Genetics inMedicine | ORIGINAL RESEARCH ARTICLE

Familial clustering of schizophrenia, bipolar disorder, and major depressive disorder

Maartje F. Aukes, PhD[1,2], Wijnand Laan, PhD[2], Fabian Termorshuizen, PhD[2], Jacobine E. Buizer-Voskamp, MSc[1,3], Eric A.M. Hennekam[4], Hugo M. Smeets, PhD[2], Roel A. Ophoff, PhD[1,3,5], Marco P.M. Boks, MD, PhD[1,2] and René S. Kahn, MD, PhD[1]

Purpose: To investigate familial clustering of schizophrenia, bipolar disorder, and major depressive disorder.

Methods: Combining data from a psychiatric case registry and Statistics Netherlands provided information on 4,673 affected probands and 18,692 matched population controls.

Results: Probands with schizophrenia had relative risks (RRs) for having a sibling with schizophrenia of 3.77 (95% confidence interval (CI): 2.60–5.46) and with bipolar disorder of 1.79 (95% CI: 0.64–4.96) as compared with a reference proband. Probands affected with bipolar disorder have an RR of 6.51 (95% CI: 2.60–16.29) for having a sibling with bipolar disorder and of 1.71 (95% CI: 0.71–4.14) for having a sibling with schizophrenia as compared with a reference proband. Probands affected with major depressive disorder also have increased risk for having a sibling with schizophrenia (RR: 2.04, 95% CI: 1.54–2.72) as compared with a reference proband, which was similar to the risk for having a sibling with major depressive disorder (RR: 1.91, 95% CI: 1.63–2.24) or bipolar disorder (RR: 2.06, 95% CI: 1.18–3.60).

Conclusion: Our findings suggest, as previous studies have, that risk across schizophrenia and bipolar disorder is considerably lower (twofold) than within diagnostic entities, whereas for major depressive disorder risk is similar within and across diagnostic entities.

Genet Med 2012:14(3):338–341

Key Words: bipolar disorder; case registry; familial clustering; major depressive disorder; schizophrenia

INTRODUCTION

Recent population-based studies suggest that schizophrenia (OMIM# 181500) and bipolar disorder (BD; OMIM# 125480) share part of their genetic vulnerability.[1,2] Several molecular genetic studies have indeed identified both shared and distinct genetic variants that are associated with these disorders. Examples of shared genetic variants are *DISC1*,[3] *ZNF804A*,[4] and polygenic variation in genome-wide association studies.[5] Six of eight of the most robustly associated loci for either schizophrenia or BD show cross-disorder effects.[4] However, another cross-disorder genome-wide analysis of schizophrenia, BD, and depression did not find genome-wide significant evidence of cross-disorder effects.[6] Although increasing literature cites overlap of these disorders based either on findings of genome-wide association studies or studies of endophenotypes,[7] familial coaggregation is a critical source of information on this issue and has not been conclusive.

Family studies on coaggregation of schizophrenia and BD have a long history, starting in the beginning of the previous century[8], followed by increasing numbers of studies in the seventh and eighth decade. Reviews of family, twin, and adoption studies (e.g., refs. 9–11) show that the risk for discordant diagnoses (affective disorders in schizophrenia families or vice versa) are increased as compared with a control population, though not as high as for concordant diagnoses (e.g., ref. 12). Still, many studies do not show an increased risk for BD among first-degree relatives of schizophrenia probands[13–19] or an increased risk for schizophrenia among first-degree relatives of BD probands.[18,20–24] Yet recent studies support the view that a wide range of mental disorders cluster in families (e.g., refs. 2,25,26).

In this study, we investigated familial clustering in families of schizophrenia, BD, and major depressive disorder (MDD; OMIM# 608516) in the Dutch population and compared the results with previous findings.

MATERIALS AND METHODS

We used a cross-sectional design using two databases. The first database was that of the Psychiatric Case Register Middle Netherlands (PCR-MN),[27] covering an urbanized region in the middle of the Netherlands. This case register records all contacts/consultations and diagnoses made in the specialist psychiatric health care. All psychiatric hospitals active in this region participate in the PCR-MN. All DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders,* 4th edition)[28] diagnoses

[1]Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Center Utrecht, Utrecht, The Netherlands; [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Department of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands; [4]Department of Clinical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands; [5]Center for Neurobehavioral Genetics, University of California, Los Angeles, Los Angeles, California, USA. Correspondence: Maartje Aukes (M.Aukes@umcutrecht.nl.)

