several linkage samples of 500–1000 pedigrees and several association samples of 1000–3000 cases and controls or proband–parent trios. Association data from very small samples remain difficult to interpret.

The next few years are likely to see the completion of the haplotype structure map ('HapMap') and a rapid decline in the cost of very high-throughput SNP genotyping. The HapMap project will identify a minimal set of approximately 100 000–500 000 SNPs, which define local 10–50 000 bp blocks of LD, i.e. the old, common variation in the human genome [155–158]. The hypothesis to be tested is that at least some of the predisposing DNA sequence variations for common complex disorders may be in LD with these blocks. However, there may be too many different predisposing variations in different populations, with little correlation between the observable phenotype and underlying genotype [159]. It is likely that cost-efficient methods will be developed to detect all sequence variations in candidate regions [160], so that one might also detect an excess of rare variations in cases. Diverse microarray strategies offer additional tools to identify functionally relevant genes, proteins and pathways, and although these will not always be causal [159], they are likely to yield insights for treatment and ultimately for better causal hypotheses.

An article by a social scientist suggested some concluding reflections: Conrad [161•] critiqued the widespread media endorsement of 'genetic optimism', 'which emphasizes the inevitability of discovering genes and the good outcomes of those discoveries, while negative or retracted findings receive no attention. Scientific colleagues in genetics and other fields are prone to similar distortions' (p. 225). However, optimism is far from the dominant theme in the scientific community. Rather, we see an unfortunate oscillation: scientists as well as the media tend to make exaggeratedly positive claims, and then the 'negative and retracted findings' have led to profound skepticism. What is needed is a balanced and steady approach for the long haul. In this author's view, the cornerstone of progress should be the logic of positional cloning: by utilizing data from linkage studies (and perhaps in the future, microarray studies) in a critical way – cognizant of methodological shortcomings and realistic about the strength of results and the power of samples – it should be possible to move from candidate regions to candidate genes to the beginnings of an understanding of schizophrenia pathophysiology in the next decade.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1 •• Straub RE, MacLean CJ, Ma Y, *et al.* Genome-wide scans of three independent sets of 90 Irish multiplex schizophrenia families and follow-up of selected regions in all families provides evidence for multiple susceptibility genes. Mol Psychiatry 2002; 7:542–559.

Genome scan results are reported for 270 Irish pedigrees. The scan was initiated and mostly completed when genotyping this large sample was considerably more expensive. It was thus divided into three subsets, each of which was scanned using a different 20–30 cM map, and positive regions as well as candidate regions reported by others were typed in all subsets. Multiple diagnostic and transmission models were tested. Results on chromosome 6p21–24 approached genome-wide significance, with a suggestion of at least two loci in the region, and suggestive evidence for linkage was observed on 5q21–31, 8p22–21 and 10p15–p11.

2 •• DeLisi LE, Shaw SH, Crow TJ, *et al.* A genome-wide scan for linkage to chromosomal regions in 382 sibling pairs with schizophrenia or schizoaffective disorder. Am J Psychiatry 2002; 159:803–812.

This is the largest genome scan published to date, including 294 families of predominantly European ancestry with 333 independent ASPs. Suggestive evidence for linkage was observed on chromosome 10p15–p13 and around the centromere of chromsome 2, with a smaller peak on chromosome 22q12.

3 •• DeLisi LE, Mesen A, Rodriguez C, *et al.* Genome-wide scan for linkage to schizophrenia in a Spanish-origin cohort from Costa Rica. Am J Med Genet 2002; 114:497–508.

Genome scan data are reported for 99 families from the Central Valley region of Costa Rica (62–102 ASPs depending on the model). Modest evidence for linkage was observed in chromosome 5q34.

4 •• Paunio T, Ekelund J, Varilo T, *et al.* Genome-wide scan in a nationwide study sample of schizophrenia families in Finland reveals susceptibility loci on chromosomes 2q and 5q. Hum Mol Genet 2001; 10:3037–3048.

Two genome scans are reported, one of 163 families (191 ASPs) from the general Finnish population, and one of 47 nuclear families (approximately 60 ASPs) from an isolated, inbred region. Results for chromosome 1q are reported in Ref. [32]. Significant findings were observed on very distal 2q (isolate sample) and 5q31 (national sample).

5 •• Gurling HM, Kalsi G, Brynjolfson J, *et al.* Genomewide genetic linkage analysis confirms the presence of susceptibility loci for schizophrenia, on chromosomes 1q32.2, 5q33.2, and 8p21–22 and provides support for linkage to schizophrenia, on chromosomes 11q23.3–24 and 20q12.1–11.23. Am J Hum Genet 2001; 68:661–673.

A genome scan is reported for 13 British and Icelandic pedigrees (56 cases with schizophrenia spectrum psychoses and 12 with broader diagnoses). Suggestive evidence for linkage was observed on chromosomes 1q32.2, 5q33.2, 8p21–22, 11q23.2–q24 and 20q12.1–11.23.

6 •• Camp NJ, Neuhausen SL, Tiobech J, *et al.* Genomewide multipoint linkage analysis of seven extended Palauan pedigrees with schizophrenia, by a Markov-chain Monte Carlo method. Am J Hum Genet 2001; 69:1278–1289.

This is a report on a genome scan of seven pedigrees from Palau (an old but genetically isolated population with an elevated – 2% lifetime prevalence – of schizophrenia), with 40 narrowly defined and 45 'spectrum' cases available. A 10 cM map was genotyped and linkage analyses performed using Markov chain Monte Carlo methods to reconstruct haplotypes followed by Non-Parametric Linkage (NPL) and parametric lod score analyses.

7 • Garver DL, Holcomb J, Mapua FM, *et al.* Schizophrenia spectrum disorders: an autosomal-wide scan in multiplex pedigrees. Schizophr Res 2001; 52:145–160.

A genome scan was performed on 30 US European and African-American pedigrees with 62 schizophrenia cases, 35 other psychoses and 23 spectrum personality disorders, using a 10 cM map and NPL analysis.

8 Lindholm E, Ekholm B, Shaw S, *et al.* A schizophrenia-susceptibility locus at •• 6q25, in one of the world's largest reported pedigrees. Am J Hum Genet 2001; 69:96–105.

This is one of the most significant findings in schizophrenia linkage research, in 6q25.2 in a large multigenerational pedigree (actually an inter-related set of such pedigrees) from northern Sweden. The relationships within this family go back 12 generations, presenting a challenge for linkage analysis, and analyses with alternative allele frequencies produced somewhat different *P* values. This is one of the few examples of highly significant results from the study of this type of rare pedigree. The linkage region is slightly distal to that reported by other groups.

9 Badner JA, Gershon ES. Meta-analysis of whole-genome linkage scans of •• bipolar disorder and schizophrenia. Mol Psychiatry 2002; 7:405–411.

A meta-analysis was carried out on published schizophrenia and bipolar linkage data, using a novel method for combining *P* values for broad regions of linkage. For schizophrenia, *P* values of less than 0.001 across studies were observed on chromosomes 1q, 2q, 8p, 13q and 22q.

10 Stefansson H, Sigurdsson E, Steinthorsdottir V, *et al.* Neuregulin 1 and •• susceptibility to schizophrenia. Am J Hum Genet 2002; 71:877–892.

