Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study

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Background Whether schizophrenia and bipolar disorder are the clinical outcomes of discrete or shared causative processes is much debated in psychiatry. We aimed to assess genetic and environmental contributions to liability for schizophrenia, bipolar disorder, and their comorbidity.

Methods We linked the multi-generation register, which contains information about all children and their parents in Sweden, and the hospital discharge register, which includes all public psychiatric inpatient admissions in Sweden. We identified 9 009 202 unique individuals in more than 2 million nuclear families between 1973 and 2004. Risks for schizophrenia, bipolar disorder, and their comorbidity were assessed for biological and adoptive parents, offspring, full-siblings and half-siblings of probands with one of the diseases. We used a multivariate generalised linear mixed model for analysis of genetic and environmental contributions to liability for schizophrenia, bipolar disorder, and the comorbidity.

Findings First-degree relatives of probands with either schizophrenia (n=35 985) or bipolar disorder (n=40 487) were at increased risk of these disorders. Half-siblings had a significantly increased risk (schizophrenia: relative risk [RR] 3·6, 95% CI 2·3–5·5 for maternal half-siblings, and 2·7, 1·9–3·8 for paternal half-siblings; bipolar disorder: 4·5, 2·7–7·4 for maternal half-siblings, and 2·4, 1·4–4·1 for paternal half-siblings), but substantially lower than that of the full-siblings (schizophrenia: 9·0, 8·5–11·6; bipolar disorder: 7·9, 7·1–8·8). When relatives of probands with bipolar disorder were analysed, increased risks for schizophrenia existed for all relationships, including adopted children to biological parents with bipolar disorder. Heritability for schizophrenia and bipolar disorder was 64% and 59%, respectively. Shared environmental effects were small but substantial (schizophrenia: 4·5%, 4·4%–7·4%; bipolar disorder: 3·4%, 2·3%–6·2%) for both disorders. The comorbidity between disorders was mainly (63%) due to additive genetic effects common to both disorders.

Interpretation Similar to molecular genetic studies, we showed evidence that schizophrenia and bipolar disorder partly share a common genetic cause. These results challenge the current nosological dichotomy between schizophrenia and bipolar disorder, and are consistent with a reappraisal of these disorders as distinct diagnostic entities.

Introduction

Opinions differ about whether schizophrenia and bipolar disorder have a common cause. Some think that schizophrenia and bipolar disorder are the clinical outcomes of entirely different processes, whereas others believe in identical processes. Several intermediate and more-complicated hypotheses can also be envisioned whereby, for example, a shared causative risk factor is responsible for part of each disorder. A common cause has been suggested by molecular genetic studies[1] by the existence of an intermediate phenotype (schizoaffective disorder), which shares diagnostic features of both disorders, and by evidence that similar endophenotypes (eg, brain white-matter density)[2] are associated with both disorders. However, evidence from genetic epidemiological studies is mixed partly because of small sample sizes.[3,4]

Genome-wide linkage screenings have shown some overlap between schizophrenia and bipolar disorder.[5,6] One meta-analysis showed genomic regions in common,[7] although a more inclusive meta-analysis suggested that no overlap of the highest-ranking regions for the two

disorders existed;[8,9] a third meta-analysis with genotype data from individual studies did not show strong overlap.[10] However, overlap can arise by chance. If we assume three 500-marker genome scans for schizophrenia and three for bipolar disorder, with a simple simulation model (α=0·05, 10 000 simulations) with no true genetic effects, the absence of positional overlap between any schizophrenia scan and any bipolar disorder scan would be uncommon (7%), one overlap would happen frequently (18%), and multiple overlaps would predominate (75%). Therefore, because there are 20 schizophrenia and 18 bipolar disorder genome-wide linkage scans,[8,9] substantial overlap across studies is to be expected purely by chance. An additional difficulty is that individuals with schizoaffective disorder are generally classified as affected in genetic studies of each syndrome.[8,9]

Some workers have investigated the genetic association of markers in candidate genes in both schizophrenia and bipolar disorder.[11–13] These studies provide evidence for an overlap in genetic susceptibility between the two disorders, and for the possibility of specific associations

	Full-siblings			Half-siblings		
	Sibling correlation	Spouse correlation	Parent–offspring correlation	Sibling correlation	Spouse correlation	Parent–offspring correlation
Additive genetic effects	0·5	0	0·5 or 0*	0·25	0	0·5 or 0*
Adult shared environmental effects (maternal and paternal)	0	1	0	0	1	0
Childhood shared environmental effects	1	0	0	1 or 0†	0	0

*Expected correlation is 0·5 between parent and biological offspring, and 0 for parent and non-biological offspring. †Expected correlation is 1 for maternal half-siblings and 0 for paternal half-siblings.

