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Review Article

Localization of genes modulating the predisposition to schizophrenia: a revision

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Abstract

The genetics of schizophrenia or bipolar affective disorder has advanced greatly at the molecular level since the introduction of probes for the localization of specific genes. Research on gene candidates for susceptibility to schizophrenia can broadly be divided into two types, i.e., linkage studies, where a gene is found near a specific DNA marker on a specific chromosome, and association studies, when a condition is associated with a specific allele of a specific gene. This review covers a decade of publications in this area, from the 1988 works of Bassett *et al.* and Sherrington *et al.* on a gene localized on the long arm of chromosome 5 at the 5q11-13 loci, to the 1997 work of Lin *et al.* pointing to the 13q14.1-q32 loci of chromosome 13 and to the 1998 work of Wright *et al.* on an HLA DRB1 gene locus on chromosome 6 at 6p21-3. The most replicated loci were those in the long arm of chromosome 22 (22q12-q13.1) and on the short arm of chromosome 6 (6p24-22). In this critical review of the molecular genetic studies involved in the localization of genes which modulate the predisposition to schizophrenia the high variability in the results obtained by different workers suggests that multiple loci are involved in the predisposition to this illness.

REVIEW

The genetics of schizophrenia and bipolar affective disorder has advanced greatly at the molecular level since the introduction of probes for the localization of specific genes (Botstein *et al*., 1980). Molecular biology has also been used to localize the genes involved in, among others, conditions such as Huntington's chorea (chromosome 4), Friedreich's ataxia (chromosome 9), cystic fibrosis (chromosome 7) and Alzheimer's syndrome (chromosome 21). Everything indicates that the psychoses and Alzheimer's syndrome are conditions which are precipitated by both environmental and genetic factors. In the specific case of schizophrenia, it is believed that as well as environmental factors many genes (polygenes), distributed on different loci, influence predisposition to the condition, and it appears reasonable to suppose that "the determinants of schizophrenia are multifactorial and polygenic" (Frota-Pessoa, 1989).

The molecular level studies on candidate genes exercising some role on susceptibility to schizophrenia can broadly be divided into two types, i.e., linkage studies, where a gene is found near a specific DNA marker on a specific chromosome, and association studies, when an illness is associated with a specific allele of a specific gene.

To gauge whether or not evidence of linkage is statistically significant "lod score" (i.e., the logarithm of the "odds score") values have always to be higher than 3 in pedigrees affected with schizophrenia.

The localization of genes influencing the predisposition to schizophrenia opens great possibilities for the study of the pathogenesis of this psychosis. In the effort to find the genetic basis of schizophrenia many genetic loci have been proposed involving many chromosomes (Table I).

Starting with the work of Sherrington *et al*. (1988), it was proposed that a gene localized on the long arm of chromosome 5 determined the predisposition to schizophrenia. That is, these authors discovered a locus (5q11-13) occupied by alleles (i.e., modulations of a gene determining opposing traits) which in some families interferred with susceptibility to schizophrenia. These findings, however, along with those of Bassett *et al*. (1988), were not confirmed by other workers (e.g., Hallmayer *et al.*, 1992; Macciardi *et al*., 1992; Gurling, 1994), with new evidence suggesting a "schizophrenia locus" (D5S111, 5p14.1-13.1) on the short arm of chromosome 5 (Silverman *et al.*, 1996).

More recently, loci involved in susceptibility to schizophrenia have also been described on chromosome 22 (Pulver *et al.*, 1994a,b; Moises *et al.*, 1995a; Schwab *et al.*, 1995b and Gill *et al.*, 1996) and chromosome 6 (6p24-22) delimited by the markers D6S296, D6S285, D6S274, D6S260 and D6S259 (Straub *et al.*, 1995; Schwab *et al.*, 1995a, Moises *et al.*, 1995b; Wang *et al.*, 1995, 1996), as well as new additional regions on chromosomes 9 and 20 (Moises *et al.*, 1995b) and 3 and 8 (Pulver *et al*., 1995). In a study of linkage, using 15 markers covering 30 centimorgans of the 8p22-21 region of chromosome 8p, Kendler *et al*. (1996) suggested that there might be a locus of vulnerability to schizophrenia on this chromosome. Riley *et al.* (1997) proposed a locus on chromosome 9 (9q34.3),

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Table I - Proposes and localization of genes modulating the predisposition to schizophrenia.

