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Familial Aggregation and Heritability of Schizophrenia and Co-aggregation of Psychiatric Illnesses in Affected Families

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Strong familial aggregation of schizophrenia has been reported but there is uncertainty concerning the degree of genetic contribution to the phenotypic variance of the disease. This study aimed to examine the familial aggregation and heritability of schizophrenia, and the relative risks (RRs) of other psychiatric diseases, in relatives of people with schizophrenia using the Taiwan National Health Insurance Database. The study population included individuals with affected first-degree or second-degree relatives identified from all beneficiaries (n = 23 422 955) registered in 2013. Diagnoses of schizophrenia made by psychiatrists were ascertained between January 1, 1996 and December 31, 2013. Having an affected co-twin, first-degree relative, second-degree relative, or spouse was associated with an adjusted RR (95% CI) of 37.86 (30.55–46.92), 6.30 (6.09–6.53), 2.44 (1.91–3.12), and 1.88 (1.64–2.15), respectively. Compared with the general population, individuals with one affected first-degree relative had a RR (95% CI) of 6.00 (5.79–6.22) and those with 2 or more had a RR (95% CI) of 14.66 (13.00–16.53) for schizophrenia. The accountability for the phenotypic variance of schizophrenia was 47.3% for genetic factors, 15.5% for shared environmental factors, and 37.2% for non-shared environmental factors. The RR (95% CI) in individuals with a first-degree relative with schizophrenia was 3.49 (3.34–3.64) for mood disorders and 3.91 (3.35–4.57) for delusional disorders. A family history of schizophrenia is therefore associated with a higher risk of developing schizophrenia, mood disorders, and delusional disorders. Heritability and environmental factors each account for half of the phenotypic variance of schizophrenia.

Key words: schizophrenia/heritability/familial aggregation/mood disorders/delusional disorders

Introduction

Schizophrenia is a chronic mental disorder presenting with positive (delusions, and hallucinations, incoherent speech, and disorganized thinking) and/or negative (restricted affect, empty speech content, decreased motivation, and social withdrawal) symptoms.[1] Although schizophrenia is a mental disease with relatively low prevalence it is a leading cause of global attributable disease burden.[2] The median point estimate of global schizophrenia prevalence is approximately 0.5% according to a recent systematic review summarizing estimates drawn from 46 countries.[3] In Taiwan, the prevalence of schizophrenia in 2001 was estimated to be 0.64% using nationwide data,[4] and the direct and indirect economic costs of the condition are substantial.[5]

Ample evidence suggests that schizophrenia is subject to strong familial predisposition, implying that both genetic and shared environmental factors contribute significantly to the phenotypic variance of the disorder. A population-based study using the Danish registry reports several environmental factors, such as urban birth and immigration status, which contribute significantly to schizophrenia susceptibility.[6] Heritability, the degree of genetic contribution to phenotypic variance, has been estimated to range between 41% and 87%.[7–13] In general,

heritability estimates derived from twin studies are higher than those based on the general population. One estimate for heritability based on a meta-analysis of 12 twin studies was 81%.[12] However, an estimate calculated from the population-based data of the Swedish Multi-generation Register was lower, though still substantial, at 64%.[13]

The heritability of schizophrenia is high, but only part of it can be explained by known associated alleles, suggesting the existence of "missing heritability." A genetic risk profile score based on 108 genetic loci reported by a large genome-wide association (GWA) study explained only 7% of the variation on the liability scale.[14] Another GWA study, which enrolled 3322 European individuals with schizophrenia and 3587 controls, reported that the variance explained by markers that tag the causal alleles ranged from 32% to 36%.[15] Furthermore, common genetic variants underlying schizophrenia and bipolar disorder have been reported using the Swedish database.[13] Rasic et al[16] reported a 1.62-fold risk of mood disorders among offspring of parents with schizophrenia in a recent meta-analysis. Offspring of parents with severe mental illness (SMI) are at increased risk for a range of psychiatric disorders and one-third of them may develop a SMI by early adulthood. Evidence for the familial co-aggregation of schizophrenia and other psychiatric illnesses has been reported rarely in other populations.