Table 1: **Expected genetic and environmental correlations in disease liability**

between genotype and type of pathology,[1] although interpretations should be drawn with caution.[14]

Studies that are based on diagnostic resemblance in familial relationships can be helpful to understand the sources of overlap between two disorders. One twin study[15] is usually cited as supporting the overlap between schizophrenia and bipolar disorder, although its conclusions are qualified by a small sample size and assessment of mania, rather than bipolar disorder per se. A small Finnish study[16] of 26 twins with bipolar disorder did not identify any co-twin with schizophrenia. High-quality family studies have suggested that schizophrenia and bipolar disorder do not overlap.[3,4] One study[5] stated "there is no increased risk for bipolar disorder among first-degree relatives of schizophrenia probands...nor is there increased risk for schizophrenia among first-degree relatives of bipolar disorder probands". However, in a large population-based study in Denmark,[17] risk of bipolar disorder was associated with a history of schizophrenia in parents and siblings.

Because the relation between schizophrenia and bipolar disorder is unclear, we have used population-based registries that contain the entire Swedish population to assess the degree of genetic overlap between these two disorders.

Methods

National registers

We linked two Swedish national registers, using the unique, individual Swedish national registration number, which was introduced in 1947 and is assigned at birth.

The multi-generation register contains information about first-degree relatives.[18] This register includes entries for an index person along with their biological and adoptive parents. To be in the register, an index person had to be registered in Sweden between Jan 1, 1961, and Dec 31, 2002, and to have been born between Jan 1, 1932, and Dec 31, 2002. The father was assumed to be the husband of the mother at the time of birth or the person acknowledged as the father by unmarried mothers.

The hospital discharge register contains all public psychiatric inpatient admissions in Sweden since 1973. Every record has admission and discharge dates, the main discharge diagnosis, and up to eight secondary diagnoses assigned by the treating physician according to the International Classification of Diseases (ICD) system.[19–21] We obtained information about all psychiatric admissions between 1973 and 2004.

Disease classifications

Patients with schizophrenia were defined as individuals identified in the hospital discharge register having at least two inpatient admissions with a discharge diagnosis of schizophrenia (ICD-8 295, ICD-9 295, ICD-10 F20, with latent schizophrenia, 295.5 and 295F, excluded). The criterion of at least two inpatient admissions was chosen to increase diagnostic precision, and in a previous study gave almost identical estimates of familial risks to those from published work.[22] Similarly, we defined bipolar disorder as two or more inpatient admissions for a core bipolar diagnosis (296 and F31).

Both diseases were diagnosed with a non-hierarchical diagnostic structure. Thus, an individual could have both schizophrenia and bipolar disorder, if the person has been diagnosed at least twice with each disease. To avoid possible misclassification between schizophrenia and bipolar disorder, admissions with the diagnoses of schizoaffective disorder (ICD codes 295.7, 295H, F25.X) were not taken into account, and 3563 individuals were therefore excluded.

Statistical analysis

The risk of disease in relatives of a proband with that disease was compared with the risk in relatives of five unaffected individuals matched by sex and year of birth for each member in the pair (for adoptive relationships, individuals were matched with 5-year age-band intervals). To ensure equal follow-up time, we additionally required that the relatives of probands and controls were alive and had not been admitted to psychiatric care in Sweden by the date the proband was first admitted. Data were analysed with a conditional logistic regression model with the PROC TPHREG procedure in SAS (version 9.1.3).[23] Because several possibly correlated pairs of relatives from every family could be included in an analysis, a robust sandwich estimator was used to adjust

	Relation to proband	Risk for schizophrenia when proband has schizophrenia		Risk for bipolar disorder when proband has bipolar disorder		Risk for schizophrenia when proband has bipolar disorder		Risk for bipolar disorder when proband has schizophrenia	
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Biological relationships									
Parent	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	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
Sibling	Maternal half-sibling	3·6	2·3–5·5	4·5	2·7–7·4	1·4	0·7–2·6	1·2	0·6–2·4
Sibling	Paternal half-sibling	2·7	1·9–3·8	2·4	1·4–4·1	1·6	1·0–2·7	2·2	1·3–3·8
Adoptive relationships									
Biological parent	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
Sibling	Adopted away biological sibling	7·6	0·7–87·8	..	..	3·9	0·2–63·3	5·0	0·3–79·9
Adoptive parent	Adoptee	..	..	1·3	0·5–3·6	1·5	0·7–3·5	..	..
Sibling	Non-biological sibling	1·3	0·1–15·1	..	..	..	..	2·0	0·1–37·8

RR=relative risk. *Adopted children whose biological parents have disease.