Author(s)	Proposed loci
Sherrington *et al.* (1988)	Long arm of chromosome 5 at 5q11-13
Crow (1988); Crow *et al.* (1989); DeLisi and Crow (1989)	Pseudoautosomic locus of the X-Y chromosomes
Pulver *et al.* (1994a); Moises *et al.* (1995a); Schwab *et al.* (1995a); Vallada *et al.* (1995); Gill *et al.* (1996); Deckert *et al.* (1997)	Long arm of chromosome 22 at 22q12-q13.1, loci D22S278, D22S304, D22S283
Straub *et al.* (1995); Schwab *et al.* (1995b); Moises *et al.* (1995b); Wang *et al.* (1995, 1996); Pujana *et al.* (1997)	Short arm of chromosome 6 at 6p24-22, loci D6S296, D6S274, D6S285, D6S260
Riley *et al.* (1997)	Chromosome 9 at 9q34.3
Moises *et al.* (1995b)	Proposed additional new regions on chromosomes 9 and 20
Kendler *et al.* (1996)	Locus of vulnerability on chromosome 8p
Pulver *et al.* (1995)	Chromosomes 3 and 8 (3p and 8p) as "potential loci"
Mulcrone *et al.* (1995)	Long arm of chromosome 11, the gene for the D_2 dopamine receptor
Williams *et al.* (1996)	Proposed an association between schizophrenia and T102C polymorphism in the gene for the type 2a serotonin receptor on the long arm of chromosome13
Lin *et al.* (1997)	Chromosome 13 at 13q14.1-q32
Gelernter *et al.* (1995)	Proposed linkage studies with the SLC6A4 locus of the gene for serotonin transporter protein on chromosome 17 at 17q12, and the D17S73 and D17S58 markers
Schwab *et al.* (1998)	Chromosome 18 at 18p
Crocq *et al.* (1992); Mant *et al.* (1994); Griffon *et al.* (1996)	Chromosome 3 at q13.3, the gene for human D_3 dopamine receptor
Silverman *et al.* (1996)	Short arm of chromosome 5 at 5p14.1-13.1, locus D5S111
Shaw *et al.* (1998)	Chromosomes 1, 2, 4, 11, 13
Wright *et al.* (1996, 1998)	HLA DRB1 gene locus on chromosome 6 at 6p21.3

corresponding to the gene for the N-methyl-D-aspartate receptor subunit. Consequently there is in the literature a tendency to admit a heterogeneity of loci (Moises *et al.*, 1995b; Straub *et al.*, 1995; Wang *et al.*, 1995), with Risch (1990) suggesting a group of interacting loci in a "multilocus model". Citing many papers in support, Baron (1996) found "negative or ambiguous results" for a locus predisposing to schizophrenia on chromosome 6 (6p24-22) (Diehl *et al.*, 1994; Mowry *et al.*, 1995; Gurling *et al.*, 1995; Antonarakis *et al.*, 1995; Riley *et al.*, 1995; Sasaki *et al.*, 1995; Moises *et al.*, 1995b), but more recent work (Wang *et al*., 1996) presents evidence of linkage disequilibrium between schizophrenia and the SCA 1 CAG repeat on chromosome 6p23 (SCA1 = gene for spinocerebellar ataxia type 1). SCA1 may be of relevance to the etiology of schizophrenia, because anticipation occurs in this disease, because mutations occur via CAG repeat expansion, and also because of this gene's map location.

