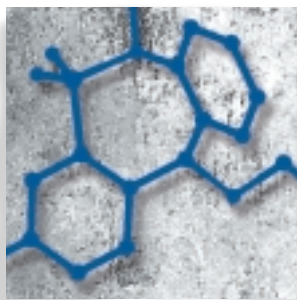


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Toward a modern search for schizophrenia genes

Marion Leboyer, MD, PhD



Genetic epidemiology has provided consistent evidence that schizophrenia has a genetic component. It is now clear that this genetic component is complex and polygenic, with several genes interacting in epistasis. Although molecular studies have failed to identify any DNA variant that clearly contributes to vulnerability to schizophrenia, several regions have been implicated by linkage studies. To overcome the difficulties in the search for schizophrenia genes, it is necessary (i) to use methods of analysis that are appropriate for complex multifactorial disorders; (ii) to gather large enough clinical samples; and (iii) in the absence of genetic validity of the diagnostic classification currently used, to apply new strategies in order to better define the affected phenotypes. For this purpose, we describe here two strategies: (i) the candidate symptom approach, which concerns affected subjects and uses proband characteristics as the affected phenotype, such as age at onset, severity, and negative/positive symptoms; and (ii) the endophenotypic approach, which concerns unaffected relatives and has already provided positive findings with phenotypes, such as P50 inhibitory gating or eye-movement dysfunctions.

Keywords: association; candidate symptom; endophenotype; genetics; linkage; schizophrenia

Author affiliations: Service de psychiatrie adulte, CHU Albert Chenevier et Henri Mondor, Université Paris XII, Créteil, France

Address for correspondence: Service de psychiatrie adulte, CHU Albert Chenevier et Henri Mondor, Université Paris XII, 40 rue de Mesley, 94000 Créteil, France
(e-mail: leboyer@im3.inserm.fr)

A century of research in genetic epidemiology has consistently supported the involvement of a major, complex, genetic component in the risk for schizophrenia. However, molecular genetic studies have produced conflicting results: several chromosomal regions have been implicated, but none of the findings met stringent statistical significance criteria and positive findings have not been replicated. This troublesome situation may be partly attributed to obstacles that complicate efforts to identify genes for any complex disorder, such as unknown mode of inheritance, genetic heterogeneity, phenocopies, incomplete penetrance, and variable expressivity.¹ However, an even greater obstacle to identifying the genes underlying the vulnerability to schizophrenic disorders is our inability to define the heritable phenotype.² Indeed, although reliable diagnostic criteria and structured psychiatric interviews have improved our understanding of the genetics of schizophrenia, little is known about how to choose the diagnostic system that best describes the most heritable form of the illness or the most heritable aspects of the psychopathology. Within apparently affected subjects, various types of phenotypic misclassifications reduce the power of linkage studies because of phenocopies or genetic heterogeneity. Furthermore, within apparently unaffected subjects or controls, our inability to identify nonaffected subjects carrying vulnerable genes, due to incomplete penetrance, also reduces the power of association studies.

Despite this apparently confusing situation, two major conclusions can be drawn from the research published so far. First, the pattern of risk in families suggests that several genes in epistasis lead to schizophrenia³; thus, instead of searching for *the* schizophrenia gene, genetic studies should now be designed to search for many genes with small effects. Second, in order to minimize the arbitrariness of categorical diagnoses, new strategies must be used to define phenotypes as subclinical quantitative traits, ie, endophenotypes.² Quantitative measures that are more

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closely related to schizophrenia genes provide more power in linkage analyses than categorical diagnoses and might be valuable for identifying common alleles with nonspecific and moderate effects on disease risk.⁴ Furthermore, an endophenotype might be underlined by a mendelian inheritance pattern, which would considerably diminish the sample size required to detect the responsible genetic mutation.⁵ This alternative phenotypic strategy has already yielded positive results: schizophrenia linkage studies using two endophenotypes, eye-tracking⁶ and P50 evoked potential measurements,⁷ as phenotypes have suggested genetic linkage in populations where the clinical diagnosis did not.

This review will first describe the classic genetic arguments in favor of the existence of a genetic component in schizophrenia and the results obtained by linkage and association studies. It will then discuss the existing literature on potential candidate symptoms or characteristics in schizophrenic probands and endophenotypes in their unaffected relatives, including the clinical, cognitive, electrophysiological, and biochemical characteristics examined in studies.