The notion of schizophrenia as a highly heritable disease is supported by current literature, but parameters that are important for genetic counseling, such as the absolute and relative risk (RR) of the disease, heritability, and the proportion of sporadic cases, are lacking for the Asian population. The sizable "missing heritability" implies either undiscovered genetic associations or overestimated heritability. The familial co-aggregation between schizophrenia and other mental disorders also needs verification.

In previous years, we have developed a nationwide genealogy, and linked this to health information derived from Taiwan's National Health Insurance (NHI) Research Database. Using the comprehensive health information and pedigree data of the entire population, this study aims to estimate the RRs of schizophrenia in individuals who have affected relatives of specific kinship, and to examine the relative contribution of genetic, shared and non-shared environmental factors to schizophrenia susceptibility. In addition, we estimated the RRs of other psychiatric illnesses associated with a family history of schizophrenia.

Methods

Study Population

This study received ethical approval from the Institutional Review Board of the Chang Gung Memorial Hospital (104-8209B). Our primary data source is the Taiwan NHI database, which contains registration and original claims data of all residents in Taiwan. The program achieved in 2013 the exceptionally high coverage rate of 99.5%.[17] Since 1995, the NHI Database records gender, date of birth, place of residence, details of insurance, family relationships, dates of inpatient and outpatient visits, medical diagnoses, medical expenditures, prescription details, vaccination status, examinations, operations, procedures, and fees incurred.

We used the registry of beneficiaries, a part of the NHI database, to construct a cohort comprising all NHI beneficiaries registered in 2013. Among them, we identified all patients with schizophrenia, mood disorders and delusional disorders from the registry of catastrophic illness patients, these diagnoses being ascertained up to December 31, 2013. Individuals with a positive family history of schizophrenia in 2013 were identified and classified according to the particular kinship of affected relatives. Individuals without valid insurance status were excluded from analysis.

Methods for genealogy reconstruction using recorded family relationships in the NHI database are reported in our previously published manuscripts.[18–20] In brief, we rely upon the recorded relationships between the insured persons and their dependents to identify family relationships. We established family relationships (parents, offspring, full siblings, twins, and spouse) using the identifiers and unique personal identification of parents, grandparents, children, grandchildren, and spouse. In addition to the direct ascertainment of relationships using information recorded in the registry, indirect identification of parent-offspring relationships was achieved using an algorithm.[18–20] Full siblings of an individual are ascertained if they had the same parents. Twins are ascertained as full siblings with the same date of birth (±1 d), but twin zygosity cannot be derived from the database. Among 29 505 197 individuals contained in the registry of beneficiaries, 7 856 663 do not have dependents or act as dependents, and therefore we could not identify their relatives. The rest of the beneficiaries were classified into 4 042 209 families. The mean family size was 5.4 persons. There were 2 to 5 generations in these families. Each individual may appear multiple times in different categories of family relationships depending on family structure.

Ascertainment of Schizophrenia, Mood Disorders, and Delusional Disorders

In Taiwan, patients with suspected mental illnesses are referred to psychiatrists for diagnosis and treatment. Patients diagnosed with schizophrenia, mood disorders, and delusional disorders are entitled to a waiver for medical co-payment. Clinical information relevant to the diagnosis is sent to the NHI Administration for review by expert panels to confirm the diagnosis before approval of waivers. In Taiwan, schizophrenia, mood disorders, and delusional disorders are diagnosed by psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), which is also used to

assist the review of certificate applications for these mental disorders.[21] The Registry for Catastrophic Illness Patients contains all information of patients with schizophrenia (International Classification of Disease, 9th Revision [ICD-9] code, 295 except 295.8), mood disorders (ICD-9 code, 296), and delusional disorders (ICD-9 code, 297). We used this registry to identify patients with these diagnoses.