Table 2: **Recurrence risks for schizophrenia and bipolar disorders**

	Additive genetic effects (A)	Childhood shared environmental effects (C)	Non-shared environmental effects (E)
Non-hierarchical diagnoses			
Schizophrenia	64·3% (61·7%–67·5%)	4·5% (4·4%–7·4%)	31·1% (25·1%–33·9%)
Bipolar disorder	58·6% (56·4%–61·8%)	3·4% (2·3%–6·2%)	38·0% (32·0%–41·2%)
Comorbidity	63·4% (62·0%–64·9%)	5·9% (4·0%–6·8%)	30·6% (28·7%–32·3%)
Hierarchical diagnoses*			
Schizophrenia	64·3% (61·5%–72·2%)	2·5% (1·9%–6·6%)	33·2% (21·2%–36·7%)
Bipolar disorder	55·1% (50·8%–60·7%)	2·8% (1·9%–7·2%)	42·1% (32·1%–47·3%)
Comorbidity	91·7% (85·2%–100·0%)	8·3% (0·6%–8·3%)	..

Data are parameter estimates (95% CI). *When hierarchical diagnoses were used, non-shared environmental effects did not contribute to comorbidity because an individual could not be diagnosed with both disorders.

Table 3: **Estimates of genetic and environmental effects for liability to schizophrenia, bipolar disorder, and their comorbidity**

for the correlated data when calculating the confidence intervals.

To separate genetic and environmental contributions to liability for schizophrenia and bipolar disorder, we analysed outcomes from different family types: nuclear, paternal half-sibling, and maternal half-sibling families. To reduce complexity in families with half-siblings, marriages of the index parent were restricted to two spouses, which excluded 8% of the half-sibling families. When more than two children were available, we analysed only the oldest two full-siblings from a nuclear family and the oldest two half-siblings from a half-sibling family. Our data include 1 984 182 nuclear families, 172 073 paternal half-sibling families, and 161 409 maternal half-sibling families.

We used a multivariate generalised linear mixed model with probit link.[24] The probability for an individual to have a disease is measured by a latent risk variable R, which corresponds to the area under the standard normal curve—ie, a small value of R indicates a small probability. Our model specified R as the sum of several effects, including family-member type (father, mother, or children), additive genetic (A_{sz}, A_{bp}), adult shared environmental (F_{sz}, F_{bp}), and childhood shared environmental (C_{sz}, C_{bp}) effects, along with a common non-shared environmental effect for both schizophrenia and bipolar disorder (E). For schizophrenia and bipolar disorder, our models were:

$$R_{sz} = \beta_{szf}I_f + \beta_{szm}I_m + \beta_{szc}I_c + A_{sz} + F_{sz} + C_{sz} + E$$

$$R_{bp} = \beta_{bpf}I_f + \beta_{bpm}I_m + \beta_{bpc}I_c + A_{bp} + F_{bp} + C_{bp} + E$$

where I_f, I_m, and I_c are indicator variables for father, mother, and children; β_f, β_m, and β_c are fixed variables associated with disease prevalence for respective family members. The random effects A, F, C, and E are assumed to be normally distributed, with mean zero and a unique variance component for each term. Thus, we have variance components σ^2_{sza}, σ^2_{bpa}, σ^2_{szf}, σ^2_{bpf}, σ^2_{szc}, and σ^2_{bpc}. The non-shared effect E is normal, with mean zero and variance σ^2_e.

For each disorder, we assumed that the random effects are independent between families, but dependent within families (table 1). The model includes cross-disease covariances: σ_{szbpa} is the additive-genetic covariance of schizophrenia and bipolar effect and, similarly, σ_{szbpf} and σ_{szbpc} are the covariances of adult and childhood environmental effects. All parameters were estimated simultaneously with the maximum likelihood method,[25] where the likelihood is computed with a fast Monte Carlo integration of the random effects.[26]

Variance and covariance parameters are reported as proportional contributions to the liability to disease. Confidence intervals for estimates were obtained with a likelihood-based procedure,[25] corrected for uncertainty due to Monte Carlo integration. A more thorough description of the bivariate model is provided elsewhere.[27] The study was supported by the Swedish Council for Working Life and Social Research, and the Swedish Research Council.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 9 009 202 unique individuals of known parentage, for whom both parents were alive and living in Sweden after 1973. 35 985 individuals met the criteria for schizophrenia and 40 487 individuals for bipolar disorder. Of those with schizophrenia, 2543 also had bipolar disorder (relative risk [RR] 16·4, 95% CI 15·1–17·7). We have previously shown the recurrence risks for schizophrenia.[22] Table 2 presents these results for parent–offspring and sibling relationships, and extends our previous work by taking into account different types of half-sibling and adoptive relationships, together with the results for bipolar disorder and the familial aggregation of comorbidity between the disorders.