Why are we looking for genes contributing to schizophrenia?

Data collected from families, twins, and adoptees have consistently supported the involvement of genetic factors in schizophrenia. The combined results from European studies⁸ yield a lifetime morbid risk in the general population of 1%, while the risk for schizophrenia in siblings or offspring of a schizophrenic proband is close to 10%. This risk varies according to the type of schizophrenia: the risk of becoming schizophrenic for a child of a hebephrenic or catatonic schizophrenic parent is 20.7% and 21.6%, respectively. This risk is decreased (10.4%) for a child of a paranoid schizophrenic parent. Risk is also increased when more relatives are affected, for example, the morbid risk of schizophrenia for a child of two affected parents is 46%. The risk for other conditions is increased among relatives of schizophrenic patients. In particular, Kendler and Diehl⁹ have shown that the risk of schizotypal or paranoid personality disorders in relatives of schizotypal patients is four times that in control families. The risks of schizoaffective disorder, schizophreniform disorder, delusional disorders, and atypical psychosis are also significantly increased in the relatives of probands.

Altogether, these data clearly demonstrate the existence of a family concentration of schizophrenia. Twin studies provide an estimation of the importance of the genetic contribution. They have shown consistent evidence of a higher concordance for monozygotic (50%) than dizygotic (17%) twins¹⁰ and estimated the heritability for schizophrenia as close to 80%.¹¹ Gottesman and Bertelsen¹² showed that rates of schizophrenia in offspring of identical twins discordant for schizophrenia were equal. These data suggest that individuals who possess the schizophrenia genotype do not necessarily express the disorder.

Studies of twins clearly show that liability to schizophrenia is not completely genetic and is more likely a complex trait determined by several genes interacting with the environment. Better knowledge of environmental risk factors may improve our ability to identify the genes for schizophrenia. In particular, there is now a reliable evidence that at least two environmental factors are involved in the etiology of schizophrenia: perinatal obstetric complications¹³ and prenatal viral infections, especially in the second trimester.¹⁴ No study has clearly answered the question of how the genetic risk interacts with environmental precipitants or is transmitted. However, the most consistent model of transmission is a multifactorial inheritance model with no major gene.¹⁵ Risch et al³ have also shown that data in schizophrenia are consistent with the existence of three to four loci interacting epistatically. It is very likely that when the number of loci increases, the risk alleles at these loci become very common in the population, of the order of 14% to 20%.¹⁶

Which chromosomal regions are the best candidates for containing schizophrenia susceptibility genes?

Molecular genetic studies have so far failed to find any DNA variant that can be demonstrated to contribute to schizophrenia risk. Replication of positive findings has been difficult to interpret and, when positive replications have been obtained, the positioning of the locus has been unreliable, leading no closer to positional cloning of the putative gene. In addition, many regions are implicated, and the lod scores obtained are always below the threshold suggested by Morton for mendelian traits.¹⁷ However, review of all the linkage studies performed over the past 10 years does suggest a number

of regions where small positive lod scores have been found several times in independent samples (for a recent review, see reference 18).