The pseudoautosomal locus which occupies a distal point on the short arms of the sex chromosomes and which is subject to XY recombination (the swapping of material between chromosomes during meiosis) has been proposed as a region genetically implicated in schizophrenia (Crow, 1988; Crow *et al.*, 1989; DeLisi and Crow, 1989). Crow and colleagues based their results on finding aneuploid sex chromosomes (XXY, XYY and XXX) in schizophrenic patients and paternally inherited sexual concordance between schizophrenic sibling pairs. Similar results have been reported by Collinge *et al.* (1991), Gorwood *et al.* (1992) and D'Amato *et al.* (1992, 1994). The link between schizophrenic loci and the pseudoautosomal X-Y chromosome locus has not been confirmed because of difficulties in replicating the previous published data (Asherson *et al.*, 1992; Wang *et al.*, 1993; Barr *et al.*, 1993; Curtis *et al.*, 1993; Ishida *et al.*, 1993; Wildenauer *et al.*, 1993) and methodological uncertainties (Curtis and Gurling, 1990). Even so, it is important to emphasize that, in the work cited above, Collinge *et al*. (1991) tested Crow's hypothesis using marker DNA for the telomeric pseudoautosomal locus, DXYS14, and concluded that, as expected, schizophrenic sibling pairs shared alleles on the DXYS14 locus, supporting the existence of a genetic link between DXYS14 and schizophrenia - result confirmed by D'Amato *et al.* (1992, 1994). Nevertheless, due to the difficulties in replicating their previous experiments, Crow and colleagues revised their hypothesis and proposed a link with pericentromeric markers on the X-chromosome near the proximal pseudoautosomal limit (Crow *et al.*, 1994; DeLisi *et al.*, 1994a), which, while not supporting the hypothesis of the existence of locus for schizophrenia or schizoaffective disorder, "did not definitively exclude it" (Crow *et al.*, 1994), reporting that their results were consistent with the presence of a gene predisposing to schizophrenia in "sex-specific regions" of the X- and Y-chromosomes. These findings were criticized in the detailed review by Baron (1995).

Okoro *et al.* (1995) did not find any experimental evidence for a link between the X-chromosome marker DXS7 and a schizophrenia locus, while Barr *et al.* (1994) also found

no evidence in favor of a link between a locus predisposing to schizophrenia and the pseudoautosomal region. Even so, DeLisi *et al*. (l994b) included in their revision two group studies on samples of Swedish and American families reporting data suggesting that the frequency of XXX and XXY aneuploid sex-chromosomes was higher in populations of patients with schizophrenia, claiming that too few had survived to determine if an association also existed in respect to XYY chromosomes. These authors also concluded that this was consistent with a sex-chromosome gene influencing the development of schizophrenia and that a sex-chromosome locus is compatible with autosomic transmission if the gene was either pseudoautosomal (i.e., inside the recombination (exchange) region) or X-Y homologous (i.e., present in a similar form on both the X and Y chromosomes, with no recombination). The hypothesis of a "psychosis continuum" between schizophrenia and bipolar affective disorder defended by Crow (1988) led to work such as that done by Yoneda *et al*. (1992), who reported an association between bipolar affective disorder and a pseudoautosomal DNA marker (pseudoautosomal locus DXYS20), although the difference between patients and controls was not very significant and was not confirmed by other authors (Parsian and Todd, 1994). Straub *et al*. (1994) present strong evidence for a vulnerability locus for bipolar affective disorder on chromosome 21 (21q22.3).