Similar to the results in our previous work,[22] first-degree relatives had increased risk of schizophrenia. Half-siblings had a significantly increased risk, albeit substantially lower than had full-siblings. Adopted children, whose biological parents had schizophrenia, and biological siblings growing up in different families also had an increase in risk of being diagnosed with the same disease. No cases existed in which both an adoptive parent and an adoptee had a diagnosis of schizophrenia.

The risk for bipolar disorder in first-degree relatives of individuals with bipolar disorder was lower than the risk for schizophrenia in first-degree relatives of individuals with that disorder. Otherwise, the familial risks were of similar magnitudes. Adopted children whose biological parents had bipolar disorder had a more than four-fold risk of bipolar disorder.

When the proband had bipolar disorder, their first-degree relatives had a significantly increased risk of schizophrenia (table 2). Half-siblings also had an increased though non-significant risk as did adoptees when the adoptive parents had bipolar disorder. Results were similar for the risk of bipolar disorder in relatives of probands with schizophrenia (table 2). No noticeable sex differences existed in familial risks (data not shown).

Heritability for schizophrenia was estimated to be 64% (table 3 and figure). For bipolar disorder, the estimate was 59%. Shared environmental effects were small but significant for both disorders.

Comorbidity was mainly due to additive genetic effects common to both disorders. The genetic correlation (r_g) was 0·60. Unique genetic effects for schizophrenia that were not in common with bipolar disorder accounted for 48% of the genetic variance in schizophrenia (and for 31% in bipolar disorder) (figure).
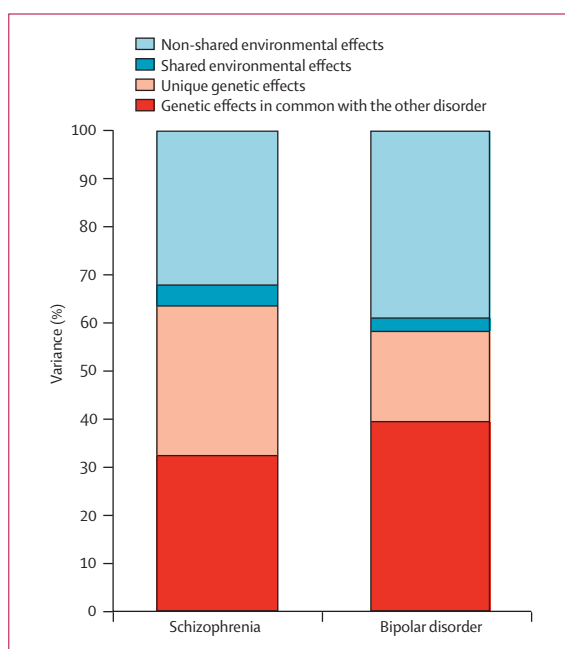
Figure: Variance accounted for by genetic, shared environmental, and non-shared environmental effects for schizophrenia and bipolar disorder
Red indicates genetic effects, with dark red for genetic effects in common with the other disorder and light red for unique genetic effects. Blue indicates environmental effects, with dark blue for shared environmental effects and light blue for non-shared environmental effects.

The use of a non-hierarchical definition of syndromes might be questioned. We therefore investigated the sibling risk of developing a disorder when both probands and siblings with comorbid schizophrenia and bipolar disorder were excluded. The risk for bipolar disorder in siblings of probands with schizophrenia was significantly increased (2·7 [2·3–3·1]). We also did the model-fitting analyses with hierarchical diagnoses, in which individuals with two or more schizophrenia diagnoses were classified as having schizophrenia (and not bipolar disorder, even if they have had two or more such diagnoses). According to this analysis, estimates were almost the same (table 3), other than for non-shared environmental effects, which did not contribute to comorbidity (because an individual could not be diagnosed with both disorders).

Another issue is how to treat individuals with schizoaffective disorder. To avoid possible misclassi-fication between schizophrenia and bipolar disorder, we excluded admissions with diagnosis of schizoaffective disorder in our main analyses. However, when we classified schizoaffective cases as schizophrenia, the results were similar, but familial risks were higher when schizoaffective cases were included than when they were not (webtables 1 and 2).

