Schizophrenia Bulletin vol. 40 no. 3 pp. 504–515, 2014
doi:10.1093/schbul/sbu016
Advance Access publication February 24, 2014

Genetic Relationships Between Schizophrenia, Bipolar Disorder, and Schizoaffective Disorder

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There is substantial evidence for partial overlap of genetic influences on schizophrenia and bipolar disorder, with family, twin, and adoption studies showing a genetic correlation between the disorders of around 0.6. Results of genome-wide association studies are consistent with commonly occurring genetic risk variants, contributing to both the shared and nonshared aspects, while studies of large, rare chromosomal structural variants, particularly copy number variants, show a stronger influence on schizophrenia than bipolar disorder to date. Schizoaffective disorder has been less investigated but shows substantial familial overlap with both schizophrenia and bipolar disorder. A twin analysis is consistent with genetic influences on schizoaffective episodes being entirely shared with genetic influences on schizophrenic and manic episodes, while association studies suggest the possibility of some relatively specific genetic influences on broadly defined schizoaffective disorder, bipolar subtype. Further insights into genetic relationships between these disorders are expected as studies continue to increase in sample size and in technical and analytical sophistication, information on phenotypes beyond clinical diagnoses are increasingly incorporated, and approaches such as next-generation sequencing identify additional types of genetic risk variant.

Key words: family studies/twin/adoption/GWAS/copy number variants

Introduction

Evidence accumulated during the 20th century for a substantial genetic contribution to the etiology of both schizophrenia and bipolar disorder,[1] with the genetic influences initially appearing to be largely distinct for each disorder. This reinforced the traditional concept of the Kraepelinian dichotomy,[2] in which the 2 disorders were viewed as etiologically independent. The picture has now significantly changed to one of partial overlap in genetic influences, although many of the details about what is shared and independent remain to be elucidated. The dichotomy concept has thus been severely weakened[3,4] but persists in diagnostic classification systems[5,6] due to its conceptual simplicity and notable differences between the disorders in, eg, risk factors, associations with indices of neurodevelopmental impairment, clinical course, and treatment response.[7–9]

In this article, we will discuss how evidence regarding the genetic relationship between schizophrenia and bipolar disorder has evolved, both in quantitative genetics—based on family, twin, and adoption studies—and in molecular genetics, particularly through genetic association studies focusing on common risk variants and studies of rarer chromosomal structural variants. We will also discuss the controversial nosological status of schizoaffective disorder, and its subtypes, in relation to schizophrenia and bipolar disorder. We will not discuss genetic relationships with other psychotic disorders, such as depressive psychosis, delusional disorder, and brief psychotic disorder, because much less is currently known about the extent of genetic influences on these disorders.[5,10,11]

Defining Disorders for Genetic Research

The way in which schizophrenia, bipolar disorder, and schizoaffective disorder are defined can have a substantial effect on the patterns of genetic relationships between them. The most common approach in psychiatric genetics research is to assign a single main-lifetime diagnosis to each individual using the relevant version of the Diagnostic and Statistical Manual of Mental Disorders (DSM)[6] or another operational diagnostic classification

system, based on the predominant clinical picture during a person's lifetime. A notable exception is the large-scale Scandinavian population register-based family studies, which usually employ International Classification of Diseases (ICD)[5] clinical diagnoses. These tend to have lower interrater reliability than operational research diagnoses,[12] but this is mitigated by the high-quality epidemiological foundations and large sample sizes of the register-based studies.

Main-lifetime diagnoses generally incorporate a diagnostic hierarchy in which schizophrenia is placed above bipolar disorder, so that, eg, a person with one or several manic episodes at one stage of their clinical history and predominantly schizophrenic symptoms at another stage will usually have a main-lifetime diagnosis of schizophrenia. This approach has the advantage of being relatively simple, but it means that a sample of people diagnosed as having schizophrenia includes those with virtually no mood symptoms and also those with notable manic or depressive symptoms at some time during their lifetime (but not substantial enough to warrant a diagnosis of schizoaffective or mood disorder). Also, a sample of people with a diagnosis of bipolar disorder (mostly bipolar I in genetic studies due to recruitment via mental health services) includes those with no psychotic symptoms, those with purely mood-congruent psychotic symptoms (such as grandiose delusions with mania), and also those with mood-incongruent psychotic symptoms that are less obviously linked with the predominant mood state and more like symptoms characteristic of schizophrenia (but not substantial enough to qualify for a diagnosis of schizoaffective disorder or schizophrenia). The most common solution to this issue is to perform secondary analyses, further dissecting phenotypes, after an initial association is found using standard main-lifetime diagnoses.

