New findings in the genetics of major psychoses

Markus M. Nöthen, MD; Vanessa Nieratschker, PhD; Sven Cichon, PhD; Marcella Rietschel, MD

Schizophrenia and bipolar disorder have a largely unknown pathophysiology and etiology, but they are highly heritable. Although linkage and association studies have identified a series of chromosomal regions likely to contain susceptibility genes, progress in identifying causative genes has been largely disappointing. However, rapid technological advances are beginning to lead to new insights. Systematic genome-wide association and follow-up studies have reported genome-wide significant association findings of common variants for schizophrenia and bipolar disorder. The risk conferred by individual variants is small, and some variants confer a risk for both disorders. In addition, recent studies have identified rare, large structural variants (copy number variants) that confer a greater risk for schizophrenia. This review summarizes recent developments in genetic research into schizophrenia and bipolar disorder, and discusses possible future directions in this field.

 Dialogues Clin Neurosci. 2010;12:85-93.

Keywords: *schizophrenia; bipolar disorder; heritability; genetic variant; linkage study; candidate gene study; copy number variation, genome-wide association study*

Schizophrenia and bipolar affective disorder (bipolar disorder, manic depression) are major psychiatric disorders. They profoundly affect thought, perception, emotion, and behavior, and their symptoms cause significant social and/or occupational dysfunction. The World Health Organization ranks both disorders among the top 10 leading causes of the global burden of disease for the 15-to-44 age group.

Schizophrenia and bipolar disorder are illnesses with a largely unknown pathophysiology and etiology. However, genetic epidemiology has demonstrated that modern psychiatric diagnostic criteria define disorders that are highly heritable. Estimates of heritability range between 70% and 90% for schizophrenia[1] and 60% and 80% for bipolar disorder.[2] It is generally accepted that the inheritance of psychiatric disorders is complex. Multiple genetic and environmental factors contribute to the development of a disorder[3-9] and it is possible that gene-gene interactions also occur.[10,11]

Extensive efforts have been made over the past 20 years to identify the susceptibility genes for psychiatric disorders on a molecular genetic level, although this has proven to be a far more difficult undertaking than was first anticipated. Until recently, the linkage approach and microscopic cytogenetic studies were the only available

Author affiliations: Department of Genomics, Life & Brain Centre and Institute of Human Genetics, University of Bonn, Bonn, Germany (Markus M. Nöthen, Sven Cichon); Division of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Mannheim, Germany (Vanessa Nieratschker, Marcella Rietschel)

Address for correspondence: Prof Dr med Markus M. Nöthen, Director, Institute of Human Genetics University of Bonn, Sigmund-Freud-Strasse 25, D-53127 Bonn, Germany
(e-mail: markus.noethen@uni-bonn.de)

methods of systematically searching the genome. A disadvantage of these two methods is their low level of resolution. Linkage studies have identified a series of chromosomal regions that are likely to contain susceptibility genes, and highly promising association findings have been obtained for several genes in these regions (eg, *neuregulin 1* [*NRG1*], *G72/G30* locus, *dystrobrevin-binding protein 1* [*DTNBP1*]).[12-14] However, it has not yet been possible to identify any genetic variant that confers a direct functional effect and which is consistently associated with disease across populations. Cytogenetic studies have also generated some highly promising candidate genes such as the *disrupted-in-schizophrenia-1* gene (*DISC1*).[15] Subsequent studies have reported highly interesting findings regarding the function of these genes and their associated pathways.[16]

Recently, however, important advances have been made as a result of rapid developments in technologies that are able to decipher the variability of the human genome at high resolution, and which allow systematic investigation of the impact of such variability in large samples. This article summarizes these developments in genetic research into schizophrenia and bipolar disorder, and discusses possible future directions in this field.