Submitted 15 May 2011; accepted 22 September 2011; published online 5 January 2012. doi:10.1016/gim.2011.16

on axis I and II made by the participating psychiatric hospitals are recorded in the PCR-MN from 1999 onward.

The cluster of schizophrenia and related psychosis was defined by a DSM-IV diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder (DSM code 295.x), brief psychotic disorder (298.8), or psychotic disorder not otherwise specified (298.9). MDD was defined by a DSM-IV diagnosis of MDD, single (296.2x) or recurrent episode (296.3x), or depression not otherwise specified (311.00). BD was defined by having either a DSM-IV diagnosis of bipolar I (296.0, 296.4x, 296.5x, 296.6x, 296.80) or bipolar II (296.89). All diagnoses made between January 2000 and January 2009 were included in the analysis.

The second database used was the parent–children database of Statistics Netherlands (Centraal Bureau voor de Statistiek, CBS). CBS is responsible for collecting and processing data in order to publish statistics to be used in practice, by policymakers, and for scientific research in the Netherlands. CBS makes its data sets available for scientific research under the condition of strict confidence and without any identifying variables. In the parent–children database of the CBS, all Dutch inhabitants have a record identifying their parents, as far as these are known to the Dutch civil registry. The percentage of identifiable parents decreases from 90% for children born after 1987 to about 0% for those born before 1947.

All cases with schizophrenia or related psychosis, MDD, or BD from the PCR-MN were linked to a record in the CBS based on the postal code, gender, and date of birth. Persons from the PCR-MN who cannot be linked to a record in the CBS either did not report an accurate address to the treating psychiatric hospital or had two or more hits with a record at the CBS.

Only cases for whom we could identify both parents and whose siblings were still alive and living in the area covered by the PCR-MN were included in the final analyses. In families with multiple cases, we randomly defined one of the affected siblings as the proband. For every sibling, we checked for records and diagnosis in the PCR-MN. Comorbid cases who received diagnoses from both the schizophrenia and BD diagnostic cluster were grouped in either of these clusters based on the most recent diagnosis. A comorbid diagnosis of MDD was overruled by a schizophrenia or BD diagnosis. In addition, we calculated for all cases the age at first diagnosis for one of the DSM-IV diagnoses within a diagnostic cluster (schizophrenia, MDD, or BD).

A control group from the parent–children database of the CBS was matched to the probands based on age and gender. The control subjects were drawn from the population of people from the area covered by the PCR-MN and included only if we could identify both the mother and the father and if all siblings were still alive and living in the area covered by the PCR-MN. This group of controls included both affected and non-affected individuals and was four times the size of the total groups of affected probands combined.

We calculated the relative risks (RRs) for having an affected sibling using the population matched group of controls as a reference group. To investigate the association of age at diagnosis to familial clustering, we calculated the intraclass correlation coefficients for each diagnostic cluster by comparing differences in variance within and between families. We compared sex ratios in familial to sporadic cases using a χ^2-test to investigate the association of sex to familial clustering.

Analyses were performed using the Statistical Package for the Social Sciences (SPSS 14.0) and STATA (version 10.1). The level of significance was set to 5% and all tests were performed using two-tailed confidence intervals (CIs). Only crude RRs are presented.

RESULTS

Using the postal code, gender, and date of birth, we were able to match 79.6% of cases from the PCR-MN to a record in the CBS database. Of the 20.4% that could not be linked, 11.9% gave more than one unique match and 8.5% gave no match to a record in the CBS database. Of those who were linked, we could identify both parents for 69.7% of the cases. After excluding families with irretrievable siblings, a final sample of 929 probands with schizophrenia, 3,425 probands with MDD, and 319 probands with BD remained. To the total of 4,673 affected probands, a group of 18,692 population controls was matched. In the groups of siblings with schizophrenia, 5 were removed from the group of siblings of probands with MDD and 13 from the group of siblings of the control population for having received a more recent diagnosis of BD. In the groups of siblings with MDD, 1 was removed from the group of siblings of probands with schizophrenia for having received a diagnosis of BD, 1 was removed from the group of siblings of the probands with BD for having received a diagnosis of schizophrenia, and 40 were removed from the group of siblings of the control population for having received a diagnosis of either schizophrenia or BD. In the groups of siblings with BD, 2 were removed from the group of siblings of probands with MDD and 10 from the group of siblings of the control population for having received a more recent diagnosis of schizophrenia. Details on the total remaining number of siblings and the diagnoses of the siblings are given in **Table 1**.