Discussion

In this study of more than 2 million Swedish families, we found evidence of a substantial genetic association between schizophrenia and bipolar disorder. All classes

of biological relatives of probands with bipolar disorder had increased risk for schizophrenia, and the genetic correlation (ie, the correlation between the genetic effects that determine the liabilities for the two disorders) was 0·60. Furthermore, adopted children whose biological parents had one of these disorders had significant increase in risks for the other disorder. These results are in line with previous molecular genetic studies,[1] and twin,[15] and family[17] studies that suggest a common genetic contribution for schizophrenia and bipolar disorder, even if they are discordant with some family studies in which clinicians have reviewed the personal interview, and hospital and outpatient records of the course of illness.[3,4]

Patients with one diagnosis sometimes evolve into the other diagnosis; whether this change is due to misclassification at first diagnosis or to the fact that the individual has both disorders is not clear. If patients with both disorders are misclassified, our approach with non-hierarchical diagnoses would give artificially increased associations. However, when we analysed sibling risks without comorbidity, a significant increase in risk remained. Furthermore, in the analyses with hierarchical diagnoses, estimates were almost the same. Thus, schizophrenia and bipolar disorder share common genetic causes. Nonetheless, a considerable proportion of genetic variance is not in common with the other disorder, both for schizophrenia and bipolar disorder. Thus, some genes are probably associated with the risk for both disorders and some with the risk for only one disorder. This possibility should be considered in future research and in clinical settings.

Estimated heritability for schizophrenia was 64%, which was lower than that (81%) in a meta-analysis of twin studies.[28] Furthermore, estimated heritability for bipolar disorder was 59%, which was also lower than previous estimates (80%) based on twin studies.[16] An issue in twin studies is their low power to estimate heritability for rare diseases. Also, they are less sensitive to age and non-additive genetic effects than are family studies. Nonetheless, both types of studies show that schizophrenia and bipolar disease are heritable (estimated heritability of 60–80% of the liabilities).

Shared environmental effects on both disorders and their comorbidity are small but significant, accounting for 3–6% of the variance and covariance, which corroborates the results from the meta-analysis[28] of twin studies on schizophrenia. Twin studies have limited power to detect shared environmental effects, especially for binary traits.[29] We suggest caution when drawing conclusions for psychiatric conditions, when small samples are used.

Non-shared environmental effects contributed to comorbidity (~30%). By contrast with non-shared environmental effects estimated in the univariate analyses, the estimate of the comorbidity due to non-shared environmental effects should be free from measurement error. One possibility is that perinatal effects are a candidate mechanism.[30]

The strength of our data is the national coverage of all inpatient treatment facilities, including care in psychiatric and somatic clinics. Similar to most developed nations, inpatient psychiatric care has been reduced in Sweden over the past two decades. However, a recent study[31] showed that, although the total number of days spent in psychiatric beds in Sweden between 1994 and 2003 fell dramatically, the number of admissions scarcely changed. A limitation of this study is the use of non-standardised diagnoses made by different clinicians with different opinions. This drawback is typical for population-based studies of this kind. Nevertheless, validation studies confirmed a low number of false-positive diagnoses.[32,33] There was 94% agreement between register diagnoses of schizophrenia and research diagnoses based on semi-structured interviews and medical records.[33] The validity of a discharge diagnosis of bipolar disorder has not been assessed, but it is likely to be high as for schizophrenia in view of the conservative and restrictive diagnostic culture for psychoses in Sweden. A few cases may have been treated entirely outside hospital. Another limitation with the bipolar diagnoses is that the strict ICD-10 definitions were only available for the past 7 years of this 31-year study.

Diagnostic bias could have happened if diagnostic assessments by physicians were influenced by knowledge of family psychiatric history; this would have probably reduced variation across diagnoses. Our data for adoptive relationships are not prone to such bias.

Cases were individuals with narrow diagnoses of schizophrenia and bipolar disorder. By restricting our analyses to at least two admissions, we increased specificity of the register diagnoses. Furthermore, we chose a conservative approach by excluding schizoaffective disorder, which is symptomatically intermediate between schizophrenia and bipolar disorder. However, when we repeated the analyses including schizoaffective cases, results were similar to those obtained in the analysis without these cases.

Overall, similar to recent results from molecular genetic studies,[1] we found evidence that schizophrenia and bipolar disorder partly share common genetic causes, which challenges the nosological dichotomy between schizophrenia and bipolar disorder. These results should inform the diagnostic classification used in linkage and association studies, and encourage further research for endophenotypic traits shared between these two disorders. Within clinical practice, the underlying structure of psychosis and the knowledge of the common causes of these disorders might be beneficial for treatment options and development of psychosis medication.

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