An alternative is to employ a nonhierarchical lifetime-ever approach.[13,14] Here, if a person has, eg, a manic episode at one time and a schizophrenic episode at another, both are counted as being present, and the person is regarded as being comorbid for manic and schizophrenic episodes. This approach retains more information about symptoms, but the relative prominence of different types of symptom is less clear, and the groups are still clinically heterogeneous: eg, a sample of people with a manic episode includes those who have only ever had manic episodes and those who have also had schizophrenic episodes at some time. This could be an issue if genetic influences on manic symptoms are notably different in these 2 subgroups, and again further dissection of phenotypes could help to resolve these issues, where there is sufficient phenotypic information and large enough samples.

Genetic studies of both schizophrenia and bipolar disorder often include people with schizoaffective disorder, or some of its subtypes, in addition to the core disorder being investigated, and the proportion of people with schizoaffective disorder might be expected to have an impact on investigations of genetic relationships between schizophrenia and bipolar disorder. Debate continues over whether schizoaffective disorder, and its subtypes, are best regarded as subtypes of schizophrenia or psychotic mood disorders; as mixtures of cases, some of whom have schizophrenia and others psychotic mood disorders; as lying between these disorders on a single liability continuum; as due to the co-occurrence of elevated liabilities to these disorders; or as partly independent disorders in their own right.[15–22] Additionally, investigations of schizoaffective disorder have to contend with its relatively low interrater reliability,[23] which could potentially cause genetic overlap between disorders to be overestimated,[24] and high diagnostic instability over time.[25,26]

Quantitative Genetics

Genetic Influences on the Individual Disorders

Prior to consideration of genetic relationships between schizophrenia, bipolar, and schizoaffective disorders, it is relevant to summarize the evidence for genetic influences on the individual disorders.

Results of family, twin, and adoption studies show a notably similar pattern for each disorder. Traditional family studies conducted during the 20th century based on clinically ascertained samples show substantial familial aggregation, with sibling relative risks of around 8–10 for schizophrenia,[27–29] bipolar disorder,[30–34] and schizoaffective disorder.[17,18,35] More recently, considerably larger studies, based on Scandinavian national population registers, have substantiated the results of the earlier family studies.[14,26,36–38] Results from the largest study,[14] based on over 2 million families, are shown in table 1.

Twin studies show concordances of around 40%–45% in monozygotic (MZ) and 0%–10% in dizygotic twin pairs for schizophrenia,[39] mania/bipolar disorder,[10,40,41] and schizoaffective disorder[10] and its manic and depressive subtypes,[10] consistent with a genetic contribution to the familial aggregation seen in these disorders, while MZ concordance of considerably less than 100% indicates that noninherited risk factors are also likely to be important.

Adoption studies during the 20th century show familial aggregation of schizophrenia in biological relatives who were separated by adoption early in life,[42–47] consistent with genetic influences. Bipolar disorder was studied less but also showed evidence of familial aggregation.[48] Subsequently, a large-scale population register-based study in Sweden has further substantiated these results by showing significant familial aggregation for schizophrenia and bipolar disorder in the adopted-away offspring of affected biological parents[14] (table 1). However, there is still a lack of substantive adoption study data for schizoaffective disorder.

Table 1. Relative Risks for Schizophrenia and Bipolar Disorder in the Family and Adoption Study of Lichtenstein et al[14]

Relationship to Proband	Relative Risk of Schizophrenia When Proband Has Schizophrenia (95% CI)	Relative Risk of Bipolar Disorder When Proband Has Bipolar Disorder (95% CI)	Relative Risk of Schizophrenia When Proband Has Bipolar Disorder (95% CI)	Relative Risk of Bipolar Disorder When Proband Has Schizophrenia (95% CI)
Family relationships with shared environment				
Offspring	9.9 (8.5–11.6)	6.4 (5.9–7.1)	2.4 (2.1–2.6)	5.2 (4.4–6.2)
Sibling	9.0 (8.1–9.9)	7.9 (7.1–8.8)	3.9 (3.4–4.4)	3.7 (3.2–4.2)
Adopted-away biological relatives				
Adopted-away offspring	13.7 (6.1–30.8)	4.3 (2.0–9.5)	4.5 (1.8–10.9)	6.0 (2.3–15.2)

Note: Reprinted from Lichtenstein et al[14], Copyright (2009), with permission from Elsevier.