Statistical Analysis

We calculated RRs of schizophrenia, mood disorders and delusional disorders as the adjusted prevalence ratios between the first- or second-degree relatives of an individual with schizophrenia and the general population,[22] using the Breslow-Cox proportional hazards model[23,24] with a robust sandwich method to handle intra-familial clustering.[25] The RR was adjusted for age, gender, occupation categories, income level quintiles, level of urbanization of residence, and family size.[13,26] We also conducted age- and sex-adjusted models, the results of which were similar to the full model. We present these results in the supplementary tables 1–3.

We fitted models separately according to the kinship and sex of affected relatives. Twins were excluded from the sibling analyses. We also compared the risk of schizophrenia in individuals with 1 or 2 affected first-degree relatives with the risk in the general population.

Heritability is the proportion of phenotypic variance attributable to genetic factors, and the familial transmission is the proportion of both genetic and shared environmental contribution, both of which are calculated using the liability threshold model.[27–29] With information on background disease prevalence and kinship-specific RR for the disease, this model partitions the phenotypic variance into genetic and environmental components for dichotomous traits such as disease diagnosis.[19,30] We used the equation developed by Yang et al[30] to estimate both the familial transmission and heritability. We used the spouse as a control to separate genetic and non-shared environmental contributions to phenotypic variance, assuming that spouses share no genetics with other blood relatives but share the family environment. Therefore, assortative mating was not considered in our model. We restricted family history to first-degree relatives and assumed an average of 2 siblings per family (details of statistical analysis are shown in the supplementary material).

All statistical hypotheses were tested on the 2-sided 5% level of significance. All analyses were performed using SAS v. 9.3 (SAS institute).

Results

Schizophrenia Prevalence in Individuals With Affected First-degree Family Members vs the General Population

The study population comprised 23 422 955 individuals enrolled in NHI in Taiwan in 2013. Among these 47.45%, 57.45%, 47.29%, and 1.51% had a parent, child, sibling, or twin identified, respectively. We identified 101 189 patients with the diagnosis of schizophrenia, giving a crude prevalence of 0.43%. Men had a slightly higher prevalence (0.46%) than women (0.40%), with a male:female ratio of 1.15:1. Other baseline characteristics are shown in table 1. In 2013, in the general population of Taiwan 160 587 (0.7%) individuals had at least 1 first-degree relative with schizophrenia, specifically: 64 154 with an affected parent; 50 660 with affected offspring; 47 570 with an affected sibling; and 328 with an affected twin. The age-specific prevalence of schizophrenia was statistically significantly higher in individuals with affected first- and second-degree relatives with schizophrenia than in the general population (figure 1).

RRs for Schizophrenia in Individuals With Affected First-Degree Relatives

Prevalence (recurrence risk) of schizophrenia in individuals with affected first- and second-degree relatives of specific types are shown in tables 2 and 3, respectively. The RRs (95% CIs) for schizophrenia were associated with the degree of genetic distance between family relatives. Overall, having an affected co-twin (50% or 100% genetic similarity depending on zygosity), an affected first-degree relative (on average 50% genetic similarity), an affected second-degree relative (on average 25% genetic similarity) or an affected spouse (no genetic similarity) was associated with an adjusted RR (95% CI) of 37.86 (30.55–46.92), 6.30 (6.09–6.53), 2.44 (1.91–3.12), or 1.88 (1.64–2.15), respectively. In addition, RRs increased with the number of types of affected first-degree relative. Compared with the general population, individuals with one type of affected first-degree relative had a RR (95% CI) of 6.00 (5.79–6.22), and those with 2 or more had a RR (95% CI) of 14.66 (13.00–16.53) for schizophrenia. The sex of the affected relative contributed minimally to the RR of schizophrenia. For example, the RR (95% CI) for individuals with an affected female first-degree relative was 6.86 (6.58–7.16), compared to 6.15 (5.88–6.44) for those with an affected male first-degree relative. The sex of the affected relative contributed to a similar extent to RR for schizophrenia in the case of second-degree relatives (table 3). The RRs (95% CIs) were: 8.58 (8.15–9.04) for those with affected siblings; 7.26 (6.94–7.6) for those with affected parents; 4.06 (3.85–4.27) for those with affected offspring; 2.54 (1.79–3.60) for those with an affected aunt or uncle; 2.03 (1.44–2.88) for those with an affected niece or nephew; 2.72 (1.88–3.94) for those with an affected grandparent; and 2.87 (1.60–5.16) for those with affected grandchildren.