In 33 Icelandic families with 105 available individuals with schizophrenia, suggestive evidence for linkage was observed on 8p12–21. The region was densely mapped in 478 schizophrenia cases and 394 controls, and evidence for association was observed within *NRG1* (neuregulin 1) ($P = 0.000067$ for a core haplotype in one of many tests). The finding is 8–10 cM centromeric to numerous other reports of 8p linkage, raising a question about whether this gene can explain that previous evidence. Hemizygous knockout mice were produced and exhibited modest evidence of deficient pre-pulse inhibition of startle and for a reduction in NMDA receptors. This thus becomes an important candidate gene for schizophrenia.

11 Straub RE, Jiang Y, MacLean CJ, *et al.* Genetic variation in the 6p22.3 gene •• *DTNBP1*, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. [Erratum appears in *Am J Hum Genet* 2002; 72:1007]. Am J Hum Genet 2002; 71:337–348.

In a candidate region (6p22) supported by several studies in diverse populations, these authors describe evidence for the association of schizophrenia with *DTNBP1*, dystrobrevin binding protein 1 or dysbindin, based on family-based association analyses of SNPs genotyped in a multiplex Irish sample in which 6p linkage was first described. Although dysbindin is part of the protein complex related to muscular dystrophy, these authors summarize evidence that it may play a role in signal transduction including in the NMDA and γ-aminobutyric acid systems. This locus will receive intensive study in schizophrenia samples in the coming years.

12 Liu H, Heath SC, Sobin C, *et al.* Genetic variation at the 22q11 *PRODH2/* •• *DGCR6* locus presents an unusual pattern and increases susceptibility to schizophrenia. Proc Natl Acad Sci U S A 2002; 99:3717–3722.

This group has been studying possible 22q candidate genes for some time. Here they present their most compelling evidence to date: several SNPs in the *PRODH2* (proline dehydrogenase) gene, in the VCFS deletion region, show association with schizophrenia in three samples: adult schizophrenia patients, childhood schizophrenic patients, and an adult replication sample from South Africa (Afrikaners). The association was observed for individuals with early age at onset. *P* values were modest ($P = 0.001$ for the strongest associations). The estimated relative risk for the most strongly associated haplotypes were in the range of 3–5. The evidence here is not definitive but this is an important hypothesis that will be carefully studied in the field.

13 Chumakov I, Blumenfeld M, Guerassimenko O, *et al.* Genetic and •• physiological data implicating the new human gene *G72* and the gene for d-amino acid oxidase in schizophrenia. Proc Natl Acad Sci U S A 2002; 99:13675–13680.

LD mapping studies on chromosome 13q34 were initiated because of previous reports of significant linkage. SNP haplotypes in a novel gene, *G72*, were found to be associated with schizophrenia in 213 French Canadian cases and 241 controls, with a modest replication in 183 Russian cases and 183 controls. Yeast two-hybrid experiments led to the identification of D-amino acid oxidase (*DAAO*, 12q24) interacting with *G72*, and a modest association with schizophrenia was demonstrated for SNPs at *DAAO*. Physiological studies supported the plausibilityof these genes as schizophrenia candidate genes.

14 Shifman S, Bronstein M, Sternfeld M, *et al.* A highly significant association •• between a *COMT* haplotype and schizophrenia. Am J Hum Genet 2002; 71:1296–1302.

New SNPs were identified within *COMT* (22q11), a gene in the VCFS deletion region, and tested with pooled genotyping in approximately 700 Ashkenazi cases and 3000–5000 controls. Positive results were followed up with individual genotyping, and a strong association of schizophrenia was observed for several SNP haplotypes.

15 Mirnics K, Middleton FA, Stanwood GD, *et al.* Disease-specific changes in • regulator of G-protein signaling 4 (RGS4) expression in schizophrenia. Mol Psychiatry 2001; 6:293–301.

Using cDNA microarrays, the authors demonstrated that in brains of schizophrenia subjects, expression was consistently decreased for *RGS4* (regulator of G-protein signalling 4, 1q21–q22), and not for other *RGS* genes or for 70 other genes in this cytogenetic region. This is one of the first sophisticated microarray studies of schizophrenia, and it is likely that these studies will yield important information that will inform genetic studies.

16 Hemby SE, Ginsberg SD, Brunk B, *et al.* Gene expression profile for •• schizophrenia: discrete neuron transcription patterns in the entorhinal cortex. Arch Gen Psychiatry 2002; 59:631–640.

In one of the first applications of sophisticated microarray technologies to schizophrenia, these authors constructed an array of 18 000 mRNAs and studied expression in EC-II stellate neurons from brains from eight schizophrenia cases (older patients with chronic illness, four on no medication) and nine controls. The most prominent differences observed in a secondary more specific analysis were the decreased expression of *GRIN1* (NMDA receptor 1, 9q34,3), *GNAI1* [guanine nucleotide binding protein (G-protein) alpha inhibiting activity polypeptide 1, 7q21], *SYP* (synaptophysin, Xp11.23–p11.22), *SNAP23* (synaptosomal-associated protein 23, 15q14) and *SNAP25* (20p12–p11.2), and the increased expression of *GNG2* (G-protein gamma subunit 2, 14q21).

17 Chowdari KV, Mirnics K, Semwal P, *et al.* Association and linkage analyses •• of *RGS4* polymorphisms in schizophrenia. Hum Mol Genet 2002; 11:1373–1380.

Mirnics *et al.* [15•] had demonstrated the reduced expression of *RGS4* (1q23.1, regulator of G-protein signalling 4) in brains from schizophrenia subjects in an elegant series of microarray studies. In this report, SNPs were identified in the region, and haplotype analysis revealed four SNPs with a modest association with schizophrenia in two independent samples with a trend in a third sample.

18 Waterwort DM, Bassett AS, Brzustowicz LM. Recent advances in the •• genetics of schizophrenia. Cell Mol Life Sci 2002; 59:331–348.

An excellent review of schizophrenia diagnosis, epidemiology, and linkage and association findings.

19 Baron M. Genetics of schizophrenia and the new millennium: progress and •• pitfalls. Am J Hum Genet 2001; 68:299–312.

An excellent review of schizophrenia linkage and association findings, focusing on methodological issues. The author argues for the use of larger pedigrees and model-based linkage analyses, but carefully reviews findings from all study designs.

20 Risch N. Linkage strategies for genetically complex diseases, with special reference to psychiatric disorders. Gene Epidemiol 1990; 7:3–16.

21 Hauser ER, Boehnke M, Guo SW, Risch N. Affected sib-pair interval mapping and exclusion for complex genetic traits: sampling considerations. Genet Epidemiol 1996; 13:117–138.

22 Suarez BK, Hampe CL, van Eerdewegh PV. Problems of replicating linkage claims in psychiatry. In: Gershon ES and Cloninger CR, editors. Genetic approaches to mental disorders. Washington, DC: American Psychiatric Press; 1994. pp. 23–46.

23 Goring HH, Terwilliger JD, Blangero J. Large upward bias in estimation of locus-specific effects from genomewide scans. Am J Hum Genet 2001; 69:1357–1369.

24 Brzustowicz LM, Hodgkinson KA, Chow EW, *et al.* Location of a major susceptibility locus for familial schizophrenia on chromosome 1q21–q22. Science 2000; 288:678–682.

25 Blouin JL, Dombroski BA, Nath SK, *et al.* Schizophrenia susceptibility loci on chromosomes 13q32, 8p21. Nat Genet 1998; 20:70–73.

26 Lander E, Kruglyak L. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. Nat Genet 1995; 11:241–247.

27 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.