Genome-wide association studies

The introduction of the genome-wide association study (GWAS) is the result of enormous technological advances. GWASs involve the use of arrays that simultaneously genotype several hundred thousand single nucleotide polymorphisms (SNPs) per individual. This enables a hypothesis–free search of every gene and most intergenic regions of the genome in samples of unrelated patients and controls. In this respect GWASs resemble genome-wide linkage studies (genome scans), but they have several major advantages: (i) they are not dependent on the recruitment of families; (ii) they have better resolution since (in contrast to linkage) they detect linkage disequilibrium with susceptibility variants, which usually extends over smaller genomic regions (in the range of a few ten thousand base pairs); and (iii) they have greater power to detect small genetic effects. In contrast to linkage studies, however, they are restricted to the investigation of common variants, since SNPs with low minor allele frequencies are poorly represented on currently available arrays. A serious difficulty in evaluating the results of GWASs is the issue of multiple testing. A large number of SNPs may be tested within the same study for their association with a disease, and this generates many nominally significant findings that are actually false positives. It is therefore necessary to correct for multiple testing to achieve the level of genome-wide significance. This level is dependent upon the number of SNPs analyzed, and the threshold for currently available GWA chips is approximately 5×10^{-8} (660 000 to 1 000 000 SNPs).[17-19] This correction method is very conservative since the association findings of each SNP are considered to be independent, and the haplotype structure of the genome is not taken into account. Conservative correction for multiple testing reduces the risk of false-positive findings, but hampers the detection of true association signals that represent small effects on disease risk.

Following the publication of the first GWAS in age-related macular degeneration,[20] successful GWASs have been conducted for a variety of common, complex diseases including type 2 diabetes, myocardial infarction, breast cancer, and Crohn's disease (for details of all published studies see http://www.genome.gov/gwastudies/).

Schizophrenia

The first GWASs for schizophrenia have recently been published.[21-30] Three of these studies used pooled DNA samples.[21,26,27] The best supported variants in these three studies failed to achieve genome-wide significance [21,26,27] *(Table I)*. This is a cost-effective method of performing GWASs and has proved to be effective in identifying disease genes (eg, refs 31,32). However, due to errors in DNA quantification, this method is less sensitive than individual genotyping and has less power. Furthermore, the evaluation of data is limited to the study of (estimated) allele frequencies at the level of individual SNPs. This method does not detect the effect of haplotypes, interactions between SNPs, or the effects of genotypes that do not show differences in allele frequencies. The first individual-genotyping-based GWAS of schizophrenia involved a very small sample of 178 cases and 144 controls.[29] The best hit was for a variant near the *colony-stimulating factor-2 receptor alpha* (*CSF2RA*) gene, but this did not achieve genome-wide significance.[29] The second GWAS of this type included 738 patients and 733 controls. Although a few signals coincided with genomic regions that had been implicated in previous linkage studies of schizophrenia, this study found no genome-

Study	N° SNPs analyzed	Supported gene	Supported variant	Genomic region	*P* value discovery	N° samples discovery	*P* value combined	N° samples, replication/ meta-analysis
Mah et al (2006)	~ 25 000	*plexin A2* (*PLXNA2*)	rs752016	1q32.2	0.006	320 cases 325 controls	0.035	200 cases (EA) 230 controls (EA)
Lencz et al (2007)	~ 500 000	*colony stimulating factor receptor 2 alpha* (*CSF2RA*)	rs4129148	Xp22.33 Yp22.32	3.7×10^{-7}	178 cases 144 controls	ND	ND
Sullivan et al (2008)	~ 500 000	nearest gene: *angiotensin II receptor-associated protein* (*AGTRAP*)	rs4846033	1p36.22	4.4×10^{-6}	738 cases 733 controls	ND	ND
O´Donovan et al (2008)	~ 500 000	*zinc finger protein 804A* (*ZNF804A*)	rs1344706	2q32.1	1.8×10^{-6}	479 cases 2937 controls	1.6×10^{-7}	7308 cases 12834 controls
Shifman et al (2008)	~ 500 000	*reelin* (*RELN*)	rs7341475	7q22.1	2.9×10^{-5} (in females)	745 cases 2644 controls	8.8×10^{-7} (in females)	2274 cases 4401 controls
Kirov et al (2009)	~ 550 000	*coiled coiled domain containing 60* (*CCDC60*)	rs11064768	12q24.23	1.2×10^{-6}	574 trios	ND	ND
Need et al (2009)	~ 550 000	*ADAMTS like 3* (*ADAMTSL3*)	rs2135551	15q25.2	1.3×10^{-6}	871 cases 863 controls	NR	1460 cases 12995 controls
Shi et al (2009)	~ 600 000	*ArfGAP with GTPase domain, ankyrin repeat and PH domain 1* (*AGAP1*)	rs13025591	2q37.2	4.6×10^{-7} (in EA)	2681 cases 2653 controls (EA)		ND
		v-erb-a erythroblastic leukemia viral oncogene homolog 4 (*avian*) (*ERBB4*)	rs1851196	2q34	2.1×10^{-6} (in AA)	1286 cases 973 controls (AA)		ND
		major histocompatibility complex (*MHC*)	rs9272219 rs9272535	6p21.32 6p21.32	ND ND		6.9×10^{-8} 8.9×10^{-8}	8008 cases (EA) 19077 controls (EA)
		cluster of histone protein genes	**rs13194053**	6p22.1	1.4×10^{-2} (in EA)		9.5×10^{-9}	
The International Schizophrenia Consortium (2009)	~ 1 000 000	*myosin XVIIIB* (*MYO18B*)	rs5761163	22q12.1	3.4×10^{-7}	3322 cases 3587 controls	ND 9.5×10^{-9}	8008 cases 19077 controls
		major histocompatibility complex (*MHC*)	rs13194053	6p22.1	ND			
Stefansson et al (2009)	~ 300 000	*major histocompatibility complex* (*MHC*)	**5 variants**	6p21.3 – 6p22.1	0.0027-0.00023	2663 cases 13498 controls	**1.1×10^{-9}-1.4×10^{-12}**	12945 cases 34591 controls
		neurogranin (*NRGN*)	**rs12807809**	11q24.2	0.00045		**2.4×10^{-9}**	
		transcription factor 4 (*TCF4*)	**rs9960767**	18q21.1	0.0011		**4.1×10^{-9}**	