Familial Resemblance and Heritability of Schizophrenia

Using a liability threshold model, we estimated the accountability for phenotypic variance of schizophrenia to be 47.3% for genetic factors (heritability), 15.5% for shared environmental factors, and 37.2% for non-shared environmental factors. Given the parameters estimated

Table 1. Baseline Characteristics of Individuals With First-Degree Relatives Diagnosed With Schizophrenia and the General Population

Variable	Women			Men		
	With Affected FDR	General Population	*P*-value	With Affected FDR	General Population	*P*-value
No.	81 387	11 903 542		80 357	11 519 413	
Age, mean (SD), y	41.9 (19.5)	39.5 (20.9)	<.0001	41.2 (19.7)	38.6 (21.0)	<.0001
Schizophrenia, No. (%)	2539 (3.12)	47 867 (0.40)		2465 (3.07)	53 322 (0.46)	
Place of residence, No. (%)						
Urban	24 519 (30.13)	3 694 254 (31.04)	<.0001	22 124 (27.53)	3 298 256 (28.63)	<.0001
Suburban	24 106 (29.62)	3 434 164 (28.85)		23 073 (28.71)	3 269 766 (28.38)	
Rural	32 762 (40.25)	4 775 054 (40.11)		35 160 (43.75)	4 951 325 (42.98)	
Income levels, No. (%)						
Quintile 1	24 184 (29.71)	2 526 384 (21.22)	<.0001	23 676 (29.46)	2 426 365 (21.06)	<.0001
Quintile 2	8800 (10.81)	1 318 491 (11.08)		7671 (9.55)	1 174 855 (10.20)	
Quintile 3	21 106 (25.93)	3 360 952 (28.23)		21 959 (27.33)	3 303 888 (28.68)	
Quintile 4	14 449 (17.75)	2 289 602 (19.23)		13 167 (16.39)	2 104 521 (18.27)	
Quintile 5	12 793 (15.72)	2 398 414 (20.15)		13 836 (17.22)	2 502 208 (21.72)	
Occupation, No. (%)						
Dependents of the insured individuals	27 449 (33.73)	4 471 275 (37.56)	<.0001	20 115 (25.03)	3 704 412 (32.16)	<.0001
Civil servants, teachers, military personnel, and veterans	3944 (4.85)	442 845 (3.72)		4743 (5.90)	570 766 (4.95)	
Nonmanual workers and professionals	23 343 (28.68)	3 398 109 (28.55)		27 082 (33.7)	3 708 631 (32.19)	
Manual workers	17 837 (21.92)	2 631 992 (22.11)		16 994 (21.15)	2 304 125 (20.00)	
Other	8814 (10.83)	959 321 (8.06)		11 423 (14.22)	1 231 479 (10.69)	

Note: FDR, first-degree relative.

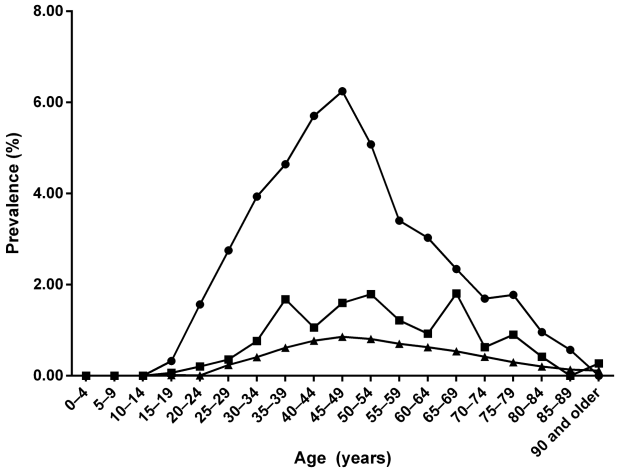

Fig. 1. Age-specific prevalence of schizophrenia in individuals with a first-degree (circle), or second-degree (square) relative with schizophrenia and in the general population (triangle) in Taiwan in 2013.

previously, the probability of a patient with schizophrenia having sporadic disease was 83.3%.