28 Straub RE, MacLean CJ, O'Neill FA, *et al.* Support for a possible schizophrenia vulnerability locus in region 5q22–31 in Irish families. Mol Psychiatry 1997; 2:148–155.

29 Kendler KS, MacLean CJ, O'Neill FA, *et al.* Evidence for a schizophrenia vulnerability locus on chromosome 8p in the Irish Study of High-Density Schizophrenia Families. Am J Psychiatry 1996; 153:1534–1540.

30 Straub RE, MacLean CJ, Martin RB, *et al.* A schizophrenia locus may be located in region 10p15–p11. Am J Med Genet 1998; 81:296–301.

31 Altmuller J, Palmer LJ, Fischer G, *et al.* Genomewide scans of complex human diseases: true linkage is hard to find. Am J Hum Genet 2001; 69:936–950.

32 Ekelund J, Hovatta I, Parker A, *et al.* Chromosome 1 loci in Finnish schizophrenia families. Hum Mol Genet 2001; 10:1611–1617.

33 Coon H, Myles-Worsley M, Tiobech J, *et al.* Evidence for a chromosome 2p13–14 schizophrenia susceptibility locus in families from Palau, Micronesia. Mol Psychiatry 1998; 3:521–527.

34 •• Maziade M, Roy MA, Rouillard E, *et al.* A search for specific and common susceptibility loci for schizophrenia and bipolar disorder: a linkage study in 13 target chromosomes. Mol Psychiatry 2001; 6:684–693.
Partial genome scan data (focused on candidate regions) for 19 Quebecoise pedigrees with 70 narrow and nine broad cases (as well as bipolar cases and some purely bipolar pedigrees). Suggestive linkage was observed on chromosomes 6p22–24 and 18q.

35 Schizophrenia Linkage Collaborative Group for Chromosomes 3, 6 and 8. Additional support for schizophrenia linkage on chromosomes 6, 8: a multicenter study. Am J Med Genet 1996; 67:580–594.

36 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. Am J Hum Genet 2000; 67:652–663.

37 • Levinson DF, Holmans PA, Laurent C, *et al.* No major schizophrenia locus detected on chromosome 1q in a large multicenter sample. Science 2002; 296:739–741.
A large multicenter sample (779 pedigrees from eight schizophrenia samples) did not produce significant evidence for linkage on chromosome 1q. The authors typed a 5 cM map spanning proximal and distal linkage findings.

38 Sullivan PF, Eaves LJ, Kendler KS, Neale MC. Genetic case–control association studies in neuropsychiatry. Arch Gen Psychiatry 2001; 58:1015–1024.

39 Schwab SG, Knapp M, Mondaboni S, *et al.* Support for association of schizophrenia with genetic variation in the 6p22.3 gene, dysbindin, in sib-pair families with linkage and in an additional sample of triad families. Am J Hum Genet 2003; 72:185–190.

40 Pulver AE, Nestadt G, Goldberg R, *et al.* Psychotic illness in patients diagnosed with velo-cardio-facial syndrome and their relatives. J Nerv Ment Dis 1994; 182:476–478.

41 Karayiorgou M, Morris MA, Morrow B, *et al.* Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. Proc Natl Acad Sci USA 1995; 92:7612–7616.

42 Murphy KC, Jones RG, Griffiths E, *et al.* Chromosome 22q11 deletions. An under-recognised cause of idiopathic learning disability. Br J Psychiatry 1998; 172:180–183.

43 Brzustowicz LM, Honer WG, Chow EW, *et al.* Linkage of familial schizophrenia to chromosome 13q32. Am J Hum Genet 1999; 65:1096–1103.

44 • Herken H, Erdal ME. Catechol-O-methyltransferase gene polymorphism in schizophrenia: evidence for association between symptomatology and prognosis. Psychiatr Genet 2001; 11:105–109.
No association with schizophrenia was observed for the val/met polymorphism in 129 cases and 165 controls from Turkey, although a modest association with the severity of illness was noted.

45 • Norton N, Kirov G, Zammit S, *et al.* Schizophrenia and functional polymorphisms in the *MAOA* and *COMT* genes: no evidence for association or epistasis. Am J Med Genet 2002; 114:491–496.
No association was observed between schizophrenia and the val158met polymorphism in *COMT* in 346 British cases and 334 controls. The A287G polymorphism was also negative in half of the sample.

46 • Liou YJ, Tsai SJ, Hong CJ, *et al.* Association analysis of a functional catechol-o-methyltransferase gene polymorphism in schizophrenic patients in Taiwan. Neuropsychobiology 2001; 43:11–14.
No association was observed between schizophrenia and the val158met polymorphism in *COMT* in 198 Chinese cases and 188 controls, although a modest association ($P = 0.005$) was reported.

47 Semwal P, Prasad S, Bhatia T, *et al.* Family-based association studies of monoaminergic gene polymorphisms among North Indians with schizophrenia. Mol Psychiatry 2001; 6:220–224.

48 • de Chaldee M, Corbex M, Campion D, *et al.* No evidence for linkage between *COMT* and schizophrenia in a French population. Psychiatry Res 2001; 102:87–90.
One of the negative association studies for older polymorphisms in *COMT*, in a small multiplex family sample, using family-based assocation and NPL analyses.

49 • Weinberger DR, Egan MF, Bertolino A, *et al.* Prefrontal neurons and the genetics of schizophrenia. Biol Psychiatry 2001; 50:825–844.
A thoughtful review of animal and human studies of the physiology of the cognitive role of prefrontal cortex, and of evidence that sequence variation in *COMT* is an example of a polymorphism that directly influences this physiology through its effects on dopaminergic transmission.

50 Wong AH, Buckle CE, Van Tol HH. Polymorphisms in dopamine receptors: what do they tell us? Eur J Pharmacol 2000; 410:183–203.

51 • Dubertret C, Gorwood P, Gouya L, *et al.* Association and excess of transmission of a DRD2 haplotype in a sample of French schizophrenic patients. Schizophr Res 2001; 49:203–212.
A modest association ($P = 0.02$–0.05) is reported by schizophrenia and two polymorphisms in *DRD2* (dopamine receptor 2, 11q22–q23) in 50 French cases versus controls and by transmission disequilibrium test (TDT) in the same cases, with a trend towards a later age of onset predicting the association. Previous *DRD2* studies are also reviewed.

52 • Virgos C, Martorell L, Valero J, *et al.* Association study of schizophrenia with polymorphisms at six candidate genes. Schizophr Res 2001; 49:65–71.
In 262 Spanish cases versus 278 controls, an association at $P = 0.035$ was observed at *DRD2*, but not at five other loci (*DRD3*, *5HTR2A*, *NT-3*, *BDNF* or *CNTF*).

53 • Hori H, Ohmori O, Shinkai T, *et al.* Association analysis between two functional dopamine D2 receptor gene polymorphisms and schizophrenia. Am J Med Genet 2001; 105:176–178.
No association was observed between schizophrenia and two polymorphisms in *DRD2* in 241 Japanese cases versus 201 controls.

54 • Rybakowski JK, Borkowska A, Czerski PM, Hauser J. Dopamine D3 receptor (*DRD3*) gene polymorphism is associated with the intensity of eye movement disturbances in schizophrenic patients and healthy subjects. Mol Psychiatry 2001; 6:718–724.
An association ($P = 0.001$–0.05) was observed between the severity of eye tracking deficits in schizophrenia patients and the Ser9Gly polymorphism in *DRD3*.