- **Chromosome 1.** Positive linkage findings have been found in the region 1q42.1,¹⁹ where the breakpoint of a balanced 1:11 translocation segregating with schizophrenia in a large schizophrenia pedigree from Scotland was found.²⁰
- **Chromosome 2.** Interest in the region 2p22-q21 came from a case report of a balanced 2:18 translocation segregating in a family with schizophrenia.²¹ Since then, there have been several reports of positive linkage with markers spread over 100 cM of the region 2p22-q21.²²
- **Chromosome 3.** Initial positive results in the region 3p²⁴ were obtained by Pulver et al,²³ but were not replicated later by the Schizophrenia Linkage Collaborative Group Study. The only further data implicating this region come from the report of an excess homozygosity for one allele of a polymorphism in the dopamine receptor D₃ gene.²⁴ Steen et al²⁵ reported an association of *DRD3* allele and tardive dyskinesia in schizophrenic patients and Krebs et al²⁶ reported an association of homozygosity with substance abuse in schizophrenic patients.
- **Chromosome 4.** Conflicting results were obtained following the initial report of a linkage with a cluster of three markers on the region 4q24-q32.²⁷ This region is interesting as positive reports have also been obtained here for bipolar disorders.²⁸
- **Chromosome 5.** After nonreplication of the first positive linkage result obtained in schizophrenia,²⁹ there was renewed interest in chromosome 5 when two separate series of positive linkages were obtained in regions 5p14.1³⁰ and 5q22-q31.³¹
- **Chromosome 6.** Several independent positive reports of the region 6p24-p22 have been published,³² and it is noteworthy that eye-tracking dysfunction, a widely used endophenotype, has been mapped to the p arm of chromosome 6. Positive linkage findings were reported in the region 6q21-q22.3, but these have not yet been replicated by an independent group.³³
- **Chromosome 7.** Two studies obtained moderately positive results in the region 7q21.1-q21.3 using three markers spread over 30 cM of the chromosome.³⁴
- **Chromosome 8.** Four independent studies have reported positive results in the region 8p22-p21 following an initial report of Pulver et al.²³
- **Chromosome 9.** Several positive results have been published for linkage to the region 9q34.3, which contains several candidate genes, such as those dopamine- β -hydroxylase (DBH) and the critical subunit of the *N*-methyl-D-aspartate (NMDA) receptor NR₁. So far, negative linkage results have been obtained with the DBH gene.³⁵
- **Chromosome 13.** The region 13q codes for the serotonin receptor 5-HT_{2A} gene, which has been reported to be associated with schizophrenia.³⁶ Positive lod scores have been obtained with independent samples from Europe, Asia, Africa, USA, or Canada.
- **Chromosome 15.** The first evidence for a possible implication of chromosome 15 was the report of linkage with P50 sensory gating deficit in the region 15q13-q14.³⁷ A positive lod score was obtained with the gene encoding the $\alpha 7$ nicotinic cholinergic receptor subunit (*CHRNA7*) when using the sensory gating phenotype; the lod score dropped when using schizophrenia as the phenotype. With polymorphic markers located in the same regions, positive results have been obtained by several groups, while two studies failed to find any evidence for involvement of this region.^{38,39}
- **Chromosome 18.** Interest in chromosome 18 began with the report of positive linkage with bipolar disorder.⁴⁰ Positive results, not always replicated, have mostly been obtained when including both affective disorders and schizophrenia as the affected phenotype.⁴¹ Positive results have been obtained with the gene encoding for the subunit of the olfactory G-protein (*GOLF*).
- **Chromosome 22.** Discrepant results have been obtained with markers spanning chromosome 22, which is also known to be associated with velocardiofacial syndrome (VCFS). Thirty percent of patients presenting with this syndrome carry a diagnosis of schizophrenia.⁴² The gene encoding for catechol-*O*-methyl transferase (COMT) is located in the region 22q11 and has been suggested to be involved with the psychotic symptoms observed in VCFS.⁴³
- **X chromosome.** The X chromosome was initially suggested to be a chromosome of interest due to the well-known gender differences in schizophrenia. A pseudoautosomal locus that would account for those differences was suggested by Crow et al.⁴⁴ Discrepant results were obtained thereafter.

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Results have already been published in the field of schizophrenia pharmacogenetics. In particular, an association has been reported between the D₄ receptor gene and good response to clozapine,⁴⁵ while nonresponders to clozapine demonstrated associations with particular alleles of the 5-HT_{2A} receptor gene.⁴⁶ These findings have not always been replicated, dampening enthusiasm.

Altogether, all these results may appear confusing. The clinical heterogeneity of the illness is one of several explanations for these discrepancies. The use of linkage analysis methods in comparison with nonparametric methods (which do not apply any assumptions on the mode of inheritance) has been thoroughly discussed. The value of performing association studies testing the implication of candidate genes is clear. However, Riley and McGuffin¹⁸ have emphasized that larger clinical samples than originally anticipated will be needed both for studies in multiply affected families and for sporadic cases. Also, because the power of molecular genetic studies derives not only from sample size, but also from the accuracy of the phenotypic definition, we and others have advocated the need for the development of more powerful phenotypic strategies.^{2,4}

What is the best strategy to improve phenotype identification?