Table I. Published genome-wide association studies (GWASs) for schizophrenia.[21-30,32] The number of variants investigated, the best associated single-nucleotide polymorphism(s)–SNP(s)—found and the gene(s) containing the SNP(s), the corresponding *P* value(s), and the number of cases and controls in the discovery and the replication/meta-analysis sample are all given. Genome-wide significant findings are highlighted in bold. EA, European Ancestry Individuals; AA, African-American Individuals; ND, no data available; NR, no replication

wide significant association.[30] O'Donovan et al initially performed a GWAS using a moderately sized patient sample (n=479). They then performed a follow-up study of 12 markers with a *P* value ≤10^{-5} in a much larger sample to enhance the statistical power.[25] Strong evidence for replication was obtained for 3 of these 12 markers (*P* ≤5 x 10^{-4}), although the best supported variant still failed to achieve genome-wide significance *(Table I)*. The highest-ranking SNP identified in this study is located in an intron of the *zinc finger protein 804A* gene (*ZNF804A*), a putative transcription factor which had never been implicated previously in the risk for schizophrenia. The case sample was then extended to include bipolar patients. The *P* value for the total sample surpassed the level of genome-wide significance (*P*=9 x 10^{-9}). The association between *ZNF804A* and schizophrenia has recently been replicated by the International Schizophrenia Consortium,[24] and *ZNF804A* is therefore a promising susceptibility gene for schizophrenia. A recent imaging genetics study of *ZNF804A* risk genotypes has provided evidence in support of these genetic findings. This study demonstrated that healthy carriers of *ZNF804A* risk genotypes display pronounced gene-dosage-dependent alterations in functional coupling between the hippocampus and the dorsolateral prefrontal cortex (DLPFC) across the two hemispheres, which mirrors findings in patients.[33]

Three recent multicenter studies have provided important insights. The initial findings of these three studies failed to surpass the level of genome-wide significance. However, a meta-analysis was then performed using the best hits from the European data of these studies and data from a replication study by Stefansson et al.[22] This revealed a cluster of genome-wide significant SNPs in the major histocompatibility (MHC) region of chromosome 6p22.1 that were in substantial linkage disequilibrium.[22-24] These results provide evidence that the immunological system may play a role in the pathogenesis of schizophrenia. Furthermore, a variant upstream of *neurogranin* (*NRGN*; *P*=2.4 x 10^{-9}) and a SNP in *transcription factor 4* (*TCF4*; *P*= 4.1 x 10^{-9}) achieved genome-wide significance in Stefansson et al's study.[22] These studies demonstrate that GWASs of large samples can overcome limitations in power and detect common risk variants for complex psychiatric disorders.

In the study by the International Schizophrenia Consortium, it was demonstrated that possible risk variants may have been among the nominally significant SNPs that failed to reach genome-wide significance. Nominally significant SNPs were grouped into a "set of score alleles" and analyzed in an independent case-control sample, and it was shown that they distinguished cases from controls.[24] This study also demonstrated that this set of genes distinguished bipolar cases from controls, thus providing further evidence for a genetic overlap between schizophrenia and bipolar disorder. Although these SNPs explained only approximately 3% of the variance in schizophrenia risk, this may be regarded as a step towards molecular genetic evidence for the polygenic inheritance of schizophrenia.