Co-aggregation of Mood Disorders and Delusional Disorders

Table 4 presents adjusted RRs (95% CIs) of other psychiatric illnesses in individuals with affected first- and second-degree relatives compared to the general population. The RR (95% CI) in individuals with an affected first-degree relative with schizophrenia was 3.49 (3.34–3.64) for mood disorders and 3.91 (3.35–4.57) for delusional disorders. For those with an affected second-degree relative the RR (95% CI) was 1.55 (1.23–1.96) for mood disorders and 3.71 (2.06–6.67) for delusional disorders.

Discussion

Principle Findings

The prevalence of schizophrenia in individuals with an affected first-degree relative is 6.3-fold higher, and with an affected second-degree relative 2.4-fold higher than in the general population, indicating a dose-response relationship between the risk of schizophrenia and genetic distance. This finding is in line with previous twin studies reporting a high concordance of schizophrenia. Familial factors contribute approximately two-thirds of phenotypic variance while genetic factors contribute approximately half of total variance. The magnitude of familial aggregation and heritability is substantial but is lower than estimates reported by previous studies.[12,13] We further report a higher prevalence of mood disorders and delusional disorders in people with a family history of schizophrenia. Despite this familial risk, similar to many other common complex diseases,[19,30] most cases of schizophrenia are expected to be sporadic.

Table 2. Relative Risks (RRs) of Schizophrenia in Individuals With First-Degree Relatives Diagnosed With Schizophrenia Adjusted for Age, Sex, and Socioeconomic Status

Type of Affected Relative	Sex of Affected Relative	Sex of Individual	No. of Cases	Prevalence (%)	RRs (95% CIs)[a]
Any	Male	Male	1285	3.20	6.01 (5.62–6.42)
		Female	1263	2.57	6.10 (5.78–6.42)
		All	2558	3.06	6.15 (5.88–6.44)
	Female	Male	1298	3.16	5.71 (5.42–6.01)
		Female	1438	3.62	7.98 (7.48–8.51)
		All	2736	3.39	6.86 (6.58–7.16)
	All	Male	2465	3.07	5.73 (5.49–5.98)
		Female	2539	3.12	6.72 (6.43–7.02)
		All	5004	3.09	6.30 (6.09–6.53)
Parent	Male	Male	268	2.09	6.39 (5.69–7.17)
		Female	147	1.25	6.23 (5.32–7.30)
		All	415	1.69	6.50 (5.91–7.15)
	Female	Male	753	3.52	6.41 (6.01–6.84)
		Female	542	2.89	8.99 (8.30–9.74)
		All	1295	3.23	7.58 (7.20–7.99)
	All	Male	1006	2.96	6.38 (6.02–6.75)
		Female	684	2.25	8.21 (7.65–8.82)
		All	1690	2.63	7.26 (6.94–7.60)
Offspring	Male	Male	184	1.35	2.57 (2.23–2.97)
		Female	627	3.51	4.99 (4.63–5.38)
		All	811	2.58	4.09 (3.83–4.37)
	Female	Male	115	1.26	2.35 (1.96–2.81)
		Female	452	4.04	5.53 (5.06–6.04)
		All	567	2.79	4.31 (3.98–4.67)
	All	Male	289	1.29	2.44 (2.18–2.73)
		Female	1025	3.57	5.03 (4.75–5.33)
		All	1314	2.57	4.06 (3.85–4.27)
Sibling	Male	Male	818	5.80	8.04 (7.41–8.73)
		Female	500	3.69	8.55 (7.87–9.29)
		All	1318	4.77	8.50 (8.00–9.03)
	Female	Male	487	4.44	7.47 (6.86–8.14)
		Female	439	4.40	11.16 (9.94–12.53)
		All	926	4.42	9.14 (8.51–9.82)
	All	Male	1263	5.09	7.69 (7.24–8.18)
		Female	898	3.86	9.36 (8.72–10.05)
		All	2161	4.49	8.58 (8.15–9.04)
Twin	Male	Male	54	36.73	24.6 (17.31–34.95)
		Female	2	5.41	12.21 (4.34–34.32)
		All	56	30.43	28.85 (21.56–38.61)
	Female	Male	1	4.17	9.08 (1.29–64.05)
		Female	55	45.45	65.93 (51.14–85.01)
		All	56	38.62	54.98 (41.92–72.11)
	All	Male	55	32.16	23.85 (16.95–33.56)
		Female	57	36.08	56.67 (44.17–72.69)
		All	112	34.04	37.86 (30.55–46.92)
Spouse	Female	Male	175	1.29	1.45 (1.25–1.68)
	Male	Female	192	2.05	2.74 (2.38–3.15)
	All	All	367	1.60	1.88 (1.64–2.15)