Heritability estimates based on twin study data are around 80% for schizophrenia,[39,49] mania/bipolar disorder,[40] and schizoaffective disorder[10] and its manic and depressive subtypes.[10] The heritability of schizophrenia and bipolar disorder has also been estimated from Scandinavian national population family and adoption data and found to be somewhat lower at around 60%.[14,50] The reasons for the difference are not clear, eg, how much due to differences in the types of relatives included or ascertainment methods, but it can still be concluded that the heritabilities of schizophrenia and bipolar disorder are substantial and similar, and in the region of 60%–80%.

Data from risks of disorders in relatives have also been used to model the most likely mode of inheritance of schizophrenia[51,52] and bipolar disorder.[53,54] For both disorders, this is likely to be multifactorial in most or all cases, with many genetic and environmental risk factors, each insufficient to cause the disorder on their own, but having a cumulative effect on risk when they occur together in the same individual.

Relationship Between Schizophrenia and Bipolar Disorder

Traditional clinically ascertained family studies during the 20th century, employing main-lifetime diagnoses, generally did not find a significant excess of bipolar disorder among the relatives of individuals with schizophrenia, or vice versa,[32,34,55,56] supporting the concept of an etiological dichotomy between the 2 disorders. However, these studies could not exclude a degree of familial coaggregation due to sample size limitations.[57]

Consistent with this, a twin study, based on the Maudsley twin register in London,[13] found no co-occurrence of schizophrenia and bipolar disorder in MZ twin pairs when a hierarchical main-lifetime diagnosis was employed, again with the caveat of sample size limitations. However, when a nonhierarchical lifetime-ever approach was taken, significant coaggregation was seen between schizophrenic and manic episodes in twin pairs, and model-fitting showed a significant genetic correlation of 0.68 between lifetime-ever schizophrenia and mania.

Subsequently, the Swedish national population register-based family/adoption study,[14] also using a nonhierarchical diagnostic approach, showed significant familial coaggregation between schizophrenia and bipolar disorder in parent–offspring, sibling–sibling, and biological parent–adopted-away offspring pairs (table 1). The cross-disorder relative risks were lower than the same-disorder relative risks, consistent with partial sharing of genetic influences, and there was a very similar genetic correlation of 0.60. For hierarchical diagnoses, the genetic correlation was 0.46 (B. Yip, personal communication). This study also found a significantly elevated risk of bipolar disorder in siblings of probands with schizophrenia (relative risk: 2.7, 95% CI: 2.3–3.1), when individuals who had both schizophrenia and bipolar disorder were excluded, showing that in the primary nonhierarchical diagnostic analysis, the familial coaggregation of schizophrenia and bipolar disorder was not solely due to individuals who had both disorders diagnosed.

Further evidence for partial overlap in familial influences on schizophrenia and bipolar disorder has come from studies based on Danish national population registers. In one study,[37] the relative risk of schizophrenia for a person whose mother had schizophrenia was 8.97 (95% CI: 6.93–11.62), while the relative risk of schizophrenia if their mother had bipolar disorder was 2.41 (95% CI: 1.59–3.65). The corresponding risks for affected fathers were 6.63 (95% CI: 4.83–9.09) and 3.15 (95% CI: 2.11–4.69). A similar pattern was also seen for the relative risk of bipolar disorder when parents or siblings had schizophrenia.[36] In another study,[38] focusing on families with 2 affected parents, where both parents had schizophrenia the absolute risk of bipolar disorder in their offspring was 10.8% (95% CI: 2.6–19.0), about 10 times higher than the general population risk of bipolar disorder.