The genetic validity of the current customary criteria for standardized diagnosis has not been demonstrated. We have suggested two complementary strategies for finding genetically valid traits: one involves a description of the affected subjects; and the other involves the identification of vulnerability traits in nonaffected relatives of affected individuals, ie, the endophenotypic approach. The first strategy utilizes affected individuals and is called the *candidate symptom approach*. It is analogous to the candidate gene approach as applied in molecular biology. The candidate symptom approach would identify several stringent clinical characteristics hypothetically associated with a disease genotype and show a pattern of inheritance related more robustly to the narrow characteristics than to the diagnosis. Identification of specific subforms of the disorder would lead to identification of homogeneous families, which are more appropriate for linkage studies.

The second strategy emphasizes the need to use broader approaches, such as related biochemical, neurophysiological, neuroanatomical, cognitive, and/or neuropsychological

markers, to identify pertinent phenotypes in nonaffected relatives carrying vulnerability genes. These subclinical associated traits, *endophenotypes*, might be valuable for identifying common alleles with nonspecific and moderate effects on disease risk. Thus, endophenotypes serve to better define the trait or its underlying genetic mechanism.⁴⁷ To meet criteria for a marker trait, an endophenotype should be measured in an objective and cost-effective fashion among clinically unaffected relatives of patients, should occur before the onset of illness, should run in families, and should be associated with increased risk of clinical illness. This strategy is recommended for psychiatric disorders in which symptoms occur as the consequence of an interaction between several vulnerability factors, each having good genetic validity but not necessarily disease-specificity.

The candidate symptom strategy

Target symptoms that could allow the identification of a homogeneous form of the illness (ie, candidate symptoms) should fulfill the following criteria: they should show good concordance rates among affected monozygotic twins and should be correlated in pairs of affected siblings.⁴⁸ This strategy has already proven helpful in the identification of subgroups in complex disorders other than psychiatric disorders. For example, subdivision according to age at onset has been particularly efficient in clarifying genetic heterogeneity in dementias of the Alzheimer's type. The amyloid precursor protein was initially falsely excluded as a susceptibility locus under the incorrect assumption that all cases of familial Alzheimer's disease were caused by the same gene.⁴⁹ Later, direct sequence analysis of the amyloid precursor protein gene revealed mutations at this locus on the q arm of chromosome 21 segregating with the disease in pedigrees of Alzheimer's disease cases with onset by age 60.⁵⁰ Later, other loci were found to be involved. Most early-onset autosomal dominant forms of Alzheimer's disease have been linked to a defective gene on the q arm of chromosome 14, whereas the late-onset sporadic forms of Alzheimer's disease are associated with the apolipoprotein E4 allele on chromosome 19. Similarly, in the field of schizophrenia, age at onset may be a good candidate symptom: early onset is associated with increased familial risk in schizophrenia.⁵¹ Furthermore, age at onset in schizophrenia appears to be sub-

stantially influenced by familial factors, since correlation with age at onset in affected pairs of siblings ranges from 0.2 to 0.4,^{52,53} and that of monozygotic twins ranges from 0.5 to 0.8.⁵² Of interest is that schizophrenic females with late onset and no family history of schizophrenia seem to form a subgroup of patients with a hormonal basis for their illness.^{54,55} Furthermore, the decrease in age at onset of schizophrenia in successive generations seems to be consistent with the phenomenon of genetic anticipation.⁵⁶

The occurrence of specific symptom constellations may also help in identifying a subgroup of genetically related schizophrenia subtypes, which are etiologically homogeneous. Anhedonia, blunted affect, poverty of speech, lack of a sense of purpose, and diminished social drive can be considered as enduring symptoms that are core manifestations of schizophrenia.⁵⁷ Indeed, negative symptoms are more stable over time than positive symptoms⁵⁸ and seem to be the main source of familial aggregation in schizophrenia. A twin study by Dworkin and Lenzenweger⁵⁹ found an increased concordance rate for schizophrenic twins with two or more negative symptoms, but not for positive symptoms. They also found that negative symptoms, but not positive symptoms, were correlated between pairs concordant for schizophrenia. Sautter et al⁶⁰ found that a family history of schizophrenia correlated with negative symptoms. Kay et al⁶¹ reported that negative symptoms were positively correlated with a family history of major psychiatric disorders, but negatively correlated with a family history of affective disorders. Tsuang⁴ showed that negative symptom ratings are higher for relatives of patients with schizophrenia, whereas positive symptom ratings are similar in relatives of schizophrenic patients and depressed controls. These findings suggest that negative symptoms could reflect familial liability to schizophrenia, whereas positive symptoms reflect a clinical endophenotype common to both affective disorders and schizophrenia. Indeed, several studies have demonstrated familial relationships between schizophrenia and affective disorders, in particular with psychotic affective disorders.⁶² Thus, one might hypothesize that the shared candidate symptom might be represented by positive symptoms. Brzustowicz et al⁶³ provided the first evidence of the value of using a quantitative dimensional approach in a linkage study in a sample of multiply affected families. Positive linkage with markers on the p arm of chromosome 6 was obtained only when using