Note: [a]Adjusted for age, gender, place of residence, quintiles of income levels, occupation, and family size.

Comparison With Previous Estimates of Heritability

Heritability reported in this study is in the lower range of previously reported estimates. However, measurements of schizophrenia heritability may be subject to variation in study design, source population, studied kinships, and case definitions of schizophrenia. Twin studies have generally reported high heritability, ranging between 41% and 87%.[7–12] A study by Lichtenstein et al[13] that involved a sample of the Swedish population found a slightly lower heritability of 64.3%, while our estimate derived from the entire population of Taiwan was even lower at 47.3%. However, our estimate of familial transmission of 62.8% is very similar to that reported in the Swedish study (68.8%).[13] The difference in heritability estimates may in part be due to differences in the methods used to partition familial transmission into heritability and

Table 3. Relative Risks (RRs) of Schizophrenia in Individuals With Second-Degree Relatives Diagnosed With Schizophrenia Adjusted for Age, Sex, and Socioeconomic Status

Type of Affected Relative	Sex of Affected Relative	Sex of Individual	No. of Cases	Prevalence (%)	RRs (95% CIs)[a]
Any	Male	Male	20	0.18	1.64 (0.94–2.88)
		Female	30	0.27	2.57 (1.77–3.74)
		All	50	0.23	2.16 (1.55–3.01)
	Female	Male	31	0.23	2.84 (2.00–4.04)
		Female	26	0.20	2.55 (1.53–4.24)
		All	57	0.21	2.74 (2.03–3.70)
	All	Male	50	0.20	2.19 (1.61–2.98)
		Female	56	0.24	2.58 (1.90–3.52)
		All	105	0.22	2.44 (1.91–3.12)
Aunt/uncle	Male	Male	8	0.13	1.50 (0.75–2.98)
		Female	14	0.24	2.89 (1.61–5.17)
		All	22	0.19	2.18 (1.35–3.53)
	Female	Male	8	0.25	3.35 (1.69–6.65)
		Female	7	0.23	3.14 (1.52–6.50)
		All	15	0.24	3.30 (2.01–5.42)
	All	Male	16	0.17	2.08 (1.28–3.37)
		Female	21	0.24	2.98 (1.89–4.71)
		All	37	0.21	2.54 (1.79–3.60)
Niece/nephew	Male	Male	8	0.80	1.49 (0.75–2.94)
		Female	7	1.25	2.20 (1.07–4.54)
		All	15	0.96	1.76 (1.07–2.88)
	Female	Male	10	1.31	2.57 (1.42–4.66)
		Female	6	1.54	2.65 (1.21–5.77)
		All	16	1.39	2.53 (1.58–4.05)
	All	Male	17	0.98	1.86 (1.17–2.95)
		Female	13	1.37	2.39 (1.40–4.06)
		All	30	1.12	2.03 (1.44–2.88)
Grandparent	Male	Male	3	0.08	2.86 (0.94–8.66)
		Female	4	0.11	3.29 (1.24–8.74)
		All	7	0.10	3.05 (1.46–6.35)
	Female	Male	12	0.13	2.73 (1.52–4.91)
		Female	10	0.11	2.52 (1.37–4.67)
		All	22	0.12	2.63 (1.71–4.03)
	All	Male	15	0.11	2.76 (1.64–4.63)
		Female	14	0.11	2.71 (1.61–4.56)
		All	29	0.11	2.72 (1.88–3.94)
Grandchildren	Male	Male	1	0.28	2.35 (0.33–16.71)
		Female	5	0.50	2.04 (0.85–4.88)
		All	6	0.44	2.63 (1.19–5.82)
	Female	Male	3	0.08	3.92 (0.55–27.94)
		Female	4	0.11	2.25 (0.86–5.93)
		All	7	0.10	3.15 (1.32–7.53)
	All	Male	4	0.10	2.95 (0.74–11.79)
		Female	9	0.20	2.16 (1.13–4.12)
		All	11	0.13	2.87 (1.60–5.16)