Additionally, a meta-analysis of family studies published between 1980 and 2006 found evidence of familial

overlap, with the first-degree relatives of probands who had schizophrenia showing a significantly elevated risk of bipolar disorder compared with relatives of controls (OR = 2.08, $P = .01$).[58]

Schizoaffective Disorder

Traditional family studies during the 20th century found evidence of familial overlap between schizoaffective disorder and both schizophrenia and bipolar disorder,[32,34,35,55,59] and again this has been substantiated by more recent Scandinavian population register-based studies.[26,36]

An investigation in the Maudsley twin series,[13] based on nonhierarchical diagnoses, found significant genetic correlations between schizoaffective disorder and both schizophrenia and mania (correlations of 0.77 and 0.88, respectively). Model-fitting of the 3 syndromes together was consistent with all of the genetic influences on schizoaffective disorder being shared with schizophrenia and mania. Caveats included limited sample size and only moderate interrater reliability for schizoaffective disorder.

Schizoaffective Subtypes. Investigations that have subdivided schizoaffective disorder have most commonly used manic/bipolar and depressive subtypes. In family studies, relatives of probands with both subtypes have shown elevated risks of schizophrenia.[34,35] The manic/bipolar subtype has been associated with a relatively high familial risk of mania/bipolar disorder in some studies,[34,53] supporting the value of focusing on the subtypes, while other studies have also found the depressive subtype to be associated with elevated familial risk of bipolar disorder,[18,35,55] supporting a focus on schizoaffective disorder as a unitary entity.

An investigation of manic/bipolar and depressive subtypes of schizoaffective disorder in the Maudsley twin series,[21] using both hierarchical and nonhierarchical diagnostic approaches, found a marked degree of familial overlap in MZ twin pairs between all of the syndromes investigated—Research Diagnostic Criteria (RDC) schizoaffective mania, schizoaffective depression, schizophrenia, and mania/bipolar disorder,[60] with a trend toward schizoaffective mania and mania/bipolar disorder having the highest degree of overlap. The pattern of results was consistent with the schizoaffective mania/bipolar subtype being due to co-occurring elevated liability to schizophrenia, mania/bipolar disorder, and probably also depressive disorder, while the results for the schizoaffective depressive subtype were also consistent with co-occurring elevated liability to schizophrenia, mania/bipolar disorder, and depressive disorder but probably with a lesser degree of elevated liability to mania/bipolar disorder than the schizoaffective mania/bipolar subtype. Again there was the caveat of only moderate interrater reliability for schizoaffective subtypes; also, sample size limitations prevented formal model-fitting for individual syndromes.

Molecular Genetic Studies

During the 20th century, genome-wide genetic linkage studies produced a range of chromosomal regions of potential interest, and genetic association studies, focusing on specific genes with limited a priori evidence and/or with limited sample sizes, found a range of significant associations,[61] but these have been difficult to replicate consistently. More recently, the focus has turned to large-scale genome-wide association studies (GWAS), as these have become technically feasible, which are geared to detect commonly occurring genetic variants that individually have a small effect on risk, and studies of large chromosomal structural variants, particularly copy number variants (CNVs), that are rarer but have a larger effect on risk when they occur.

Genome-Wide Association Studies

Analysis of Individual Genetic Markers. GWAS typically investigate a million or more measured or imputed genetic markers spread along each chromosome, with sample sizes rising in recent years to tens of thousands of cases and controls.[62–64] The genetic markers are usually single-nucleotide polymorphisms (SNPs) where, at a particular point in the DNA sequence, the nucleotide base varies in the population, eg, individuals may carry either a C or an A allele. The study investigates whether one of the variants occurs more frequently than expected in cases than controls. If so, this statistical association may indicate the presence of a causal genetic variant nearby (in linkage disequilibrium) or, less commonly, that the genetic marker variant itself may have a causal effect. False positive associations are also likely, particularly due to the large numbers of markers being tested, so a very high degree of statistical significance is required (so-called genome-wide significance is usually $P < 5 \times 10^{-8}$).