scores on positive symptoms as phenotypes among schizophrenic patients and their nonaffected relatives. Negative linkage results were obtained with negative scores or with a classical nosographical approach.

The endophenotype strategy

Endophenotypes are traits that are associated with the expression of an illness and are believed to represent the genetic liability of the disorder among nonaffected subjects. Using the endophenotypic strategy, schizophrenia can be conceptualized as an illness caused by the interaction of several elementary neurobiological dysfunctions—each underlined by a specific defect in a particular candidate gene—with nongenetic factors. There are several examples of somatic diseases in which “endophenotypic” level helped define the genetic basis of the illness in molecular terms. For instance, understanding the mode of inheritance of idiopathic hemochromatosis was unclear until serum iron concentration was selected as a biological indicator of intrinsic liability to the disease. Including serum iron in the analysis uncovered a linkage with the HLA-A locus.⁶⁴ In order to identify a genetic susceptibility factor in juvenile myoclonic epilepsy, investigators chose a subclinical trait (ie, an abnormal electroencephalogram) as an endophenotype in affected and nonaffected family members, and found linkage to chromosome 6.⁶⁵ Focusing on families with the highest serum glucose levels as a specific phenotype led to the discovery of a genetic deficit that results in type 2 diabetes.⁶⁶

In schizophrenia, several neurochemical, electrophysiological, and cognitive abnormalities have been reported among nonaffected relatives of schizophrenic patients. Two endophenotypes in particular, eye tracking⁶ and P50 evoked potential measurements,⁷ have already been used as phenotypes, and yielded positive linkage results.

Neurochemical abnormalities

Investigations of neurochemical abnormalities among unaffected relatives of schizophrenic patients is a convenient method to explore biochemical predisposition to schizophrenia in natural conditions, without any pharmacological challenge and in the absence of confounding factors, such as chronicity of illness or effects of medication. Dopaminergic abnormalities have been explored in nonpsychotic relatives under the hypothesis that neg-

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ative and positive symptoms are associated with decreased and increased brain dopamine (DA) functions, respectively. Decreased plasma homovanillic acid (HVA), the major DA metabolite, has been observed in healthy first-degree relatives of schizophrenic probands.⁶⁷ Few studies of the proteins involved in DA uptake and metabolism have been performed in unaffected relatives of schizophrenic patients. However, increased densities of DA receptors (³H]spiperone binding sites) on lymphocytes has been reported in one third of the well relatives of schizophrenic probands.⁶⁸ Regarding serotonergic parameters, two studies have reported higher cerebrospinal fluid 5-hydroxyindoleacetic acid (5-HIAA) concentrations in schizophrenia patients with a strong positive family history of schizophrenia.^{69,70} To our knowledge, studies of neuroendocrine measures and platelet markers of 5-HT function have not yet been undertaken in individuals at risk for schizophrenia.

Electrophysiological markers

Cognitive event-related potentials (ERPs) have been widely used as potential indicators of risk for schizophrenia. ERPs are usually measured in terms of amplitude, latency, and topography of a component. ERPs elicited by infrequent auditory targets, for example, during an oddball paradigm, are characterized successively by (i) an early component, N100, which reflects the sensory analysis of the physical parameters of the stimulus⁷¹; (ii) N200, which evaluates selective attention processes leading to stimulus categorization⁷²; and (iii) P300, which is classically related to the postperceptual updating of short-term working memory traces of expected environmental stimuli. The ERP technique is a safe, noninvasive approach to the study of psychophysiological correlates of human mental processes.