Pulver *et al*. (1994a) reported that a gene predisposing to schizophrenia was present on chromosome 22 (22q12-q13.1), but they, and other workers, failed to replicate these findings in other studies (Coon *et al*., 1994; Pulver *et al*., 1994b). However, Moises *et al*. (1995a) reported a locus on the long arm of chromosome 22 (locus D22S278 at 22q12), suggesting the existence of an "oligogenic gene" in a multigenic system for schizophrenia. Schwab *et al*. (l995a) also succeeded in replicating Pulver's 1994 findings by using 4 microsatellite markers in region 22q12-q13.1 to study schizophrenia in 30 Israeli and German families, obtaining significant results for a dominant inheritance model for marker D22S304, suggesting that a "genetic factor" predisposing to schizophrenia occurs in region 22q12-q13.1 of chromosome 22. Vallada *et al*. (1995) found evidence favoring both Moises's D22S278 locus and locus D22S283 of chromosome 22, suggesting that these regions contain a gene contributing to the etiology of schizophrenia. To resolve once and for all this problem, Gill *et al*. (1996) developed an analysis combining genotypic data on the D22S278 marker alleles in multiple families affected with schizophrenia from 11 independent research groups throughout the world. This marker was chosen because it was the marker that demonstrated the most evidence of being linked to schizophrenia in 3 independent studies (Polymeropoulos *et al*., 1994; Lasseter *et al*., 1995; Vallada *et al*., 1995). The methodology used was "extended sib-pair (ESP) analysis" and a probability-based statistical analysis for sibling comparison. In the ESP analysis, using pairs of affected siblings with parents' genotypic data fully known, an excess of shared alleles was found in affected individuals. These results were statistically significant at the $P = 0.001$ level, indicating that there could be a schizophrenia susceptibility locus at chromosomal region 22q12.

In a study based on 571 schizophrenic patients (including those with schizo-affective disorder), ethnically paired with 639 controls and covering 7 European countries, Williams *et al*. (1996) proposed an association between schizophrenia and T102C polymorphism of the 5-hydroxy-tryptamine (serotonin) type 2a-receptor gene (5-HT_{2a}) situated on the long arm of chromosome 13. These workers suggested that this gene, or a locus in linkage disequilibrium with it, conferred susceptibility to schizophrenia because the proportion of allele 2 and genotype 2/2 of the T102C polymorphism was higher than expected in schizophrenic patients and was associated with the pathogenesis of this condition. Although similar results were observed in Japanese patients and controls (Inayama *et al*., 1996), the findings of Williams *et al*. have been criticized by various authors (Clifford and Nunez, 1996; Malhotra *et al*., 1996; Arranz *et al.*, 1996; Sasaki *et al*., 1996; Crow, 1996). The investigations of Williams *et al.* and Inayama *et al*. were repeated in another study by Erdmann *et al*. (1996) who demonstrated that there was structural variability (2 amino-acid substitutions) in the human 5-HT_{2a} receptor but that receptor variants were encountered at similar frequencies in both schizophrenic individuals and normal controls, indicating that the presence of these variants were not etiologically related to schizophrenia. However, they also remarked that future studies might determine whether or not the 5-HT_{2a} receptor variants were associated with other pathological phenotypes or, as suggested by Propping and Nöthen (1995), had any pharmacogenetic relevance and that they had been able to replicate the findings of Williams *et al.* and Inayama *et al.* in that there was an association between "non-coding T102C polymorphism" and the development of schizophrenia. Erdmann *et al*. also stated that even though T102C polymorphism does not involve variation in the amino-acid sequence of the 5-HT_{2a} receptor (i.e, is non-coding), the association with schizophrenia could be explained by disequilibrium linkage with an unidentified functional variant occurring on a regulatory area of the gene. Lin *et al.* (1997) have suggested the existence of a potential schizophrenia susceptibility locus on chromosome 13 (13q14.1-q32) at markers D13S122 and D13S128, particularly in European families.

In a study on the metabolism of serotonin and the physiopathology of schizophrenia, using a polymerase chain reaction (PCR) product and restriction fragment length polymorphism (RFLP), Gelernter *et al.* (1995) proposed that schizophrenia and other neuropsychiatric disorders could be studied using the SLC6A4 locus of the gene for serotonin-transporting protein (occurring on chromosome 17 near region 17q12) and the D17S58 and D17S73 loci, because the localization of these loci was consistent with the observed crossovers.