Note: [a]Adjusted for age, gender, place of residence, quintiles of income levels, occupation, and family size.

shared environmental factors. We used the spouse as a control, while Lichtenstein analyzed outcomes from nuclear, paternal half-sibling, and maternal half-sibling families. Our methods could have underestimated heritability due to the effect of assortative mating, which nullifies the assumption of zero genetic correlation between spouses.[31] However, assortative mating has been found to be of minor relevance in family studies,[32] although ideally this needs confirmation in our population. In addition, the fact that the heritability estimate cannot be higher than that of familial transmission suggests that only if shared environmental factors were nonexistent would the heritability of schizophrenia approach previous estimates, while environmental factors such as birth place and season seem to account for more population impact on the risk of schizophrenia.[10] Therefore the environmental contribution to schizophrenia susceptibility seem to be greater than previously thought.

Currently schizophrenia is subject to much missing heritability since only a fraction of heritability can be explained by GWA studies.[33] Factors such as a heritable epigenetic component or structural variation,[34]

Table 4. Relative Risks (RRs) of Mood and Delusional Disorders in Individuals With First-Degree Relatives Diagnosed With Schizophrenia Adjusted for Age, Sex, and Socioeconomic Status

		With Affected Relatives		General Population		
Psychiatric Illnesses	Sex	No. of Cases	Prevalence (%)	No. of Cases	Prevalence (%)	RRs (95% CIs)[a]
With first-degree relatives diagnosed with schizophrenia						
Mood disorders	Male	835	1.04	29 693	0.24	3.52 (3.29–3.77)
	Female	1264	1.55	48 905	0.41	3.43 (3.25–3.62)
	All	2099	1.30	78 598	0.33	3.49 (3.34–3.64)
Delusional disorders	Male	61	0.08	2328	0.02	3.42 (2.67–4.38)
	Female	93	0.11	2752	0.02	4.31 (3.52–5.26)
	All	154	0.10	5080	0.02	3.91 (3.35–4.57)
With second-degree relatives diagnosed with schizophrenia						
Mood disorders	Male	32	0.13	29 693	0.24	1.73 (1.21–2.46)
	Female	39	0.08	48 905	0.41	1.42 (1.04–1.93)
	All	71	0.15	78 598	0.33	1.55 (1.23–1.96)
Delusional disorders	Male	6	0.03	2328	0.02	4.33 (1.82–10.31)
	Female	5	0.02	2752	0.02	2.99 (1.35–6.62)
	All	11	0.02	5080	0.02	3.71 (2.06–6.67)

Note: [a]Adjusted for age, gender, place of residence, quintiles of income levels, occupation, and family size.

gene–gene interactions among loci,[35] and contributions from rare variants[36] may partly explain missing heritability, and in general it is hard to ascertain these factors in GWA studies. Another possibility is that the heritability of schizophrenia is lower than that estimated previously in twin studies and therefore the extent of missing heritability might be overestimated.

