Molecular genetics of schizophrenia: a review of the recent literature
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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


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

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 [5••,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.
### Table 1. Stages of positional cloning studies

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical sample</th>
<th>Molecular strategy</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Genome scan</td>
<td>Multiply affected pedigrees</td>
<td>Genotype microsatellite DNA markers at 5,000,000–10,000,000 bp (5–10 cM spacing, or denser SNP markers)</td>
<td>Evidence for linkage in 10–30 cM candidate region(s)</td>
</tr>
<tr>
<td>Fine-mapping</td>
<td>Multiply affected pedigrees</td>
<td>Genotype microsatellite markers in candidate regions at 1–2 cM spacing (or denser SNPs)</td>
<td>Evidence for linkage in 2–10 cM candidate region(s)</td>
</tr>
<tr>
<td>LD mapping</td>
<td>Cases versus controls or case–parent trios</td>
<td>Genotype markers (primarily SNPs) at 10,000–50,000 bp (10–50 kb) spacing</td>
<td>Evidence for association of small sets of adjacent markers with disease, implicating one or two specific genes Plausible evidence that the gene plays a role in disease susceptibility; detection of other interacting genes and proteins</td>
</tr>
<tr>
<td>Functional genomics</td>
<td>Animal models (e.g. ‘knockout’ mice), cases, postmortem tissue</td>
<td>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</td>
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</table>

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).

Gurve 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 Quebecois 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 Waterworth 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 \( P < 0.001 \) 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

<table>
<thead>
<tr>
<th>Gene(s)</th>
<th>Location</th>
<th>Study population(s)</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Neuregulin 1 (NRG1) [10••]</td>
<td>8p12-21</td>
<td>Icelandic. Linkage: 33 pedigrees. Association: 478 cases versus 394 controls</td>
<td>NRG1 lies outside the 8p region where positive linkage evidence has been reported, and might not explain those reports. 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. Association was observed in early-onset cases. Sample sizes were small and P values were modest (&lt; 0.001), but positive evidence was observed in three samples.</td>
</tr>
<tr>
<td>Proline dehydrogenase (PRODH2)</td>
<td>22q11</td>
<td>107 US triads (adult schizophrenia); 29 US childhood schizophrenia triads; 75 Afrikaner cases and 109 controls</td>
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<tr>
<td>G72 (o-amino acid oxidase; DAAO)</td>
<td>13q34 (12q24)</td>
<td>213 French Canadian cases and 241 controls; 183 Russian cases and 183 controls</td>
<td>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.</td>
</tr>
<tr>
<td>Catechol-O-methyltransferase (COMT) [14••]</td>
<td>22q11</td>
<td>Ashkenazi. Association: 714–724 cases and 2849–4899 controls</td>
<td>COMT is in the VCFS deletion region. It degrades catecholamines including dopamine.</td>
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</tbody>
</table>

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 mitochondrial 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 (HTRA1, 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 (SLC6A4, formerly 5HTT, 17q11.1-q12) [61], and a very modest replication (P = 0.043) was reported in the same population [62*]. Negative studies of 5HTTR1B (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 GRM4 (metabotropic 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, 2q22.11) [69*] and GRM2 (metabotropic glutamate receptor 2, 3p12–p11) [70*].

Chromosome 1q
Significant linkage was reported on chromosome 1q21–q22 (≈158 MB from pter on chromosome 1) in a ‘Celtic’ Canadian sample [24]; and suggestive linkage was reported on 1q21–q23 (≈165 MB) in Icelandic and British pedigrees [55*], on 1q41–q42 (≈208 MB) in families from a genetic isolate in Finland [55*,32], and on 1q42.1 (≈230 MB) in a Finnish general population affected sib-pair sample [55*,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]. TheDisc1 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 KCN3 (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 D7NBP1 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 NAIT) [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*,94]. 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 [99*]. 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 UFIDIL (ubiquitin fusion degradation 1-like) in two small samples [100*], and SNAP29 (synaptosomal-associated protein, 29,000 M,) [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, 22q13.33) [108*]. Finally, Minnack 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 \([114\textsuperscript{*}}\). Similarly, 268 Japanese cases showed increased homozygosity at linked SNPs in GRIN2B (the NMDA-2B receptor, 12p12) versus 337 controls \((P = 0.004)\) \([115\textsuperscript{*}}\). Maes \textit{et al.} \([116\textsuperscript{*}}\) 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 \textit{et al.} \([117\textsuperscript{*}}\) 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 \([137\textsuperscript{*}}\). 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 \([139\textsuperscript{*}}\).