Persico *et al.* (1995) excluded a close link between schizophrenia spectrum disorders (SSD) and the dopamine transporter (DT) gene because allele variants at this locus did not contribute to schizophrenia. These authors used polymorphic markers for the DT gene in 156 subjects from 16 multiplex pedigrees exhibiting schizophrenia and SSD, and excluded a close link between the DT gene locus and SSD in both dominant and recessive models, thereby excluding a causal link between genetic mutations in the DT locus and phenotypic illness.

There has also been interest in the role played by the human D3 dopamine receptor (DRD3) gene (Giros *et al.*, 1990) in the pathogenesis of schizophrenia. This gene was localized in region q13.3 of chromosome 3 by Le Coniat *et al.* (1991), but studies of the link between DRD3 polymorphisms and schizophrenia have consistently given negative results (Wiese *et al.*, 1993; Coon *et al.*, 1993a; Sabaté *et al.*, 1994). In 2 independent association studies on French and British subjects, Crocq *et al*. (1992) found an excess of homozygotes for both *Bal*I polymorphic DRD3 alleles (reflecting a deviation from Hardy-Weinberg equilibrium) in schizophrenic patients, suggesting that DRD3 could exercise a subtle influence on the predisposition to schizophrenia. These results were confirmed by Mant *et al.* (1994) as well as by Griffon *et al.* (1996), who worked with 119 chronic schizophrenics evaluated according to Diagnostic and Statistical Manual of Mental Disorders - III Edition, Revised (DSM-III-R) and 85 controls. But the work of Crocq *et al.* was not confirmed by other studies (Jönsson *et al.*, 1993; Nöthen *et al.*, 1993; Yang *et al.*, 1993; Sabaté *et al.*, 1994; Laurent *et al.*, 1994).

In their revision, Portin and Alanen (1997) considered the numerous contradictory results and affirmed that "it seems that molecular genetic studies lend only minor support to the dopamine theory of schizophrenia", citing the many studies which had unsuccessfully tried to associate schizophrenia with genes for the dopamine D1, D2, D3, D4 and D5 receptors, as well as studies on other candidate genes such as the beta 1 GABA-A receptor gene (Asherson *et al.*, 1991; Coon *et al.*, 1993b). More recent studies by Tanaka *et al.* (1996) and Rothschild *et al.* (1996) have also failed to show an association between D2 and D3 receptors and schizophrenia, as have studies on Italian pedigrees by Grassi *et al.* (1996), who found no evidence for a link between schizophrenia and D2 receptor locus. However, Shaikh *et al.* (1996) have suggested an allelic association between schizophrenia and Ser-9-Gly polymorphism in the DRD3 gene.

With a view to finding an association between genetic variation and schizophrenia, genetic linkage studies have been made using the long arm of human chromosome 11 which contains the gene locus for the D2 dopamine receptor. Working with 5 Israeli families affected with multiple cases of schizophrenia, Mulcrone *et al.* (1995) used microsatellite dinucleotide DNA markers to examine the segregation of schizophrenia along chromosome 11q and, testing the hypothesis of linkage under genetic homogeneity of causation, found no linkage analysis evidence for significant causal mutations in the D11S420 delimited region of chromosome 11q13-24, although they considered the possibility that "a gene of major effect" exists in this region, either with low penetration or with heterogeneity. In a study of pedigrees from a region of eastern Quebec (extending up to the north of New Brunswick) densely affected with schizophrenia, Maziade *et al.* (1995) analyzed the link between schizophrenia and 11 microsatellite polymorphism CA repeat markers located at chromosomal region 11q21-22 containing the DRD2 gene for the D2 dopamine receptor. The diagnostic evaluation in cases of schizophrenia in probands and relatives was made through a consensus procedure using DSM-III-R, with the results showing no evidence in favor of a major gene effect influencing schizophrenia. Of the 4 families studied, the maximum lod score was 3.41 (for locus D11S35) in only one large family affected with schizophrenia, the authors concluding that this tendency to positive linkage in the pedigree which gave a significant lod score "may, or may not, reflect true linkage".