55 • Anney RJ, Rees MI, Bryan E, *et al.* Characterisation, mutation detection, and association analysis of alternative promoters and 5′ UTRs of the human dopamine D3 receptor gene in schizophrenia. Mol Psychiatry 2002; 7:493–502.
No association was observed between schizophrenia and polymorphisms in alternative promoter and 5′UTR regions of *DRD3*, and the finding of excess homozygosity of *DRD3* (dopamine 3 receptor, 3q13.3) in schizophrenia (previously reported by this and other groups) was not observed.

56 • Muir WJ, Thomson ML, McKeon P, *et al.* Markers close to the dopamine D5 receptor gene (*DRD5*) show significant association with schizophrenia but not bipolar disorder. Am J Med Genet 2001; 105:152–158.
Modest associations were observed between schizophrenia and a polymorphism in *DRD5* (dopamine 5 receptor, 4p16) ($P = 0.024$) and in a nearby microsatellite marker, *D4S615* ($P = 0.001$), although the two markers were not in linkage disequilibrium (150 kb region).

57 Williams J, Spurlock G, McGuffin P, *et al.* Association between schizophrenia and T102C polymorphism of the 5-hydroxytryptamine type 2a-receptor gene. European Multicentre Association Study of Schizophrenia (EMASS) Group. Lancet 1996; 347:1294–1296.

58 Williams J, McGuffin P, Nothen M, Owen MJ. Meta-analysis of association between the 5-HT2a receptor T102C polymorphism and schizophrenia. EMASS Collaborative Group. European Multicentre Association Study of Schizophrenia. Lancet 1997; 349:1221.

59 Chen RY, Sham P, Chen EY, *et al.* No association between T102C polymorphism of serotonin-2A receptor gene and clinical phenotypes of Chinese schizophrenic patients. Psychiatry Res 2001; 105:175–185.

60 Haider MZ, Zahid MA. No evidence for an association between the 5-hydroxytryptamine 5-HT2a receptor gene and schizophrenia in Kuwaiti Arabs. Psychiatry Clin Neurosci 2002; 56:465–467.

61 Liu W, Gu N, Feng G, *et al.* Tentative association of the serotonin transporter with schizophrenia and unipolar depression but not with bipolar disorder in Han Chinese. Pharmacogenetics 1999; 9:491–495.

62 • Tsai SJ, Ouyang WC, Hong CJ. Association for serotonin transporter gene variable number tandem repeat polymorphism and schizophrenic disorders. Neuropsychobiology 2002; 45:131–133.
Very modest replication ($P = 0.043$) was reported for the association of the serotonin transporter gene (*5-HTT*) with schizophrenia in Han Chinese (114 cases versus 127 controls), the population in which such an association was previously reported.

63 Sanders AR, Cao Q, Taylor J, *et al.* Genetic diversity of the human serotonin receptor 1B (*HTR1B*) gene. Genomics 2001; 72:1–14.

64 Niesler B, Weiss B, Fischer C, *et al.* Serotonin receptor gene *HTR3A* variants in schizophrenic and bipolar affective patients. Pharmacogenetics 2001; 11:21–27.

65 • Schiffer HH. Glutamate receptor genes: susceptibility factors in schizophrenia and depressive disorders? Mol Neurobiol 2002; 25:191–212.
A useful review of the evidence supporting a role for glutamatergic mechanisms in schizophrenia.

66 Begni S, Popoli M, Moraschi S, *et al.* Association between the ionotropic
• glutamate receptor kainate 3 (*GRIK3*) ser310ala polymorphism and schizophrenia. Mol Psychiatry 2002; 7:416–418.
A modest association ($P=0.0105$) was reported between schizophrenia and a ser310ala polymorphism in *GRIK3* (ionotropic glutamate receptor kainate 3, 1p34–33) in 99 Italian cases and 116 controls.

67 Marti SB, Cichon S, Propping P, Nothen M. Metabotropic glutamate receptor
• 3 (GRM3) gene variation is not associated with schizophrenia or bipolar affective disorder in the German population. Am J Med Genet 2002; 114:46–50.
An association observed between schizophrenia and *GRM3* (metabatropic glutamate receptor 3, 7q21.1–q21.2) in 265 cases versus 227 controls ($P=0.0022$) could not be confirmed in an additional 288 cases versus 162 controls and 128 trios (German).

68 Ohtsuki T, Toru M, Arinami T. Mutation screening of the metabotropic
• glutamate receptor mGluR4 (*GRM4*) gene in patients with schizophrenia. Psychiatr Genet 2001; 11:79–83.
No association was observed between schizophrenia and *GRM4* (metabotropic glutamate receptor 4, 6p21.2), using nine newly discovered sequence variants, in Japanese cases and controls.

69 Shibata H, Joo A, Fujii Y, *et al.* Association study of polymorphisms in the
• GluR5 kainate receptor gene (*GRIK1*) with schizophrenia. Psychiatr Genet 2001; 11:139–144.
No association was observed between schizophrenia and *GRIK1* (ionotropic glutamate receptor kainate 1, 21q22.11) using three new and three previously described SNPs in approximately 200 Japanese cases and controls per analysis.

70 Joo A, Shibata H, Ninomiya H, *et al.* Structure and polymorphisms of the
• human metabotropic glutamate receptor type 2 gene (*GRM2*): analysis of association with schizophrenia. Mol Psychiatry 2001; 6:186–192.
No association was observed between schizophrenia and *GRM2* (metabotropic glutamate receptor 2, 3p12–p11) in 213 Japanese cases and 220 controls.

71 Blackwood DHR, Fordyce A, Walker MT, *et al.* Schizophrenia and affective disorders – cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes: clinical and p300 findings in a family. Am J Hum Genet 2001; 69:428–433.

72 Millar JK, Christie S, Anderson S, *et al.* Genomic structure and localisation
•• within a linkage hotspot of *Disrupted In Schizophrenia 1*, a gene disrupted by a translocation segregating with schizophrenia. Mol Psychiatry 2001; 6:173–178.
This is the initial report on the genes *DISC1* and *DISC2* (parallel antisense genes) found in the 1q breakpoint region of a (1;11) (q42.1; q14.3) translocation that segregates with schizophrenia and other psychiatric disorders in a large Scottish pedigree.

73 Devon RS, Anderson S, Teague PW, *et al.* Identification of polymorphisms
• within *Disrupted in Schizophrenia 1* and *Disrupted in Schizophrenia 2*, and an investigation of their association with schizophrenia and bipolar affective disorder. Psychiatr Genet 2001; 11:71–78.
Two plausible candidate genes for schizophrenia were discovered in the breakpoint of a (1;11) (q42.1; q14.3) translocation that segregates with schizophrenia and other psychiatric disorders in a previously described very large Scottish pedigree. Although association with schizophrenia was not observed for the SNPs described here in these genes, these genes may be of importance given that this is one of the few relevant cytogenetic findings in schizophrenia.

74 Semple CA, Devon RS, Le Hellard S, Porteous DJ. Identification of genes
• from a schizophrenia-linked translocation breakpoint region. Genomics 2001; 73:123–126.
This paper describes the possible schizophrenia candidate genes in the breakpoint region on chromosome 11, for the 1;11 breakpoint described in this group's papers on the 1q breakpoint region. No association data for schizophrenia are presented.