The most robust finding is that of reduced P300 amplitude and increased amplitude using an oddball paradigm in schizophrenic patients compared with controls. This finding can be considered as a trait marker, since it has been reported in unmedicated schizophrenic patients using an auditory modality, whereas the visual modality may serve as state marker.⁷³⁻⁷⁵ Altogether, the delayed P300 in schizophrenic patients appears to be independent of a medication effect, the clinical state,⁷⁶ the duration of symptoms, and the clinical subtype of the illness.⁷⁵ However, reduced P300 is not specific to

schizophrenia, since it has been reported in a variety of different disorders, such as dementia, alcoholism, and bipolar disorder.

Several high-risk studies have provided evidence that P300 abnormalities can be considered as a vulnerability indicator. For example, Blackwood et al⁷⁷ found P300 amplitude reduction and latency prolongation in a sample of patients with schizophrenia, and half of their non-schizophrenic relatives showed prolonged P300 latency. However, these results have not always been replicated. Other abnormalities of the components of the ERPs have been observed in schizophrenia. Schizophrenic patients and their relatives showed similar amplitude reduction and latency prolongation of the N100, N200, and P300 waves compared with controls.⁷⁸ However, N100 reduction is not specific to schizophrenia since it is also observed in patients with major depressive disorder. The N100 reduction might be the result of an overlapping component, the processing negativity, which is elicited during selective attention paradigms and appears to be reduced in schizophrenia patients. A reduction in processing negativity is consistent with the deficits in selective attention that have been proposed to account for some schizophrenic symptomatology.

To date, the only endophenotype whose linkage analysis has pointed to a specific candidate mechanism for neuronal dysfunction in schizophrenia comes from the work on the sensory gating dysfunction by the group led by Freedman.⁵ The paradigm used was to present to the subject pairs of identical stimuli. Normal subjects diminish the amplitudes of the P50 wave response to the second stimulus, whereas schizophrenic patients consistently have a deficit in P50 inhibition.⁷⁹ This deficit is present in the unaffected parents of schizophrenic probands, who have themselves an ancestral family history of schizophrenia, but not in parents without such histories.⁸⁰ Furthermore, the families of early-onset schizophrenia show bilineal inheritance of the P50 inhibitory deficit, ie, both parents are affected.⁸¹ Thus, bilineal inheritance may be related to more severe and earlier illness onset. Animal studies showed that the inhibition of the second stimulus is mediated through cholinergic activation of hippocampal interneurons mediated via $\alpha 7$ nicotinic receptors. In schizophrenics and their relatives, nicotine transiently normalizes the deficit in P50 inhibition,⁸² as predicted from the animal model. The gene encoding the $\alpha 7$ nico-

nic receptor is localized in the region 15q14, a region of chromosome 15 found to be linked to schizophrenia in several genome scans. Freedman et al³⁷ showed that the P50 defect maps to the site of the $\alpha 7$ nicotinic receptor gene with a lod score of 5.3 under an autosomal dominant model. Replication of these data, identification of the molecular abnormality, and determination of the role of the abnormality in the pathogenesis of schizophrenia are necessary as the next steps.

Eye movement

Hundreds of studies have described the characteristic eye-movement dysfunction (EMD) in schizophrenic patients (for a review, see reference 83). This smooth pursuit dysfunction is stable over time,⁸⁴ present during symptom remission,⁸⁵ and familial, as it is found in almost 50% of unaffected relatives.⁸⁵ Schizophrenic patients and their relatives also demonstrate a deficiency in their ability to inhibit reflex saccades to the target.⁸⁶ Antisaccades EMD is found only in relatives of schizophrenic patients who themselves have increased rates of errors. These data suggest that abnormal smooth pursuit and saccade dysfunction are familial.⁸⁷ Although both types of abnormalities have been related to impaired frontal cortex functioning, especially in the A9 region, it is not yet known if these two dysfunctions are related to a distinct genetic risk or a single neural factor. In particular, no study has simultaneously investigated the relationship between smooth pursuit and saccadic system among schizophrenic patients. Only one study used abnormal smooth pursuit as an endophenotype in a linkage study reporting linkage of pursuit EMD to chromosome 6.⁶ However, these results need to be replicated.