In one of six families in a multiplex study, Kosower *et al.* (1995) observed co-segregation of schizophrenia with Duffy blood group alleles and a variant of region 1qH of chromosome 1 containing the locus for pseudogene 2 (1q21.1) for the D5 dopamine receptor transcribed in normal lymphocytes. Consequently, in general, we see a growing preocupation in the literature with gene loci for dopamine and serotonin, alterations which are believed to be related to the physiopathology of schizophrenia.

More recently, a series of molecular genetic studies have continued to propose various loci which could be related to a predisposition to schizophrenia. In one study alone, involving 70 families with at least one chronic schizophrenic member, Shaw *et al.* (1998) proposed loci on 12 chromosomes (1, 2, 4, 5, 8, 10, 11, 12, 13, 14, 16 and 22) having at least one region potentially involved in schizophrenia. This linkage study used 388 markers spanning the genome all pedigrees, giving an average resolution of 10.5 cM between 0 and 31 cM, and an average heterozygosity of 74.3% per marker. In 5 chromosomes (1, 2, 4, 11 and 13) there was at least one marker with a lod score greater than 2.0, indicating heterogeneity. In another study, Schwab *et al.* (1998) provided support for a locus 0.5 cM distal to the G-olfalpha (18p) region as conferring susceptibility to functional psychosis in families with schizophrenia. Genes in two regions of chromosome 18 (18p11.3 and 18q21.1) were also proposed as being involved in the genesis of schizophrenia and affective bipolar disorder, these results being very interesting because they suggest common genetic loci for these two psychosis, or, in other words, that these chromosome 18 loci are possibly not specific for schizophrenia (Mors *et al.*, 1997). Defending the theory of commutative polygenes, Frota-Pessoa (1993) theorized that certain polygenes can favor the appearance of bipolar affective disorder as

well as predisposing to schizophrenia, depending on the general influence of polygenes and environmental factors.

Other studies have proposed various loci predisposing to schizophrenia, including the work of Dann *et al.* (1997) on an X-chromosome locus at Xp11, of Morris-Rosendahl *et al.* (1997) on a tentative association between the gene for dentatorubral-pallidoluysian atrophy and schizophrenia on chromosome 12, of Freedman *et al.* (1997) on the 15q13-14 locus of chromosome 15 and of Deckert *et al.* (1997) on chromosome 22 at locus 22q12-13.

Various loci and regions have been cited for chromosome 6, including 6q13-q26 by Cao *et al.* (1997), D6S1960 on chromosome 6p by Brzustowicz *et al.* (1997), D6S274 and D6S285 on 6p by Turerki *et al.* (1997), 6p23-p24 by Olavesen *et al.* (1997), 6p22-24 by Pujana *et al.* (1997) and 6p24-22 with markers D6S296 and D6S277 by Maziade *et al.* (1997), who again raised the hypothesis that this locus may be a common locus for both schizophrenia and affective bipolar disorder. The work on chromosome 6p at the HLA-DRB1 (6p21.3) locus by Wright *et al.* (1996, 1998) and the HLA-DQB1 locus by Grobetakopf *et al.* (1998) focused on the role of the human leukocyte antigen (HLA) complex and the autoimmune theory of schizophrenia.