**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) \([140\textsuperscript{*}}\). 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 \([141\textsuperscript{*}}\).

**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 \([142\textsuperscript{*}}\). 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 \textit{et al.} \([144\textsuperscript{*}}\) 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 \([145\textsuperscript{*}}\). Kendler \([146\textsuperscript{*}}\), 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 \([147\textsuperscript{*}}\). In another study \([148\textsuperscript{*}}\), schizophrenia patients without a known family history of schizophrenia had significantly older fathers than those with a family history. Malaspina \([149\textsuperscript{*}}\) 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 \([149\textsuperscript{*}}\).

**Neurodevelopmental hypotheses**

Lewis and Levitt \([150\textsuperscript{*}}\) 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 \textit{et al.} \([151\textsuperscript{*}}\) proposed a two-hit model requiring genetic or early environmental predisposing factors plus triggering factors closer to onset. Schiffman \textit{et al.} \([152\textsuperscript{*}}\) 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 \([153\textsuperscript{*}}\) reviewed evidence for neurodevelopmental hypotheses, focusing on physical anomalies and the implications of syndromes such as VCFS. DeLisi \([154\textsuperscript{*}}\) 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, G72DAAO 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 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

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 5p21–31, 6p22–21 and 10p15–11.

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 chromosome 2, with a smaller peak on chromosome 22q12.

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 3q34.

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, Brynjolfsson 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.
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, 11q23.3–q24 and 20q12.1–11.23.

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.

A genome scan was performed on 30 US European and African-American pedigrees with 62 schizophrenia cases, 36 other psychoses and 23 spectrum personality disorders, using a 10 cm map and NPL analysis.


13. Chumakov I, Blumenfeld M, Guerra Sarapenko O, et al. Genetic and physiological data implicating the new human gene G72 and the gene for dihydroxyacetone kinase in brains from schizophrenia subjects in an candidate region (6p22) supported by several studies in diverse populations, these authors summarize evidence that it may play a role in signal transduction including in the NMDA and G-protein coupled systems. This locus will receive intensive study in schizophrenia samples in the coming years.


example of a polymorphism that directly influences this physiology through its effects on dopaminergic transmission.

Part of the polymorphism candidate (focused on candidate regions) for 19 Quebecois 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 19q.


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.


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.


No association was observed between schizophrenia and the val/158met polymorphism in COMT in 108 Chinese cases and 118 controls, although a modest association (P = 0.009) was reported.


One of the negative association studies for older polymorphisms in COMT, in a small multiplex family sample, using family-based association and NPL analyses.


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.


A modest association (P = 0.02-0.05) is reported by schizophrenia and two polymorphisms in DRD2 (dopamine receptor 2; 1q22-23) 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.


In 263 Spanish cases versus 278 controls, an association at P = 0.036 was observed at DRD2, but not at five other loci (DRD3, SHTR2A, NT-3, BDNF or CNTF).


No association was observed between schizophrenia and two polymorphisms in DRD2 in 241 Japanese cases versus 201 controls.

Rybakowski JK, Borkowska A, Czerski PM, Hauser J. Dopamine D3 receptor gene (DRD3) 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.


No association was observed between schizophrenia and polymorphisms in alternative promoter and 5'UTRs of DRD3, and the finding of excess homozygosity of DRD3 (dopamine receptor 3, 3q13.3) in schizophrenia (previously reported by this and other groups) was not observed.


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).


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.


A useful review of the evidence supporting a role for glutamatergic mechanisms in schizophrenia.