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Cognitive markers

Numerous studies suggest that relatives of schizophrenic patients exhibit neuropsychological impairments that are milder than, and yet similar to, those observed in schizophrenic patients. In particular, the relatives of schizophrenic patients have been demonstrated to show disturbances of executive functioning, verbal memory, auditory attention, mental control, and verbal ability.⁸⁸ These abnormalities are stable over time⁸⁹ and are observed in nonschizophrenic family members of patients; moreover, nonschizophrenic, monozygotic cotwins produce more persevering responses in the Wisconsin Card Sorting Test than controls.^{90,91}

Another relevant strategy to identify endophenotypes is to perform high-risk studies on offspring of schizophrenic patients. Offspring were shown to have attention difficulties, poor performance on memory tasks, poor global adjustment, poor social competence, and anhedonia.⁹² Abnormalities in verbal short-term memory, related to amplitude decrements in the P300 component of ERP, and attention digit-span tasks predicted 83% of the offspring who developed adulthood schizophrenia.⁹³ Before demonstrating that a neurocognitive abnormality is an endophenotype, many variables must be tested for replicability over studies, stability over time, and heritability.

Conclusions

Altogether, research into the genetic basis of schizophrenia is productive but complex, and can be frustrating. Nevertheless, the field is slowly moving toward new methods of analysis, by searching alternative phenotypic definition and making collaborative efforts to gather samples large enough for analysis. □

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Hacia una investigación moderna de los genes de la esquizofrenia

La epidemiología genética ha aportado evidencias consistentes acerca del componente genético que tiene la esquizofrenia. Hoy en día está claro que este componente genético es complejo y poligénico, con algunos genes que actúan en la epistasia. Aunque los estudios moleculares han fracasado en la identificación de alguna variante del ADN que claramente contribuya a la vulnerabilidad para la esquizofrenia, mediante estudios de enlace se han propuesto varias regiones que pudieran estar involucradas. Para superar las dificultades en la investigación de la esquizofrenia es necesario: 1) emplear métodos de análisis que sean apropiados para los trastornos multifactoriales complejos, 2) reunir muestras clínicas bastante grandes y 3) en ausencia de una validez genética de la clasificación diagnóstica actualmente en uso, aplicar estrategias de manera de definir mejor los fenotipos afectados. Para este propósito, nosotros describimos aquí dos estrategias: 1) la aproximación del síntoma candidato, que incluye a los sujetos afectados y se vale de las características del probando en cuanto al fenotipo afectado como son la edad de comienzo, la severidad y los síntomas negativos / positivos y 2) la aproximación endofenotípica, que incluye a los familiares no afectados y que ya tienen hallazgos positivos con los fenotipos, como la onda P50 inhibitoria o disfunciones de la motilidad ocular.

Vers une modernisation de la recherche sur les gènes de la schizophrénie

L'épidémiologie génétique a fourni des résultats concordants prouvant que la schizophrénie a une composante génétique. Il est maintenant clair que cette composante génétique est complexe et polygénique avec plusieurs gènes interagissant en épistasie. Bien que les études moléculaires n'aient pas réussi à identifier un quelconque variant d'ADN qui contribue de façon certaine à la vulnérabilité à la schizophrénie, plusieurs régions ont été impliquées par les études de liaison. Pour surmonter les difficultés de la recherche des gènes intervenant dans la schizophrénie, il est nécessaire : (1) d'utiliser des méthodes d'analyse qui sont adaptées aux troubles multifactoriels complexes ; (2) de réunir des échantillons cliniques suffisamment larges ; et (3) en l'absence de validation génétique de la classification diagnostique habituellement utilisée, d'appliquer de nouvelles stratégies afin de mieux définir les phénotypes impliqués. Pour atteindre cet objectif nous exposons ici deux stratégies : (1) l'approche du symptôme candidat, qui concerne les patients atteints de la maladie et qui utilise les caractéristiques des patients comme phénotype affecté tels l'âge de survenue, la sévérité de la maladie et les symptômes négatifs et positifs; et (2) l'approche endophénotypique, qui concerne les proches parents non atteints et qui a déjà fourni des résultats positifs avec les phénotypes, tels que le niveau d'inhibition P50 ou les dysfonctionnements des mouvements oculaires.

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