The RRs are shown in **Table 2**. Probands affected with schizophrenia have a significantly increased RR (95% CI) of 3.77 (2.60–5.46) for having a sibling with schizophrenia as compared with a reference proband. The RR is 1.79 (95% CI: 0.64–4.96) for having a sibling with BD. Probands affected with BD have an RR of 6.51 (95 % CI: 2.60–16.29) for having a sibling with BD and of 1.71 (95% CI: 0.71–4.14) for having a sibling with schizophrenia as compared with a reference proband. Probands affected with MDD also have increased risk for having a sibling with schizophrenia (RR: 2.04, 95% CI: 1.54–2.72) as compared with a reference proband, which was similar to the risk for having a sibling with MDD (RR: 1.91, 95% CI: 1.63–2.24) or BD (RR: 2.06, 95% CI: 1.18–3.60).

The relative frequencies of a diagnosis of schizophrenia, MDD, or BD in the siblings for each group of probands were not significantly different from the relative frequencies in the control population (Fisher's exact *P* values: 0.404, 0.887, 0.098, respectively).

Table 1. Absolute number of probands and siblings for each diagnostic category

Diagnosis of proband	Number of probands	Age of probands[a]	Number of siblings	Age of siblings[a]	Average number of siblings	Number of siblings with schizophrenia	Number of siblings with MDD	Number of siblings with BD
Schizophrenia	929	35 ± 9	1,755	34 ± 11	1.89	32	90	4
MDD	3,425	34 ± 10	6,544	34 ± 12	1.91	64	196	17
BD	319	37 ± 10	547	37 ± 11	1.71	5	27	5
Population	18,692[b]	34 ± 10	30,577	34 ± 12	1.64	171	560	45

BD, bipolar disorder; MDD, major depressive disorder.

[a]Mean age ± s.d. on 1 January 2009. [b]Of whom, 106 probands suffered from schizophrenia, 396 from MDD, and 29 from a BD.

Table 2. Relative risks (and 95% confidence intervals) for a proband affected with schizophrenia, MDD, or BD for having a sibling with one of these diagnoses as compared with a reference proband

Diagnosis proband	Diagnosis sibling		
	Schizophrenia	MDD	BD
Schizophrenia[a]	3.77 (2.60–5.46)	3.23 (2.61–4.00)	1.79 (0.64–4.96)
MDD[b]	2.04 (1.54–2.72)	1.91 (1.63–2.24)	2.06 (1.18–3.60)
BD[c]	1.71 (0.71–4.14)	2.83 (1.95–4.09)	6.51 (2.60–16.29)
Population	Reference	Reference	Reference

BD, bipolar disorder; MDD, major depressive disorder.

[a]Estimates indicate the relative risks (and 95% confidence intervals) for a proband affected with schizophrenia for having a sibling with schizophrenia, MDD, or BD as compared with a reference proband. [b]Estimates indicate the relative risks (and 95% confidence intervals) for a proband affected with MDD for having a sibling with schizophrenia, MDD, or BD as compared with a reference proband. [c]Estimates indicate the relative risks (and 95% confidence intervals) for a proband affected with BD for having a sibling with schizophrenia, MDD, or BD as compared with a reference proband.

Age at diagnosis clustered in families with schizophrenia (intraclass correlation coefficient: 0.57, 95% CI: 0.36–0.78) and even more strongly in families with MDD (intraclass correlation coefficient: 0.78, 95% CI: 0.73–0.82). The intraclass correlation coefficient for age of diagnosis in families for BD was 0.78; however, the CI could not be calculated because of the low number of familial cases.

Sporadic schizophrenia cases had a non-significant lower proportion of males (69%) than familial cases (73%). Sporadic cases with MDD had a significantly lower proportion of males (35%) than familial cases (40%, $P = 0.04$). The proportion of males was higher in the sporadic cases with BD (45%) as compared with familial cases (40%), although not significantly.

DISCUSSION

We found a more than threefold increased risk for schizophrenia when the proband carries the diagnosis of schizophrenia and a more than sixfold increased risk for BD when the proband carries the diagnosis of BD. Also, we found lower, but non-significant, increased risks across diagnoses, e.g., the risk for schizophrenia is 1.7 when the proband has BD and vice versa. Our risk estimates for schizophrenia are somewhat lower than recent studies in the Swedish,[1] US,[11] and Danish populations,[2] although the estimates show the same decrease (about twofold) for cross-wise schizophrenia–BD risk as compared with within-diagnoses risk. Although the number of cases with BD in our sample was low and therefore results should be interpreted with care, our findings reiterate the fact that although there may be shared familial vulnerability between schizophrenia and BD, we and others find considerably lower risks (about twofold) across diagnostic entities.[1,2,11]

Of interest, for MDD, risk was similar within and across diagnostic entities. The shared vulnerability among schizophrenia and MDD supports earlier findings.[2,18,29] However, we could not distinguish between genetic and environmental contributions to familial risks. This distinction is especially relevant for MDD, as it is more strongly affected by environmental factors than schizophrenia or BD.