75 Maziade M, Fournier A, Phaneuf D, *et al.* Chromosome 1q12–q22 linkage
• results in eastern Quebec families affected by schizophrenia. Am J Med Genet 2002; 114:51–55.
Linkage was not observed on proximal chromosome 1q in 21 large French Canadian pedigrees.

76 Imamura A, Tsujita T, Kayashima T, *et al.* Lack of association between the
• hKCa3 gene and Japanese schizophrenia patients. Psychiatr Genet 2001; 11:227–229.
No association was observed between schizophrenia and a CAG repeat in *KCNN3* (1q21.2) in 112 Japanese cases and 102 controls.

77 Ritsner M, Modai I, Ziv H, *et al.* An association of CAG repeats at the
• *KCNN3* locus with symptom dimensions of schizophrenia. Biol Psychiatry 2002; 51:788–794.
Longer alleles of the CAG repeat in *KCNN3* (1q21.2) predicted a greater severity of negative symptoms and of paranoid symptoms and an earlier age at onset in 117 Israeli cases ($P<0.001$ overall multivariate analysis of variance).

78 Boin F, Zanardini R, Pioli R, *et al.* Association between G308A tumor
• necrosis factor alpha gene polymorphism and schizophrenia. Mol Psychiatry 2001; 6:79–82.
In 84 patients versus 138 controls, modest association ($P=0.0024$) is reported between schizophrenia and an SNP in *TNF2A* (tumor necrosis factor alpha) in 6p21.1–21.3, the most centromeric portion of the rather broad candidate region on 6p.

79 Wei J, Hemmings GP. The NOTCH4 locus is associated with susceptibility to schizophrenia. Nat Genet 2000; 25:376–377.

80 Sklar P, Schwab SG, Williams NM, *et al.* Association analysis of *NOTCH4* loci in schizophrenia using family and population-based controls [Journal Article]. Nat Genet 2001; 28:126–128.

81 McGinnis RE, Fox H, Yates P, *et al.* Failure to confirm *NOTCH4* association with schizophrenia in a large population-based sample from Scotland. Nat Genet 2001; 28:128–129.

82 Fan JB, Tang JX, Gu NF, *et al.* A family-based and case–control association
• study of the *NOTCH4* gene and schizophrenia. Mol Psychiatry 2002; 7:100–103.
No association was observed between schizophrenia and *NOTCH4* SNPs in 544 Han Chinese cases and 621 controls, as well as an analysis of over 300 trios.

83 Imai K, Harada S, Kawanishi Y, *et al.* The (CTG)n polymorphism in the
• *NOTCH4* gene is not associated with schizophrenia in Japanese individuals. BMC Psychiatry 2001; 1:1.
No association was observed between schizophrenia and *NOTCH4* SNPs in 102 Japanese cases versus 100 controls.

84 Ujike H, Takehisa Y, Takaki M, *et al.* *NOTCH4* gene polymorphism and susceptibility to schizophrenia and schizoaffective disorder [Journal Article]. Neurosci Lett 2001; 301:41–44.

85 Schwab SG, Hallmayer J, Freimann J, *et al.* Investigation of linkage and
• association/linkage disequilibrium of *HLA A*-, *DQA1*-, *DQB1*-, and *DRB1*-alleles in 69 sib-pair- and 89 trio-families with schizophrenia. Am J Med Genet 2002; 114:315–320.
In 69 sib-pair families and 89 trios (mostly European, a few non-Ashkenazi Israelis), no significant association was observed between schizophrenia and *DQB1*, *DRB1*, *DQA1*, or *HLA-A* alleles or haplotypes, although this group continued to observe suggestive evidence of linkage ($P=0.0004$) peaking at *HLA-DQB/CAR* (6p21.2).

86 Matsumoto S, Sasaki T, Imamura A, *et al.* HLA class I distribution in
• Japanese patients with schizophrenia. Am J Med Genet 2002; 114:42–45.
No association was observed between schizophrenia and any of 45 class I HLA alleles (i.e. the lowest uncorrected *P* value was 0.01), in 98 Japanese cases versus 393 controls.

87 Li T, Underhill J, Liu XH, *et al.* Transmission disequilibrium analysis of HLA
• class II *DRB1*, *DQA1*, *DQB1* and *DPB1* polymorphisms in schizophrenia using family trios from a Han Chinese population. Schizophr Res 2001; 49:73–78.
In 165 Han Chinese proband–parent trios, no significant association of HLA *DRB1*, *DQA1*, *DQB* or *DPB* alleles or haplotypes was observed after correction for multiple tesing (the lowest global *P* value was 0.019).

88 Blaveri E, Kalsi G, Lawrence J, *et al.* Genetic association studies of
• schizophrenia using the 8p21–22 genes: prepronociceptin (*PNOC*), neuronal nicotinic cholinergic receptor alpha polypeptide 2 (*CHRNA2*) and arylamine *N*-acetyltransferase 1 (*NAT1*). Eur J Hum Genet 2001; 9:469–472.
No association with schizophrenia was observed for markers in three genes in the 8p21–22 region implicated by schizophrenia linkage studies.

89 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.

90 Freedman R, Adams CE, Adler LE, *et al.* Inhibitory neurophysiological deficit as a phenotype for genetic investigation of schizophrenia. Am J Med Genet 2000; 97:58–64.

91 Freedman R, Adams CE, Leonard S. The alpha7-nicotinic acetylcholine receptor and the pathology of hippocampal interneurons in schizophrenia. J Chem Neuroanat 2000; 20:299–306.

92 Freedman R, Leonard S, Gault JM, *et al.* Linkage disequilibrium for schizophrenia at the chromosome 15q13–14 locus of the alpha7-nicotinic acetylcholine receptor subunit gene (*CHRNA7*). Am J Med Genet 2001; 105:20–22.

93 Freedman R, Leonard S, Olincy A, *et al.* Evidence for the multigenic
•• inheritance of schizophrenia. Am J Med Genet 2001; 105:794–800.
The authors re-analysed all families from the NIMH Genetics Initiative schizophrenia project, combining European and African-American pedigrees (they had previously been separately analysed) and using a parametric analysis under a dominant transmission. Significant linkage was observed on chromosome 15q near the *CHRNA7* locus.

94 Liu CM, Hwu HG, Lin MW, *et al.* Suggestive evidence for linkage of • schizophrenia to markers at chromosome 15q13–14 in Taiwanese families. Am J Med Genet 2001; 105:658–661.
Suggestive evidence for linkage was observed to markers near *CHRNA7* ($P = 0.0003$ and 0.0008 under broad and narrow diagnostic models by NPL analysis) in 52 Taiwanese schizophrenia families.

95 Tsuang DW, Skol AD, Faraone SV, *et al.* Veterans Affairs Cooperative Study. • Examination of genetic linkage of chromosome 15 to schizophrenia in a large Veterans Affairs Cooperative Study sample. Am J Med Genet 2001; 105:662–668.
Modest evidence for linkage to markers near *CHRNA7* on chromosome 15q was observed in 166 schizophrenia families (216 affected sib-pairs), with a maximum NPL score of 1.65.

96 Gejman PV, Sanders AR, Badner JA, *et al.* Linkage analysis of schizophrenia • to chromosome 15. Am J Med Genet 2001; 105:789–793.
Modest evidence for linkage to markers near *CHRNA7* on chromosome 15q was observed in 68 schizophrenia families with a maximum lod score (Genehunter Plus) of 2.0.