The first substantive GWAS result in schizophrenia was for a marker in the zinc finger–binding protein 804A gene (*ZNF804A*) on chromosome 2q32.[65] In order to investigate whether this association might involve a genetic variant that influenced risk of both schizophrenia and bipolar disorder, a bipolar disorder sample was added to the analysis. The effect size remained similar (OR = 1.12), while the P value became notably more significant ($P = 9.96 \times 10^{-9}$), consistent with the presence of a genetic variant that has a small effect on the risk of both disorders. These findings have been further substantiated by larger meta-analysis (schizophrenia: $P = 2.5 \times 10^{-11}$, OR = 1.10; schizophrenia and bipolar disorder combined: $P = 4.1 \times 10^{-13}$, OR = 1.11).[66]

As GWAS sample sizes increased, thanks to large-scale international collaborations, genome-wide significant associations were found with markers in or near the major histocompatibility complex region on chromosome 6[67] and the genes encoding neurogranin (*NRGN*) (11q24) and transcription factor 4 (*TCF4*) (18q21).[68]

Concurrently, collaborative GWAS of bipolar disorder identified genome-wide significant associations with markers in the genes encoding the alpha 1C subunit of the L-type voltage-gated calcium channel (*CACNA1C*) (12p13) and ankyrin 3 (*ANK3*) (10q21).[69] Subsequently, the Psychiatric Genomics Consortium (PGC) published the largest GWAS "mega-analysis" of bipolar disorder to date, involving over 60 000 participants.[64] The *CACNA1C* association was further substantiated and there was a new genome-wide significant association with a marker in *ODZ4* (11q14).

At the same time, a GWAS mega-analysis of schizophrenia, also from the PGC and involving over 50 000 participants,[62] found genome-wide significant associations at 7 loci, 5 of which were new (1p21.3, 2q32.3, 8p23.2, 8q21.3 and 10q24.32-q24.33) and 2 of which had been previously implicated (6p21.32-p22.1 and 18q21.2). The strongest of the new findings was for a marker in the gene encoding microRNA 137 (*MIR137*), which has a role in the regulation of neuronal development. The study also reported analyses of combined schizophrenia and bipolar disorder samples, with associations at 3 loci, *CACNA1C*, *ANK3*, and *ITIH3-ITIH4*, being genome-wide significant and showing increased levels of statistical significance in the combined analysis, consistent with genetic variants in these regions influencing risk of both disorders.

A subsequent review summarized the strongest published GWAS findings for schizophrenia, bipolar disorder, and both disorders combined[70] (table 2). In keeping with the focus of GWAS, the associations each involve a small effect on risk (ORs around 1.1) and are consistent with a partial overlap in genetic influences from commonly occurring genetic variants on the 2 disorders. There is also evidence that most of these associations occur in and around genes.[71,72]

Recently, the PGC Cross-Disorder Group has published a broader investigation encompassing 5 psychiatric disorders: schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorder, and attention-deficit hyperactivity disorder (ADHD).[73] In the primary analysis of all 5 disorders combined, markers in 4 regions achieved genome-wide statistical significance. In 2 cases (on chromosomes 3p21 and 10q24), the causal variant behind the marker association could be located in or between a number of genes within the region, while in the other 2 cases, the associations were in calcium channel signaling genes (*CACNA1C* on chromosome 12 and *CACNB2* on chromosome 10), and additional pathway analysis further supported the role of calcium channel activity genes influencing all 5 disorders.

The study also investigated the diagnostic specificity of genome-wide significant associations for schizophrenia and bipolar disorder found in previous PGC analyses. In keeping with previous findings, the results ranged from associations confined to one disorder to associations encompassing all 5 disorders (table 3).

Table 2. Genome-Wide Association Study Findings for Schizophrenia and Bipolar Disorder From the Review by Sullivan et al[70]

Phenotype	Chromosome Where Marker Is Located	Nearest Gene	OR
Schizophrenia	1	*MIR137*	1.12
	2	*VRK2*	1.09
	2	*ZNF804A*	1.10
	2	*PCGEM1*	1.20
	6	*MHC*	1.22
	8	*MMP16*	1.10
	8	*CSMD1*	1.11
	8	*LSM1*	1.19
	10	*CNNM2*	1.10
	10	*NT5C2*	1.15
	11	*AMBRA1*	1.25
	11	*NRGN*	1.12
	18	*CCDC68*	1.09
	18	*TCF4*	1.20
Bipolar disorder	11	*ODZ4*	1.14
	12	*CACNA1C*	1.14
	19	*NCAN*	1.17
Schizophrenia and bipolar disorder combined	2	*ZNF804A*	1.11
	3	*ITIH3-ITIH4*	1.12
	10	*ANK3*	1.22
	12	*CACNA1C*	1.11

Notes: Based on studies with large samples (minimum of around 10 000 cases and 10 000 controls) and SNP markers showing associations at genome-wide level of statistical significance ($P < 5 \times 10^{-8}$). Reprinted from Sullivan et al[70], Copyright (2012), with permission from Macmillan Publishers Ltd.