Age at diagnosis was associated with familial clustering for schizophrenia and MDD and possibly for BD, which is in line with earlier findings that suggest that familial factors, which may be genetic, influence the age at onset of these disorders.[30]

The most important limitation of this study is that we had limited observations for calculating cross-wise schizophrenia–BD risk estimates. Therefore, we cannot conclude that the familial association is absent (we cannot reject the null hypothesis that the risk for BD in the siblings of schizophrenia families is the same as in the general population). With a larger sample size, this discordant RR may become significant. Our findings indicate that the cross-wise schizophrenia–BD risk is lower (about twofold) than the within-diagnostic risks, which is in line with previous findings. The low number of observations (in all cells) is a result of our including only probands of whom all siblings live in the area covered by the PCR-MN. Although this selection of families could introduce a selection bias of families that did not move or were not otherwise lost, it circumvents an information bias of including families with (multiple) members of unknown status. Potential selection mechanisms, such as older siblings that may be more likely to have moved away and larger families having a higher chance of being excluded from analyses, have not necessarily affected our results as they are present in both affected and control families. A potential bias may exist if BD patients move more often than schizophrenia patients. One study did report different numbers of patients that completed a residential move within 1 year: 25% of patients with BD, 20% with schizophrenia, and 16% with depression.[31] This may have affected all families similarly, as we find a lower number of patients with BD in all

groups. Because we used data from a specialist care registry, the MDD group may include more severe depressions.

Both genetic and environmental factors can contribute to familial risks. A potential environmental factor could be contamination in diagnosis, as siblings may receive a diagnosis that is similar to their sibling for reasons not due to shared genes. The contribution of this phenomenon could not be addressed in our study, although it could be an important factor.

The strength of our study is that we used a registry-based sample of psychiatric patients. Therefore, there is no attrition bias introduced by nonparticipation because of lack of willingness or difficulty in locating participants, as is often the case in clinic-based research. Further, our diagnostic classification may be more uniform than those of other population samples because of a limited area and time span used in our data collection.

Overall, our findings are consistent with other large population-based studies, suggesting that schizophrenia and BD may share familial vulnerability, and risk for similar diagnoses is higher than across diagnostic categories. However, for MDD, risk was similar within and across diagnostic entities. These data as well as previous reports are consistent with a model in which there are underlying genetic or environmental factors that give rise to broad, as well as specific, familial vulnerabilities to psychiatric disorders.