97 Xu J, Pato MT, Torre CD, *et al.* Evidence for linkage disequilibrium between • the alpha 7-nicotinic receptor gene (*CHRNA7*) locus and schizophrenia in Azorean families. Am J Med Genet 2001; 105:669–674.
An association between *CHRNA7* and schizophrenia was observed in 31 families from the Azores, with $P = 0.0004$ for one marker. Differences related to paternally and maternally transmitted alleles were also observed. The small sample size limits the interpretation of these findings.

98 Meyer J, Ortega G, Schraut K, *et al.* Exclusion of the neuronal nicotinic • acetylcholine receptor alpha7 subunit gene as a candidate for catatonic schizophrenia in a large family supporting the chromosome 15q13–22 locus. Mol Psychiatry 2002; 7:220–223.
These authors had observed linkage between the region of 15q containing *CHRNA7* and an alternative phenotype (periodic catatonia), but assocation with markers in *CHRNA7* was not observed.

99 Arinami T, Ohtsuki T, Takase K, *et al.* Screening for 22q11 deletions in a • schizophrenia population. Schizophr Res 2001; 52:167–170.
Of 300 Japanese schizophrenia patients, one had a 22q11.2 (VCFS) deletion, with no obvious stigmata of VCFS.

100 De Luca A, Pasini A, Amati F, *et al.* Association study of a promoter • polymorphism of *UFD1L* gene with schizophrenia. Am J Med Genet 2001; 105:529–533.
In 88 patients and 92 controls from Italy, evidence for the association of schizophrenia with *UFD1L* was observed ($P = 0.009$ for the variant allele), with a modest confirmation ($P = 0.03$) in 38 proband–parent trios from Canada. This is an ubiquitin family gene in the VCFS deletion region.

101 Saito T, Guan F, Papolos DF, *et al.* Polymorphism in *SNAP29* gene promoter • region associated with schizophrenia. Mol Psychiatry 2001; 6:193–201.
A modest association ($P = 0.009$) was observed for *SNAP29* (a gene in the VCFS deletion region) and schizophrenia, but not bipolar disorder.

102 Takase K, Ohtsuki T, Migita O, *et al.* Association of *ZNF74* gene genotypes • with age-at-onset of schizophrenia. Schizophr Res 2001; 52:161–165.
Association ($P < 0.0001$) is reported here for age at onset of schizophrenia (but not schizophrenia) with SNPs in the *ZNF74* gene in 22q11.2 in the VCFS deletion region, in 300 Japanese cases versus 300 controls, and the finding was replicated in a second sample of 169 schizophrenia patients ($P = 0.0001$), making this one of the few findings replicated in samples this large.

103 Feinstein C, Eliez S, Blasey C, Reiss AL. Psychiatric disorders and • behavioral problems in children with velocardiofacial syndrome: usefulness as phenotypic indicators of schizophrenia risk. Biol Psychiatry 2002; 51:312–318.
The authors compared 28 children with VCFS with 29 children with comparable cognitive function, and found similar behavioral and psychiatric disorders. They suggest that the specificity of the association of schizophrenia with the VCFS deletion is unproved. However, they fail to account for the high rate of schizophrenia in adults with VCFS, certainly higher than in other groups with mild mental retardation.

104 Meyer J, Huberth A, Ortega G, *et al.* A missense mutation in a novel gene • encoding a putative cation channel is associated with catatonic schizophrenia in a large pedigree. Mol Psychiatry 2001; 6:302–306.
These authors had reported linkage of periodic catatonia (a phenotypic variant of schizophrenia) to chromosome 22q13. Here they report the co-segregation of a missense mutation in *WKL1* (22q13.33) with the disorder in one extended pedigree.

105 Devaney JM, Donarum EA, Brown KM, *et al.* No missense mutation of *WKL1* • in a subgroup of probands with schizophrenia. Mol Psychiatry 2002; 7:419–423.
A negative study of the association of schizophrenia with the *WKL1* gene on 22q13.33, a region where linkage had been reported to the periodic catatonia phenotype.

106 Jorgensen TH, Borglum AD, Mors O, *et al.* Search for common haplotypes • on chromosome 22q in patients with schizophrenia or bipolar disorder from the Faroe Islands. Am J Med Genet 2002; 114:245–252.
This is a report on progress towards finding shared haplotypes on chromosome 22q in schizophrenia cases from a population isolate. No missense mutations were found in *WKL1*, a gene in the region of interest in these families.

107 McQuillin A, Kalsi G, Moorey H, *et al.* A novel polymorphism in exon 11 of the *WKL1* gene, shows no association with schizophrenia. Eur J Hum Genet 2002; 10:491–494.

108 Gross J, Grimm O, Ortega G, *et al.* Mutational analysis of the neuronal • cadherin gene *CELSR1* and exclusion as a candidate for catatonic schizophrenia in a large family. Psychiatr Genet 2001; 11:197–200.
A negative association study in periodic catatonia (a phenotypic variant of schizophrenia) for a 22q13.3 gene.

109 Mimmack ML, Ryan M, Baba H, *et al.* Gene expression analysis in • schizophrenia: reproducible up-regulation of several members of the apolipoprotein L family located in a high-susceptibility locus for schizophrenia on chromosome 22. Proc Natl Acad Sci U S A 2002; 99:4680–4685.
This is an intriguing study. A custom-made microarray was used to screen brains of schizophrenia and control subjects for differences in expression. Upregulation was detected for *APOL1* (apolipoprotein L1) (2.6-fold), a finding that was then replicated in a second brain collection. *APOL2* and *APOL4* were then shown to be similarly upregulated in two brain collections. All of these loci are in 22q12, near but not in the VCFS region.

110 Tachikawa H, Harada S, Kawanishi Y, *et al.* Linked polymorphisms • ($-333G > T$ and $-286A > G$) in the promoter region of the *CCK-A* receptor gene may be associated with schizophrenia. Psychiatry Res 2001; 103:147–155.
Association is reported between schizophrenia and linked polymorphisms in the *CCKAR* promoter region.

111 Wang Z, Wassink T, Andreasen NC, Crowe RR. Possible association of a • cholecystokinin promoter variant to schizophrenia. Am J Med Genet 2002; 114:479–482.
Modest association ($P < 0.05$ in several tests) was reported between schizophrenia and a polymorphism in the *CCK* promoter region, in 85 cases versus 247 controls, and in 60 trios (from the same cases).

112 Hattori E, Yamada K, Toyota T, *et al.* Association studies of the CT repeat polymorphism in the 5′ upstream region of the cholecystokinin B receptor gene with panic disorder and schizophrenia in Japanese subjects. Am J Med Genet 2001; 105:779–782.

113 Yoshikawa T, Kikuchi M, Saito K, *et al.* Evidence for association of the myo- • inositol monophosphatase 2 (*IMPA2*) gene with schizophrenia in Japanese samples. Mol Psychiatry 2001; 6:202–210.
Association ($P = 0.031$–0.0001) was reported between schizophrenia and three SNPs in myo-inositol monophosphatase 2 (*IMPA2*, 18p11.2), in 302 Japanese schizophrenia cases versus 308 controls and 205 affective disorder cases.

114 Jun TY, Pae CU, Chae JH, *et al.* Polymorphism of *CTLA-4* gene at position • 49 of exon 1 may be associated with schizophrenia in the Korean population. Psychiatry Res 2002; 110:19–25.
CTLA4 (cytotoxic T-lymphocyte antigen-4, 2q33) was studied in 116 cases versus 149 controls from Korea, based on an immune hypothesis. Modest evidence for association was reported ($P = 0.003$ for alleles).