GWAS continue to increase in sample size.[63,74–77] For example, in studies of schizophrenia, this has included the addition of substantial numbers of patients treated with clozapine[74] and a Swedish national sample,[63] which has resulted in 22 genome-wide significant loci being identified. Further analysis of these loci across disorders is awaited. There has also been an initial GWAS directly comparing cases of schizophrenia and bipolar disorder, with a view to identifying genetic differences between the 2 disorders.[77] The study was underpowered to achieve genome-wide significant results, but further larger studies are likely to follow soon.

Combined Analysis of Genetic Markers Using Polygenic Scores. An alternative to analyzing each genetic marker individually is to combine markers that show some evidence of association, taking a low statistical threshold, eg, $P < .5$, which aims to include many associations with variants that are probably causal but have not yet achieved genome-wide statistically significant association, eg, as sample sizes are not yet large enough, and accepting a degree of noise from markers that show trends toward association by chance. Scores are assigned to each individual based on the number of markers where they carry the putative risk variant, weighted by the effect size for

Table 3. Disorder Specificity of Genome-Wide Association Study Findings for Schizophrenia and Bipolar Disorder in the Psychiatric Genomics Consortium Cross-Disorder Group Study of 5 Psychiatric Disorders (2013)[73]

Phenotype in Original GWAS	Chromosome Where Marker Is Located	Nearest Gene	Disorders Showing Association
Schizophrenia	1	*MIR137*	SZ, ASD
	2	*PCGEM1*	SZ, ASD
	6	*MHC*	SZ
	8	*MMP16*	SZ
	8	*CSMD1*	SZ
	10	*CNNM2*	SZ, MDD
	10	*NT5C2*	SZ, BPD, MDD, ASD, ADHD
	11	*STT3A*	SZ
	18	*CCDC68*	SZ, BPD, MDD
	18	*TCF4*	SZ, ASD
Bipolar disorder	6	*SYNE1*	BPD
	10	*ANK3*	BPD
	11	*ODZ4*	BPD
	12	*CACNA1C*	BPD, SZ, MDD

Notes: Analysis of associations with 5 psychiatric disorders at loci showing genome-wide statistically significant association with schizophrenia or bipolar disorder in previous PGC analyses. SZ, schizophrenia; BPD, bipolar disorder; MDD, major depressive disorder; ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder. Reprinted from Cross-Disorder Group of the Psychiatric Genomics Consortium[73], Copyright (2013), with permission from Elsevier.

each marker. These are known as polygenic scores, the term relating to the focus on investigating the cumulative effect of many commonly occurring genetic risk variants.

In the first such analysis for schizophrenia,[78] polygenic scores calculated in an initial (discovery) sample significantly distinguished between cases and controls in an independent (test) schizophrenia sample (with higher scores in cases), and further modeling was consistent with the effect coming from a large number of common risk variants. The variance in the test sample explained by the polygenic score was modest (3%), but further analysis, eg, accounting for attenuation of associations based on markers rather than the actual causal variants, suggested that at least one-third of the variance in risk could be explained by polygenic effects. These findings have been substantiated in larger samples[62,63] and by further analysis[79] and have also been found to apply to bipolar disorder.[64]

In the original study,[78] the polygenic scores in the initial schizophrenia discovery sample also significantly distinguished between bipolar disorder cases and controls in 2 independent samples, but with the variance explained dropping from 3% to 1.9% and 1.4%, consistent with partial overlap in the polygenic contribution to risk of schizophrenia and bipolar disorder. In contrast, the schizophrenia polygenic scores did not significantly distinguish between cases and controls in samples with 6 nonpsychiatric medical conditions, including coronary artery disease, rheumatoid arthritis, and type I and type II diabetes.