Bipolar disorder

Six GWASs have been published to date for bipolar disorder[34-39] *(Table II)* including the landmark study by the Wellcome Trust Case Control Consortium (WTCCC) which investigated seven common disorders.[36] These studies were all based upon individual genotyping, with the exception of the study by Baum et al[39] which involved DNA pooling. Although there has been some inconsistency across studies in terms of their most associated genomic regions,[35-39] meta-analyses of some of these studies have revealed common association signals. A meta-analysis of the Baum et al[39] and the WTCCC[36] datasets found a consistent association between bipolar disorder and variants in the genes *junction adhesion molecule 3* (*JAM3*) (rs10791345, *P*=1 x 10^{-6}), and *solute carrier family 39 (zinc transporter), member 3* (*SLC39A3*) (rs4806874, *P*=5 x 10^{-6}).[40] A combined analysis of the Sklar et al[35] and WTCCC[36] studies, which included a total of 4387 patients and 6209 controls, identified the first genome-wide significant association signal for bipolar disorder for *ankyrin 3, node of Ranvier* (*ANK3*) (rs10994336, *P*=9.1 x 10^{-9}).[34] The second most strongly associated region was marked rs1006737 in *calcium channel, voltage-dependent, L type, alpha 1C subunit CACNA1C* (*P*=7 x 10^{-8}). Further independent support for *ANK3* rs10994336 has recently been obtained by Schulze et al[41] in samples from Germany and the United States (US); this study also found evidence for allelic heterogeneity at the *ANK3* locus.

Although GWASs of bipolar disorder have identified a number of potentially relevant genetic variants, the widely acknowledged formal threshold for genome-wide significance of *P*=5 x 10^{-8} has only been surpassed so far for variation in *ANK3*.

Study	N° SNPs analyzed	Supported gene	Supported variant	Genomic region	*P* value discovery	N° samples, discovery	*P* value combined	N° samples, replication/ meta-analysis
Baum et al (2007)	~ 550 000	*diacylglycerol kinase eta (DGKH)*	rs1012053	13q14.11	0.0002	461 cases 563 controls	1.5×10^{-8}	772 cases 876 controls
Welcome Trust Case Control Consortium (WTCCC; 2007)	~ 500 000	*partner and localizer of BRCA2 (PALB2)*	rs42059	7q21.3	6.3×10^{-8}	1868 cases 2938 controls	ND	ND
Sklar et al (2008)	~ 400 000	*tetraspanin-8 (TSPAN8)*	rs1705236	12q21.1	6.1×10^{-7}	1461 cases 2008 controls	NR	3329 cases 4946 controls
		myosin5B (MYO5B)	rs4939921	18q21.1	1.7×10^{-7}		NR	
		voltage-dependent calcium channel, L-type, alpha 1C subunit (CACNA1C)	rs1006737	12p13.33	8.8×10^{-4}		3.1×10^{-6}	
Ferreira et al (2008)	~ 1 800 000 (imputed) ~ 300 000 (genotyped)	ankyrin G (ANK3)	**rs10994336**	10q21.2	0.0002	1098 cases 1267 controls	**9.1×10^{-9}**	4387 cases 6209 controls
			rs1938526	10q21.2	0.0002		**1.3×10^{-8}**	
		voltage-dependent calcium channel, L-type, alpha 1C subunit (CACNA1C)	rs1006737	12p13.33	0.0108		7.0×10^{-8}	
Scott et al (2009)	~ 550 000	*inter-alpha (globulin) inhibitor H1 (ITIH1)*	rs1042779	3p21.1		2076 cases 1676 controls	1.8×10^{-7}	3683 cases 14507 controls
		multiple C2 domains, transmembrane 1 (MCTP1)	rs17418283	5q15	ND		1.3×10^{-7}	
		nuclear factor 1 A-type (NF1A)	rs472913	1p32.1			2.0×10^{-7}	
Smith et al (2009)	~ 700 000	*nck-associated protein 5 (NAP5)*	rs10193871	2q21.2	9.8×10^{-6}	1001 cases 1033 controls (EA)	ND	ND
		dpy-19-like 3 (DPY19L3)	rs2111504	19q13.11	1.5×10^{-6}	345 cases 670 controls (AA)		

Table II. Published genome-wide association studies (GWASs) for bipolar disorder.[34-39] The number of variants investigated, the best associated single-nucleotide polymorphism(s)–SNP(s)—found and the gene(s) containing that SNP(s), the corresponding *P* value(s), and the number of cases and controls in the discovery and the replication/meta-analysis sample are all given. Genome-wide significant findings are highlighted in bold. EA, European Ancestry Individuals; AA, African-American Individuals; ND, no data available; NR, no replication

Future studies involving larger samples, the pooling of datasets, and higher statistical power are expected to identify additional specific risk factors for bipolar disorder and schizophrenia.