Familial Co-aggregation of Schizophrenia and Other Mental Disorders

A family history of schizophrenia is also a risk factor for mood and delusional disorders. Although several smaller studies have found no association between a family history of schizophrenia and mood disorders,[37–39] more recent studies generally support the theory that families with schizophrenia patients are enriched with cases of unipolar[40] or bipolar disorder.[41] A recent meta-analysis found an increased risk for a range of psychiatric disorders, including schizophrenia and mood disorders, among offspring of parents with SMI.[16] A nationwide study from Sweden found that having a parent or sibling with schizophrenia was associated respectively with a 5.2- and 3.7-fold increased risk of bipolar disorder. In addition to epidemiological evidence, data from the International Schizophrenia Consortium (ISC) case-control sample, which genotyped 3322 European individuals with schizophrenia and 3587 controls, found substantial shared genetic liability between schizophrenia and bipolar disorder.[15] Furthermore, the genetic correlation is estimated to be 0.68 between schizophrenia and bipolar disorder, and 0.43 between schizophrenia and major depression.[42] Previous evidence for familial co-aggregation between schizophrenia and delusional disorders is insufficient and conflicting.[43–45] Our data support the co-aggregation of schizophrenia with both mood disorders and delusional disorders. This suggests that these other psychiatric illnesses share part of the pathogenesis of schizophrenia.

Limitations

There are several limitations to the present study. Firstly, the case definitions are based purely on the diagnosis recorded in the Registry for Catastrophic Illness Patients. Detailed information on patients' clinical findings is not available in the database, therefore we cannot validate the diagnoses. Nevertheless, our case definitions are based on a psychiatrist-made diagnosis that is corroborated by an expert panel so we consider these case definitions to be stringent. Secondly, the zygosity of twins is not recorded in the database so we cannot estimate heritability using a classic twin study design. Thirdly, because we estimated heritability using the liability threshold model the results are subject to the assumption that diseases result from underlying liability that is normally distributed in the population. Although this is a potential caveat, a previous study of other mental diseases supports the validity of this model and the application of this model to mental diseases.[46] Additionally, recent GWA studies strongly support the polygenic basis of schizophrenia.[15,47] Fourthly, we could not account for the effects of assortative mating. If these effects are not negligible, heritability could have been underestimated. Patients with schizophrenia also tend to have fewer offspring, and we adjusted the family size to account for this effect. Fifthly, this study was restricted to Taiwan, and it is possible that different results would be obtained in different populations and environments. Therefore, further studies in other

countries are required to determine the generalizability of this study's findings. Furthermore, we reconstructed nationwide genealogy based on the family relationships that are recorded in the NHI in order to grant eligibility of dependent status, therefore the complete ascertainment of family relationships was not possible since some people do not need family relationships to maintain NHI eligibility. For example, migrants, foreigners living in Taiwan for more than 6 months, people relying on government subsidies, and Taiwanese citizens living overseas are also eligible for NHI. Nevertheless, it was possible to ascertain familial relationships in the majority of permanent residents in Taiwan. Also ascertainment of cases with psychiatric illnesses and family relationships are unrelated processes, so any differential ascertainment of schizophrenia cases is expected to be minimal. Lastly, residual confounding may exist. We adjusted for residence, income, occupation, and family size,[26] which may contribute to the risk of schizophrenia.[26] However, other factors, such as level of education, have been implicated as risk factors but these are not available in the NHI database so cannot be considered.

Conclusions

This nationwide family study confirms that in Taiwan a positive family history of schizophrenia is one of the strongest risk factors for schizophrenia and other psychiatric illnesses. Differential risk associated with different kinships suggests a strong genetic component in susceptibility to schizophrenia. These findings may be useful in counseling the families of schizophrenia patients.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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