The recent PGC cross-disorder study,[73] and a further study,[80] using different analytic approaches, further substantiated the partial overlap in polygenic influences on schizophrenia and bipolar disorder, with a genetic correlation due to common SNP markers of 0.68.[81]

CNV Studies

While GWAS results are showing evidence for notable genetic overlap between schizophrenia and bipolar disorder, studies of larger (>100 kb) chromosomal structural variants, particularly CNVs, are showing differences between the 2 disorders.

CNVs involve deletions or duplications of sections of chromosomes, between 1 kilobase and several megabases in length. An early identified CNV is the microdeletion on chromosome 22q11, which causes velocardiofacial, or DiGeorge, syndrome,[82] and which is associated with a relatively high risk of developing psychotic disorders.[83] Subsequently, many more CNVs have been identified in the human genome.[84–86]

Some studies have focused on the frequency of CNVs overall,[87,88] while others have focused on CNVs at particular chromosomal locations.[87,89,90] Both approaches have shown an elevation of large, rare (frequency < 0.01) CNVs in individuals with schizophrenia compared with controls. The list of specific CNVs associated with schizophrenia is gradually increasing and currently includes chromosomal deletions and/or duplications on chromosomes 1q21, 2p16 (*NRXN1*), 3p26, 3q29, 5p13, 7q11, 7q22, 7q36 (*VIPR2*), 15q11, 15q13, 16q11, 16p13, 17p12, 17q12 and 22q11.[70,91–93] Frequencies are typically in the order of 0.2% in cases and 10 times rarer in controls, with ORs of 2.1–20.3.[70] Thus, CNVs are considerably rarer than the variants that are the focus of GWAS but have a

considerably greater effect on risk of schizophrenia when they occur.

Large CNVs, including those associated with schizophrenia, are also associated with other neurodevelopmental disorders such as mental retardation/intellectual disability, autism spectrum disorder, ADHD, and generalized epilepsy.[70,91,94–96] Interestingly, most of the CNVs associated with schizophrenia are associated with even greater risk of earlier onset disorders such as congenital malformation, developmental delay, and autism spectrum disorder, with the overall penetrance, including schizophrenia, ranging between 10% and 100%.[97] This means that pathogenic CNVs tend to be associated with markedly reduced fecundity and, in consequence, are selected out of the population a few generations after occurring de novo. They continue to be seen because of relatively high mutation rates at these loci.[98]

In contrast to findings in schizophrenia, studies of bipolar disorder have tended to find no evidence for increased burden of large, rare CNVs and moreover point to the possibility that such events might be even less common than in controls.[99–101] There is also some evidence that such CNVs are enriched in bipolar disorder cases with early age at onset,[102,103] although not all studies have observed this.[101] Given that large CNVs have adverse consequences on brain development and cognition,[104] these findings are consistent with the view that a diagnosis of bipolar disorder is unlikely to be made in the presence of cognitive and other sequelae of neurodevelopmental impairment and that what we refer to as schizophrenia has a stronger neurodevelopmental component than bipolar disorder.[4,95]

Molecular Genetic Studies of Schizoaffective Disorder

As discussed above, most studies include schizoaffective disorder or its subtypes as adjunctive phenotypes, when the main focus of the study is schizophrenia or bipolar disorder. However, some studies have focused on individuals with schizoaffective disorder within these samples.

For example, a study of RDC schizoaffective disorder, bipolar subtype (which has a broader definition of the disorder than DSM-IV), found an association with markers in γ-aminobutyric acid A ($GABA_A$) receptor genes, but no significant association with schizophrenia or bipolar disorder.[105] This finding was replicated in an independent sample.[106] If further investigation confirms this as a true association, it remains to be seen whether it is specific to the bipolar subtype of schizoaffective disorder or whether associations with schizophrenia and bipolar disorder become more evident, eg, with larger sample sizes.

Polygenic score analysis has also been applied to the RDC schizoaffective disorder bipolar subtype. Polygenic scores from schizophrenia[78] were used to test differences between subphenotypes in 2 bipolar disorder samples.[107] This study found that individuals with schizoaffective disorder bipolar subtype had higher scores than individuals with bipolar disorder, consistent with the polygenic influences on schizophrenia having a greater overlap with those for schizoaffective disorder bipolar subtype than with those for bipolar disorder.

It has also been noted that RDC schizoaffective disorder, bipolar subtype, may have particular utility for picking up association signals in GWAS studies,[108] so it may be worthy of more research attention if the problems with interrater reliability can be overcome.