Copy number variations

Small chromosomal aberrations (microdeletions and microduplications, collectively known as copy number variations, CNV) may confer a risk for schizophrenia, as illustrated by the 22q11.2 deletion syndrome (22q11.2DS). This is a common microdeletion syndrome with congenital and late-onset features. Patients have a high risk for neuropsychiatric diseases including psychotic disorders and major depression.[42-44] It has not been possible to correlate the extent of the deletion with the occurrence of schizophrenia in these patients, and there is experimental evidence that increased susceptibility may require the altered expression of several genes within the 22q11.2 region.[45,46] This may explain why no replicable results have

been obtained from attempts to implicate individual genes within the deletion region as susceptibility genes for schizophrenia.[47]

Schizophrenia

The application of new technologies such as comparative genomic hybridization (CGH) and SNP arrays in GWASs has enabled the identification of small chromosomal aberrations on a genome-wide scale. Initial studies reported an increased rate of aberrations in schizophrenia[48,49] and subsequent studies have implicated specific chromosomal regions.[28,50-54] Implicated aberrations include microdeletions in chromosomal regions 1q21.1, 2p16.3, 15q11.2, and 15q13.3, as well as microduplications in chromosomal regions 15q13.1 and 16p11.2. Although all of these variants are observed more frequently in patients than in controls (with odds ratios of >10 for some variants), the frequency of each individual variant in schizophrenia patients is low (<1%). Further studies are required to determine the penetrance and mutation rate of these aberrations, as well as their phenotypic spectrum. Research has shown that some variants also occur more frequently in patients with other central nervous system phenotypes such as autism, mental disability, and epilepsy.[55-58] The mechanisms that underlie the phenotypic outcome however, remain unknown. The fact that de novo mutations are found in a proportion of patients with CNVs supports the hypothesis that the negative effect on reproductive fitness observed in schizophrenia patients may be at least partly offset by the occurrence of new mutations.

Bipolar disorder

There have been few CNV studies of bipolar disorder.[59-61] Lachman et al investigated a mixed cohort of Caucasian patients (n=227) and controls (n=276) from the Czech Republic and the United States, and found that CNVs involving the gene *glycogen synthase kinase 3 beta* (*GSK3beta*) were significantly increased in patients compared with controls.[59] Using a European American sample of 1001 BD patients and 1034 controls, Zhang et al investigated singleton microdeletions (ie, those occurring only once in the total dataset of patients and controls) of more than 100 kb and found that they were overrepresented in patients.[60] The effect was strongest in a subgroup of patients with an early onset of mania (<18 years of age). A recent study of a three-generation Older Amish pedigree with segregating affective disorder[61] identified a set of 4 CNVs on chromosomes 6q27, 9q21, 12p13, and 15q11 that were enriched in affected family members and which altered the expression of neuronal genes.

No CNV with a genetic effect comparable to those identified for neuropsychiatric disorders such as schizophrenia or autism has yet been identified for bipolar disorder. In view of the limited number of studies performed, it is not possible to evaluate the influence of CNVs on disease development.

Outlook

The first GWASs of schizophrenia and bipolar disorder have recently been published, and many more are in progress. Large international collaborations have been initiated to combine GWAS data sets in order to increase statistical power, the largest being the Psychiatric GWAS Consortium, which is expected to publish its first results in 2010 (The Psychiatric GWAS Consortium Steering Committee 2009). Currently available research findings suggest that the variants identified through GWASs confer only small individual risks. The major limitation of GWASs is that they are only able to investigate common variants. If a large fraction of the genetic contribution is conferred by rare variants, other approaches will be necessary to identify them. A successful first step in this direction has been the identification of associations between rare CNVs and psychiatric diseases, in particular schizophrenia. However, due to methodological constraints, this approach remains restricted to the investigation of aberrations of at least several thousand base pairs. Continuing technological developments will provide future studies with increasing resolution, and the availability of low-cost whole genome sequencing technology will ultimately make it possible to obtain the complete genomic sequences of large patient samples for comparison with controls. In principle, this will allow the systematic identification of rare variants that are associated with disease risk, although the existence of a myriad of rare variants in the human genome will render this a complex task. It is hoped that some rare variants confer a larger disease risk, as this will facilitate the detection of association in large case-control samples. Rare variants with small disease risk may be extremely difficult to detect, since prohibitively large sample sizes may be required to demonstrate any significant association.