Even the loci on chromosomes 6 and 22, most cited in this paper as probably involved in modulating susceptibility to schizophrenia, have not shown evidence of linkage in some more recent publications. Cao *et al.* (1997) were not able to confirm previous reports of linkage with the short arm of chromosome 6 (6p), while two other studies (Garner *et al.*, 1996; Daniels *et al.*, 1997) found no linkage between schizophrenia and the 6p24-22 region. Parsian *et al.* (1997) were not able to replicate the findings of Pulver *et al.* (1994a) and obtained no evidence of linkage between schizophrenia and 22q12, thus excluding all the region between the D22S268 and D22S307 markers. Working with South-African Bantu families affected with schizophrenia, Riley *et al.* (1996) found no evidence of linkage with markers on chromosome 22. However, using a dominant inheritance model and marker D22S303, Lachman *et al.* (1997) suggested a possible locus for bipolar disorder near the velo-cardio-facial syndrome region of chromosome 22 (22q11), and obtained a maximum lod score of 2.51 in families affected with this condition. As has been stated earlier in this revision, Schwab *et al.* (1995a) suggested a locus for schizophrenia at 22q12-q13.1, obtaining significant results for the same type of inheritance with marker D22S304. In other words, two loci situated close together on the same chromosome and sharing the same dominant inheritance model have been proposed for two psychosis.

Mowry *et al.* (1997) revised various findings related to chromosomes 3, 6, 8, 13, 18, 22 and the X-chromosome, and concluded that the experimental evidence pointed to the loci 6p24-22, 8p22-21 and 22q12-q13.1 as being responsible for susceptibility to schizophrenia. These authors also considered that in the light of the molecular genetics findings available, schizophrenia was a "genetically complex disease with an unclear mode of transmission".

To conclude this critical revision of a decade of studies on the molecular genetics involved in the search for genes modulating the predisposition to schizophrenia, we can summarize as follows:

1. Even though a great number of studies using sophisticated molecular biology techniques have been published and many loci, involving more than half the chromosome complement, have been suggested which may predispose to schizophrenia, neither its genetic locus nor its exact mode of transmission is known.
2. The most cited loci correspond to chromosomal regions 6p24-22 and 22q12-13.
3. The more recent literature is most concerned with human gene loci for the receptors for the neurotransmitters dopamine and serotonin, which are potentially involved in the physiopathology of schizophrenia.
4. Work on some more recently implicated loci on chromosomes 6, 18 and 22 suggests that there may exist genetic loci which are not specific for schizophrenia, but which can also predispose to other psychosis such as bipolar disorder.
5. More recently published work on the chromosome 6 locus for human leukocyte antigen complex points to an autoimmune theory for schizophrenia.
6. The highly variable results in the published research suggest that multiple loci are involved in the predisposition to schizophrenia, pointing to heterogeneity which, as was discussed earlier in this revision, is more polygenic (various genes acting together) than monogenic (a different gene for each family).

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RESUMO

A genética da esquizofrenia (como também do distúrbio bipolar) teve grande avanço a partir da descoberta, a nível de genética molecular, da técnica de localização de genes com uso de sondas de DNA (Botstein *et al.*, 1980). Os estudos que procuram "genes candidatos" a exercerem algum papel na susceptibilidade à esquizofrenia são, basicamente, de dois tipos: de ligação ("linkage") e de associação. Quando, à luz da genética molecular, um gene é localizado próximo a um marcador de DNA específico no cromossomo, fala-se em estudo "de ligação". Por outro lado, quando a doença é associada a um alelo específico de um determinado gene, fala-se em estudo "de associação". Esta revisão cobriu uma década de publicações sobre o assunto, desde os primeiros trabalhos de Bassett *et al.* e de Sherrington *et al.*, ambos divulgados em 1988 (gene localizado no braço longo do cromossomo 5, loco em "5q11-13") até as recentes propostas de Lin *et al.* (1997), apontando para o loco "13q14.1-q32" no cromossomo 13 e de Wright *et al.* (1998) para o loco genético "HLA DRB1" no nível de "6p21.3" no cromossomo 6. Os locos mais replicados foram: no braço longo do cromossomo 22 ("22q12-q13.1") e no braço

curto do cromossomo 6 ("6p24-22"). Nesta revisão crítica de estudos sobre genética molecular envolvidos na localização de genes que modulam a predisposição à esquizofrenia, observou-se grande variabilidade nos resultados, sugerindo múltiplos locos envolvidos na predisposição à doença.

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