Conclusions and Future Directions

In summary, there is now strong evidence for partial overlap of genetic influences on schizophrenia and bipolar disorder, with a genetic correlation of around 0.6. It is likely that part of the overlap is due to commonly occurring genetic variants, as detected by GWAS, that have a small effect on risk individually, but where a person's risk increases as they carry more risk alleles. It is also likely that there are common risk variants that are not shared between the 2 disorders. Additionally, current evidence suggests that large, rare CNVs are likely to have a greater influence on the risk of schizophrenia than bipolar disorder. Evidence from twin analysis is consistent with all genetic risk factors for schizoaffective episodes also being risk factors for schizophrenic and manic episodes, while association studies hint at the possibility of some relatively specific genetic risk factors for the bipolar subtype of schizoaffective disorder.

In addition to the balance of genetic and environmental risk factors with varying specificity for disorders, the clinical presentation may also be influenced by the overall quantitative burden of risk factors[109] and by additional modifying factors that do not influence the risk of developing a disorder but influence the clinical picture among individuals with a disorder.[110,111]

In terms of future research developments, as GWAS continue to increase in sample size, to include more samples with ancestries other than European, and to be analyzed in more sophisticated ways,[112] it is expected that many more commonly occurring risk variants will emerge. This is most likely to further substantiate the current pattern of partial genetic overlap between schizophrenia and bipolar disorder, and further dissection of the clinical phenotypes may show more substantive evidence of graded relationships,[20] eg, bipolar disorder with mood-incongruent psychotic symptoms and the bipolar subtype of schizoaffective disorder having progressively closer genetic relationships with schizophrenia compared with more clinically pure forms of bipolar disorder.

At the same time, further CNVs associated with schizophrenia are likely to be identified. It will be interesting to see whether any associations with bipolar disorder tend to be predominantly with more schizophrenia-like subforms, eg, where there are mood-incongruent psychotic

symptoms or cognitive impairment, and also the effect of CNVs on schizoaffective disorder.

Between the commonly occurring variants detectable by GWAS and rarer CNVs, there are likely to be genetic risk variants of intermediate frequency and effect size, and also rare single-nucleotide mutations.[70] High-throughput next-generation genetic sequencing studies are underway, aimed at uncovering both inherited and de novo genetic variants in these ranges.[113–116] It is an open question at present how much or little these will show associations in common between disorders.

In order to understand how candidate genetic risk variants play a causal role, it is necessary to elucidate their functional consequences, eg, at the level of RNA expression[66,117] and in animal models,[118–120] to consider effects at the level of biological systems,[4,70,121] and to incorporate environmental effects, including those acting via epigenetic mechanisms.[122] Investigations in each domain have the potential to further elucidate relationships between clinical disorders. It is hoped that such investigations will lead to the development of improved treatments, which again could have shared or relatively specific effects on different disorders.

In addition to diagnosis-based phenotypes, other clinical phenotypes, such as quantitative symptom dimensions of psychotic and mood symptoms,[77,109,123,124] illness history variables, such as age at onset and illness course, and endophenotypes, eg, based on cognitive profiles and neuroimaging,[125–131] that have common and relatively distinct associations with clinical disorders, are likely to be valuable in providing further insights into genetic relationships.[112,132–134] Initiatives include the NIMH Research Domain Criteria (RDoC) project, which focuses on research integrating dimensions of behavior and neurobiology.[135] Also, longitudinal studies, eg, following up large cohorts of twins from early childhood through adult life, have potential to give further insights into how genetic and environmental influences on development link with the emergence of clinical disorders, and also the etiological relationships between clinical disorders and the occurrence of subclinical psychotic and mood symptoms in the general population.[136–140]

As part of this process, the predominant use of current main-lifetime diagnostic categories may change to a more flexible approach[141] in which categorical or dimensional syndromes, networks of correlated symptoms, and/or endophenotypes are increasingly employed according to particular research or clinical requirements.

Funding

Work in Cardiff was supported by Medical Research Council (MRC) Centre (G0800509) and Program Grants (G0801418) and the European Community's Seventh Framework Programme (HEALTH-F2-2010–241909 [Project EU-GEI]).

Acknowledgment

The authors have declared that there are no conflicts of interest in relation to the subject of this article.

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