It is likely, however, that even after the identification of all common and rare risk variants a substantial fraction of the familial clustering will remain unexplained. This "missing heritability" in complex diseases is the subject of intense debate and several potential explanations have been proposed, including epistasis and epigenetic mechanisms.[62-64] It will be necessary to apply specific research strategies to further investigate this issue, although these may require prohibitively large sample sizes or tissue samples that are difficult to access in human subjects.

It is not yet clear whether any of the association findings identified by GWASs represent causal variants. Systematic resequencing of the associated genomic regions will provide a comprehensive overview of such variants. In cases where association findings are due to linkage disequilibrium, it is possible that the causal variants have a stronger genetic effect than has been previously suspected. It is also theoretically possible that a given association finding is not attributable to a common causal variant. A simulation study has shown that the "synthetic" effect of multiple rare variants may be responsible for signals detected for common variants. It has also been shown that the location of these variants may be relatively far (up to 2 megabases) from the site identified in GWASs.[65] If this were the case for an associated locus, resequencing over large genomic distances in large samples would be required to identify the true causative variants. Ultimately, it is necessary to identify a direct functional effect for each potential causal variant, such as an effect on the function or expression of a gene.

GWASs performed to date have indicated that certain genes contribute to a susceptibility to both schizophrenia and bipolar disorder. It is clear that some of these genes convey a rather nonspecific susceptibility that overlaps diagnostic boundaries, and it is highly probable that this also overlaps with other psychiatric disorders. Other genes, however, convey specific effects. Future studies of the phenotypic dimensions that are most strongly associated with a specific gene will include analysis of clinical symptoms and endophenotypes. The latter may be particularly suited to guiding researchers in the selection of the most promising phenotypes for animal studies.[66]

The identification of disease-associated genes is likely to increase our knowledge of the underlying pathophysiology of psychiatric disorders in an as-yet unforeseen manner. The identification of biological pathways has the potential to revolutionize diagnostics and treatment. ❑

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Nuevos hallazgos en la genética de las principales psicosis

La esquizofrenia y el trastorno bipolar tienen una etiología y una fisiopatología en gran medida desconocidas, pero son altamente heredables. Aunque los estudios de ligamiento y de asociación han identificado una serie de regiones cromosómicas que contienen probablemente genes susceptibles, el progreso en la identificación de genes causales ha sido muy decepcionante. Sin embargo, los rápidos avances tecnológicos están dando origen a nuevos conocimientos. Los estudios sistemáticos de asociación del genoma completo y de seguimiento han informado acerca de hallazgos de asociación significativa del genoma completo y variantes comunes para la esquizofrenia y el trastorno bipolar. El riesgo que determinan las variantes individuales es pequeño y algunas de ellas confieren un riesgo para ambos trastornos. Además, estudios recientes han identificado variantes estructurales largas y raras (variantes de número de copias) que otorgan un mayor riego para la esquizofrenia. Esta revisión resume los desarrollos recientes en la investigación genética de la esquizofrenia y del trastorno bipolar y discute las posibles direcciones futuras en este campo.

Nouvelles découvertes en génétique des principales psychoses

La physiopathologie et l'étiologie de la schizophrénie et des troubles bipolaires restent largement méconnues mais fortement héréditaires. Des études de liaison et d'association ont identifié des séries de régions chromosomiques contenant probablement des gènes de susceptibilité, mais l'identification des gènes de causalité est extrêmement décevante. Des avancées technologiques rapides commencent cependant à voir le jour. Des études systématiques d'association sur le génome entier et de suivi ont découvert une association significative au niveau du génome entier de variants communs pour la schizophrénie et les troubles bipolaires. Le risque inhérent aux variants individuels est faible, et certains variants comportent un risque pour les deux pathologies. De plus, des études récentes ont identifié des variants structurels importants et rares (CNV = copy number variants*, variants du nombre de copies) liés à un risque plus élevé de schizophrénie. Cet article résume les avancées récentes de la recherche génétique concernant la schizophrénie et les troubles bipolaires et analyse les perspectives possibles dans ce domaine.*

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