ACKNOWLEDGMENTS

We thank the participating hospitals of the Psychiatric Case Register Middle Netherlands (PCR-MN) and the Statistics Netherlands (Centraal Bureau voor de Statistiek) for kindly providing the data necessary for these analyses. The PCR-MN is funded by the Ministry of Health, Welfare and Sport and participating hospitals. These parties had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Lichtenstein P, Yip BH, Björk C, et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. Lancet 2009;373:234–239.
2. Mortensen PB, Pedersen MG, Pedersen CB. Psychiatric family history and schizophrenia risk in Denmark: which mental disorders are relevant? Psychol Med 2010;40:201–210.
3. Chubb JE, Bradshaw NJ, Soares DC, Porteous DJ, Millar JK. The DISC locus in psychiatric illness. Mol Psychiatry 2008;13:36–64.
4. Williams HJ, Craddock N, Russo G, et al. Most genome-wide significant susceptibility loci for schizophrenia and bipolar disorder reported to date cross-traditional diagnostic boundaries. Hum Mol Genet 2011;20: 387–391.
5. Purcell SM, Wray NR, Stone JL, et al.; International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 2009;460:748–752.
6. Huang J, Perlis RH, Lee PH, et al. Cross-disorder genomewide analysis of schizophrenia, bipolar disorder, and depression. Am J Psychiatry 2010;167:1254–1263.
7. Maziade M, Rouleau N, Gingras N, et al. Shared neurocognitive dysfunctions in young offspring at extreme risk for schizophrenia or bipolar disorder in eastern quebec multigenerational families. Schizophr Bull 2009;35: 919–930.
8 Rüdin E. Zur Vererbung und Neuentslehung der Dementia Praecox. Springer: Berlin, Germany, 1916.
9. Taylor MA. Are schizophrenia and affective disorder related? A selective literature review. Am J Psychiatry 1992;149:22–32.
10. Berrettini W. Bipolar disorder and schizophrenia: not so distant relatives? World Psychiatry 2003;2:68–72.
11. Goldstein JM, Buka SL, Seidman LJ, Tsuang MT. Specificity of familial transmission of schizophrenia psychosis spectrum and affective psychoses in the New England family study's high-risk design. Arch Gen Psychiatry 2010;67:458–467.
12. Tsuang MT, Winokur G, Crowe RR. Morbidity risks of schizophrenia and affective disorders among first degree relatives of patients with schizophrenia, mania, depression and surgical conditions. Br J Psychiatry 1980;137:497–504.
13 Kety SS, Rosenthal D, Wender PH, Schulsinger F. The types and prevalence of mental illness in the biological and adoptive families of adopted schizophrenics. In: Rosenthal D, Kety SS (eds). *The Transmission of Schizophrenia*. Pergamon Press: Oxford, UK, 1968:345–362.
14. Frangos E, Athanassenas G, Tsitourides S, Katsanou N, Alexandrakou P. Prevalence of DSM III schizophrenia among the first-degree relatives of schizophrenic probands. Acta Psychiatr Scand 1985;72:382–386.
15. Baron M, Gruen R, Kane J, Asnis L. Modern research criteria and the genetics of schizophrenia. Am J Psychiatry 1985;142:697–701.
16. Coryell W, Zimmerman M. The heritability of schizophrenia and schizoaffective disorder. A family study. Arch Gen Psychiatry 1988;45: 323–327.
17. Onstad S, Skre I, Edvardsen J, Torgersen S, Kringlen E. Mental disorders in first-degree relatives of schizophrenics. Acta Psychiatr Scand 1991;83: 463–467.
18. Maier W, Lichtermann D, Minges J, et al. Continuity and discontinuity of affective disorders and schizophrenia. Results of a controlled family study. Arch Gen Psychiatry 1993;50:871–883.
19. Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D. The Roscommon Family Study. IV. Affective illness, anxiety disorders, and alcoholism in relatives. Arch Gen Psychiatry 1993;50:952–960.
20. Helzer JE, Winokur G. A family interview study of male manic depressives. Arch Gen Psychiatry 1974;31:73–77.
21. James NM, Chapman CJ. A genetic study of bipolar affective disorder. Br J Psychiatry 1975;126:449–456.
22 Gershon ES, Mark A, Cohen N, Belizon N, Baron M, Knobe KE. Transmitted factors in morbid risk of affective-disorders–controlled-study. J Psychiatr Res 1975;12:283–299.
23. Baron M, Gruen R, Asnis L, Kane J. Schizoaffective illness, schizophrenia and affective disorders: morbidity risk and genetic transmission. Acta Psychiatr Scand 1982;65:253–262.
24. Weissman MM, Gershon ES, Kidd KK, et al. Psychiatric disorders in the relatives of probands with affective disorders. The Yale University–National Institute of Mental Health Collaborative Study. Arch Gen Psychiatry 1984;41:13–21.
25. Dean K, Stevens H, Mortensen PB, Murray RM, Walsh E, Pedersen CB. Full spectrum of psychiatric outcomes among offspring with parental history of mental disorder. Arch Gen Psychiatry 2010;67:822–829.
26. Gottesman II, Laursen TM, Bertelsen A, Mortensen PB. Severe mental disorders in offspring with 2 psychiatrically ill parents. Arch Gen Psychiatry 2010;67:252–257.
27. Smeets HM, Laan W, Engelhard IM, Boks MP, Geerlings MI, de Wit NJ. The psychiatric case register middle Netherlands. BMC Psychiatry 2011; 11:106.
28. American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Health Disorders*, 4th edn. Washington, DC.
29. Argyropoulos SV, Landau S, Kalidindi S, et al. Twins discordant for schizophrenia: psychopathology of the non-schizophrenic co-twins. Acta Psychiatr Scand 2008;118:214–219.
30. Kendler KS, Tsuang MT, Hays P. Age at onset in schizophrenia. A familial perspective. Arch Gen Psychiatry 1987;44:881–890.
31. McCarthy JF, Valenstein M, Blow FC. Residential mobility among patients in the VA health system: associations with psychiatric morbidity, geographic accessibility, and continuity of care. Adm Policy Ment Health 2007;34: 448–455.