A modest association (P = 0.0105) was reported between schizophrenia and a ser310ala polymorphism in GRK3 (ionotropic glutamate receptor kainate 3, 1p34-35) in 99 Italian cases and 116 controls.


An association observed between schizophrenia and GRM3 (metabotropic 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 tinos (German).


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.


No association was observed between schizophrenia and GRKI (ionotropic glutamate receptor kainate 1, 21022.11) using three new and three previously described SNPs in approximately 200 Japanese cases and controls per analysis.


No association was observed between schizophrenia and GRM2 (metabotropic glutamate receptor 2, 3p12-p11) in 213 Japanese cases and 220 controls.


Two plausible candidate genes for schizophrenia were discovered 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.


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.


This paper describes the possible schizophrenia candidate genes in the breakpoint region on chromosome 11, for the 11 breakpoint described in this group’s papers on the 1q breakpoint region. No association data for schizophrenia are presented.


Linkage was not observed on proximal chromosome 1q in 21 large French pedigrees.


No association was observed between schizophrenia and a CAG repeat in KCNN3 (1q21.2) in 112 Japanese cases and 102 controls.


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).


In 84 patients versus 130 controls, modest association (P = 0.0024) was 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.


In 69 sib-pair families and 89 trios (mostly European, a few non-Ashkenazi Israelis), no significant association was observed between schizophrenia and DQA1, DQB1, DQA1, or HLA-A alleles or haplotypes, although this group continued to observe suggestive evidence of linkage (P = 0.0004) peaking at HLA-DQA1 (6p21.2).


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 99 controls.

87 Li T, Underhill J, Liu XH, et al. Transmission disequilibrium analysis of HLA class II DRB1, DQA1, DQB1 and DRB1 alleles 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, DQB1 or DRB1 haplotypes was observed after correction for multiple testing (the lowest global P value was 0.019).


No association with schizophrenia was observed for markers in three genes in the 8p21-22 region implicated by schizophrenia linkage studies.


No associated was observed 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.


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 CHRN7A locus.
A negative study of the association of schizophrenia with the WKL| gene on phenotype. 22q13.33, a region where linkage had been reported to the periodic catatonia pedigree. missense mutation in WKL| (22q13.33) with the disorder in one extended schizophrenia) to chromosome 22q13. Here they report the co-segregation of a ‘encoding a pulative cation channel is associated with catatonic schizophrenia. 105 Devaney JM, Donarum EA, Brown KM, et al. No missense mutation of WKL| in a subgroup of probands with schizophrenia. Mol Psychiatry 2002; 7:419-423.

Modest evidence for linkage to markers near CHRNA7 on chromosome 15 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.

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. 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 a large family supporting the chromosome 15q13-23 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 association 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 stigma of VCFS.

100 De Luca A, Passini A, Amati F, et al. Association study of a promoter polymorphism of UFD1L gene with schizophrenia. Am J Med Genet 2001; 102:252-255. 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 intriguing study. A custom-made microarray was used to screen brains 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.

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, Migitia O, et al. Association of ZNF74 gene genotypes with age-at-onset of schizophrenia. Schizophr Res 2001; 52:161-165. Association (P=0.011) 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, Blassey 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 20 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.


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.


Based on a unique set of analyses of ‘obligate carriers’ (well individuals who are relatives of schizophrenia patient and who also have a schizophrenic offspring), a reduced volume of the amygdala/prefrontal cortex is suggested to be a specific correlate of genetic risk.


An upward bowing of the corpus callosum was suggested to be a neuronato-
mical marker for vulnerability to schizophrenia in the co-twins of cases.


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.


Using the data for schizophrenia, manic and depressive syndromes were shown to be heritable in twins, although less so than the categorical diagnosis of schizophrenia.


Using the 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].


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.


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.


The author reviews neurodevelopmental disorders previously associated with de-novo gene mutations in older fathers, and discusses mechanisms by which this effect can occur, relating it to data for schizophrenia.


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 (perinatal, 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.


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.
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.

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.

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.


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.