115 Ohtsuki T, Sakurai K, Dou H, *et al.* Mutation analysis of the NMDAR2B • (*GRIN2B*) gene in schizophrenia. Mol Psychiatry 2001; 6:211–216.
Although only modest evidence of association ($P = 0.004$ for homozygosity of linked SNPs) was reported between schizophrenia and *GRIN2B* (12p12), the NMDA receptor 2B, the sample size of 268 Japanese cases and 337 controls makes the study of some interest in generating hypotheses.

116 Maes M, Delanghe J, Bocchio Chiavetto L, *et al.* Haptoglobin polymorphism • and schizophrenia: genetic variation on chromosome 16. Psychiatry Res 2001; 104:1–9.
Modest association is reported between schizophrenia and Hp (haptoglobin, 16q22.1), in 98 schizophrenia cases compared with established genotype and plasma level distributions in this northern Italian population. The authors present a brief but useful summary of evidence for involvement in the inflammatory system in schizophrenia; Hp is one of the acute phase inflammatory reaction proteins.

117 Hong CJ, Tsai SJ, Wang YC. Association between tryptophan hydroxylase • gene polymorphism (*A218C*) and schizophrenic disorders. Schizophr Res 2001; 49:59–63.
Association between schizophrenia and the *A218C* polymorphism in *TPH* (tryptophan hydroxylase, 11p14–p15.3) was observed ($P = 0.002$) in 196 Han Chinese cases versus 251 controls. This is the rate-limiting enzyme for serotonin biosynthesis.

118 Chen CH, Hung CC, Wei FC, Koong FJ. Debrisoquine 4-hydroxylase (*CYP2D6*) genetic polymorphisms and susceptibility to schizophrenia in Chinese patients from Taiwan. Psychiatr Genet 2001; 11:153–155.

119 Chiu HJ, Wang YC, Chen JY, *et al.* Association study of the p53-gene Pro72Arg polymorphism in schizophrenia. Psychiatry Res 2001; 105:279–283.

120 Chowdari KV, Brandstaetter B, Semwal P, *et al.* Association studies of cytosolic phospholipase A2 polymorphisms and schizophrenia among two independent family-based samples. Psychiatr Genet 2001; 11:207–212.

121 Ishiguro H, Ohtsuki T, Okubo Y, *et al.* Association analysis of the pituitary adenyl cyclase activating peptide gene (*PACAP*) on chromosome 18p11 with schizophrenia and bipolar disorders. J Neural Transm – Gen Sect 2001; 108:849–854.

122 Ishiguro H, Okubo Y, Ohtsuki T, *et al.* Mutation analysis of the retinoid X receptor beta, nuclear-related receptor 1, and peroxisome proliferator-activated receptor alpha genes in schizophrenia and alcohol dependence: possible haplotype association of nuclear-related receptor 1 gene to alcohol dependence. Am J Med Genet 2002; 114:15–23.

123 Jun TY, Pae CU, Chae JH, *et al.* Report on IL-10 gene polymorphism at position 819 for major depression and schizophrenia in Korean population. Psychiatr Clin Neurosci 2002; 56:177–180.

124 Chiavetto LB, Boin F, Zanardini R, *et al.* Association between promoter polymorphic haplotypes of interleukin-10 gene and schizophrenia. Biol Psychiatry 2002; 51:480–484.

125 Kunugi H, Kato T, Fukuda R, *et al.* Association study of *C825T* polymorphism of the G-protein b3 subunit gene with schizophrenia and mood disorders. J Neural Transm – Gen Sect 2002; 109:213–218.

126 Lee K, Kunugi H, Nanko S. Glial cell line-derived neurotrophic factor (*GDNF*) gene and schizophrenia: polymorphism screening and association analysis. Psychiatr Res 2001; 104:11–17.

127 Leroy S, Griffon N, Bourdel MC, *et al.* Schizophrenia and the cannabinoid receptor type 1 (*CB1*): association study using a single-base polymorphism in coding exon 1. Am J Med Genet 2001; 105:749–752.

128 Matsumoto C, Ohmori O, Hori H, *et al.* Analysis of association between the Gln192Arg polymorphism of the paraoxonase gene and schizophrenia in humans. Neurosci Lett 2002; 321:165–168.

129 Ouyang WC, Wang YC, Hong CJ, Tsai SJ. Estrogen receptor alpha gene polymorphism in schizophrenia: frequency, age at onset, symptomatology and prognosis. Psychiatr Genet 2001; 11:95–98.

130 Ventriglia M, Bocchio Chiavetto L, Bonvicini C, *et al.* Allelic variation in the human prodynorphin gene promoter and schizophrenia. Neuropsychobiology 2002; 46:17–21.

131 Segman RH, Shapira Y, Modai I, *et al.* Angiotensin converting enzyme gene insertion/deletion polymorphism: case–control association studies in schizophrenia, major affective disorder, and tardive dyskinesia and a family-based association study in schizophrenia. Am J Med Genet 2002; 114:310–314.

132 Zhang B, Tan Z, Zhang C, *et al.* Polymorphisms of chromogranin B gene associated with schizophrenia in Chinese Han population. Neurosci Lett 2002; 323:229–233.

133 Hattori M, Kunugi H, Akahane A, *et al.* Novel polymorphisms in the promoter region of the neurotrophin-3 gene and their associations with schizophrenia. Am J Med Genet 2002; 114:304–309.

134 Leszczynska-Rodziewicz A, Czerski PM, Kapelski P, *et al.* A polymorphism of the norepinephrine transporter gene in bipolar disorder and schizophrenia: lack of association. Neuropsychobiology 2002; 45:182–185.

135 Feng J, Zheng J, Gelernter J, *et al.* An in-frame deletion in the alpha (2C) adrenergic receptor is common in African-Americans. Mol Psychiatry 2001; 6:168–172.

136 Frieboes RM, Moises HW, Gattaz WF, *et al.* Lack of association between schizophrenia and the phospholipase-A(2) genes *cPLA2* and *sPLA2*. Am J Med Genet 2001; 105:246–249.

137 Tuulio-Henriksson A, Haukka J, Partonen T, *et al.* Heritability and number of • quantitative trait loci of neurocognitive functions in families with schizophrenia. Am J Med Genet 2002; 114:483–490.
Based on data from 264 schizophrenia patients and their relatives from a genetically isolated region in Finland, the authors suggest that measures of working memory show strong heritability, perhaps as a result of a very small number of genetic loci, and could be used for mapping studies.

138 Cosway R, Byrne M, Clafferty R, *et al.* Neuropsychological change in young people at high risk for schizophrenia: results from the first two neuropsychological assessments of the Edinburgh High Risk Study. Psychol Med 2000; 30:1111–1121.

139 Cosway R, Byrne M, Clafferty R, *et al.* Sustained attention in young people at • high risk for schizophrenia. Psychol Med 2002; 32:277–286.
Measures of attention were not found to differentiate significantly between the relatives of schizophrenia and control subjects.

140 Steel RM, Whalley HC, Miller P, *et al.* Structural MRI of the brain in • presumed carriers of genes for schizophrenia, their affected and unaffected siblings. J Neurol, Neurosurg Psychiatry 2002; 72:455–458.
Based on a unique set of analyses of 'obligate carriers' (well individuals who are siblings of a schizophrenia patient and who also have a schizophrenic offspring), a reduced volume of the amygdalohippocampal complex is suggested to be a specific correlate of genetic risk.

141 Narr KL, Cannon TD, Woods RP, *et al.* Genetic contributions to altered • callosal morphology in schizophrenia. J Neurosci 2002; 22:3720–3729.
An upward bowing of the corpus callosum was suggested to be a neuroanatomical marker for vulnerability to schizophrenia in the co-twins of cases.

142 Egan MF, Hyde TM, Bonomo JB, *et al.* Relative risk of neurological signs in • siblings of patients with schizophrenia. Am J Psychiatry 2001; 158:1827–1834.
Neurological signs were found to be increased in the relatives of schizophrenia patients, but the low relative risk suggested that these signs might be poor markers for genetic studies.

143 Scutt LE, Chow EW, Weksberg R, *et al.* Patterns of dysmorphic features in schizophrenia. Am J Med Genet 2001; 105:713–723.

144 Cardno AG, Sham PC, Farmer AE, *et al.* Heritability of Schneider's first-rank • symptoms. Br J Psychiatry 2002; 180:35–38.
First-rank psychotic symptoms were shown to be heritable in twins, although less so than the categorical diagnosis of schizophrenia.

145 Cardno AG, Rijsdijk FV, Sham PC, *et al.* A twin study of genetic relationships • between psychotic symptoms [see Comments]. Am J Psychiatry 2002; 159:539–545.
Using the Maudsley twin series, the authors suggest that if schizophrenic, manic and depressive syndromes are assigned non-hierarchically, they show substantial overlap in their genetic etiology. See comment by Kendler [146•].

146 Kendler KS. Hierarchy and heritability: the role of diagnosis and modeling in • psychiatric genetics. Am J Psychiatry 2002; 159:515–518.
Commenting on Cardno *et al.* [144•], the author points out that their data are more consistent with genetic factors influencing mood syndromes in individuals with schizophrenia, rather than for genetic overlap in the etiology of schizophrenia and bipolar disorder.

147 Brown AS, Schaefer CA, Wyatt RJ, *et al.* Paternal age and risk of •• schizophrenia in adult offspring. Am J Psychiatry 2002; 159:1528–1533.
Using a birth cohort from which individuals with schizophrenia spectrum disorders had previously been ascertained, the authors demonstrate a small but significant relationship between advancing paternal age and the risk of these disorders, after controlling for confounding variables such as maternal age. This suggests the possibility of de-novo genetic mutations in older fathers as factors in schizophrenia.

148 Malaspina D, Corcoran C, Fahim C, *et al.* Paternal age and sporadic • schizophrenia: evidence for de novo mutations. Am J Med Genet 2002; 114:299–303.
Schizophrenia patients without a family history had significantly older fathers than those with a family history, supporting the hypothesis of de-novo genetic mutations in older fathers.

149 Malaspina D. Paternal factors and schizophrenia risk: de novo mutations and • imprinting. Schizophr Bull 2001; 27:379–393.
The author reviews neurodevelopmental disorders previously associated with de-novo germline mutations in older fathers, and discusses mechanisms by which this effect can occur, relating it to data for schizophrenia.

150 Lewis DA, Levitt P. Schizophrenia as a disorder of neurodevelopment •• [Review]. [118 refs] Annu Rev Neuroscience 2002; 25:409–432.
This is a comprehensive review of evidence favoring a neurodevelopmental etiology ('pathogenetic biological events are present much earlier in life than the onset of the features of the illness', p. 411). Evidence for such influences are reviewed by time period (prenatal, perinatal, childhood and adolescence). Emphasis is placed on the strength of evidence for a relationship between schizophrenia and complications during labor and delivery, and the presence of subtle behaviors that predate active illness by many years. A polygenic-multifactorial model is favored whereby genetic predisposition which alters development, gene–environment interactions that influence or trigger the genetic effects, and cumulative effects over time of the altered development, leading to a comparably stable state that is relatively difficult to alter.

151 Maynard TM, Sikich L, Lieberman JA, LaMantia AS. Neural development, • cell–cell signaling, and the two-hit hypothesis of schizophrenia. Schizophr Bull 2001; 273:457–476
These authors argue for a 'two-hit' hypothesis of schizophrenia whereby genetic or environmental factors alter early development, and then a second factor closer to the time of onset triggers the actual disease.

152 Schiffman J, Ekstrom M, LaBrie J, *et al.* Minor physical anomalies and •• schizophrenia spectrum disorders: a prospective investigation. Am J Psychiatry 2002; 159:238–243.
In this unique study, 265 children from a 1959–1961 Danish birth cohort (90 with a parent with schizophrenia, 93 with a parent with some other psychiatric disorder, and 82 with no record of a psychiatrically ill parent) had been rated for minor physical anomalies at 11–13 years of age. Psychiatric diagnosis was then determined at 31–33 years by direct interview or records. Of 131 children with three or more anomalies, 20 (15.3%) developed a schizophrenia spectrum disorder, compared with six out of 111 children with two or fewer anomalies (5.4%) ($P<0.01$). For the high-risk group the proportions were 12 out of 39 (30.1%) versus five out of 42 (11.9%) ($P<0.04$). These are striking results suggesting early, physical-developmental effects of genetic factors, although the high rate of schizophrenia spectrum disorders in this study population is a bit surprising.

153 Bassett AS, Chow EW, O'Neill S, Brzustowicz LM. Genetic insights into the • neurodevelopmental hypothesis of schizophrenia. Schizophr Bull 2001; 27:417–430.
This article provides a useful review of neurodevelopmental research in schizophrenia from a group that has focused on the study of classic genetic features such as physical anomalies and the VCFS syndrome.

154 DeLisi LE. Speech disorder in schizophrenia: review of the literature and • exploration of its relation to the uniquely human capacity for language. Schizophr Bull 2001; 27:481–496.
Based on data from a study of structured ratings of elements of language in free-form speech, the author proposes that the pathology of schizophrenia may be related to genes underlying uniquely human characteristics of language.

155 Judson R, Salisbury B, Schneider J, *et al.* How many SNPs does a genome-wide haplotype map require? Pharmacogenomics 2002; 3:379–391.

156 Gabriel SB, Schaffner SF, Nguyen H, *et al.* The structure of haplotype blocks in the human genome. Science 2002; 296:2225–2229.

157 Daly MJ, Rioux JD, Schaffner SF, *et al.* High-resolution haplotype structure in the human genome. Nat Genet 2001; 29:229–232.

158 Bouchie A. Haplotype map planned. Nat Biotechnol 2001; 19:704.

159 Weiss KM, Terwilliger JD. How many diseases does it take to map a gene with SNPs? Nat Genet 2000; 26:151–157.

160 Faham M, Baharloo S, Tomitaka S, *et al.* Mismatch repair detection (MRD): high-throughput scanning for DNA variations. Hum Mol Genet 2001; 10:1657–1664.

161 Conrad P. Genetic optimism: framing genes and mental illness in the news. • Cult Med Psychiatry 2001; 25:225–247.
The author analyzes news reports about psychiatric genetics findings and critiques the 'genetic optimism' that emphasizes the inevitability of discovering genes and the good outcomes of those discoveries, whereas negative or retracted findings receive no attention. Scientific colleagues in genetics and other fields are prone to similar distortions, as discussed in the present article.