Acta Psychiatr Scand 2007: 116 (Suppl. 436): 20–32
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DOI: 10.1111/j.1600-0447.2007.01076.x

ACTA PSYCHIATRICA SCANDINAVICA

Hospital-treated psychosis and suicide in a rural community (1877–2005). Part 2: Genetic founder effects

Andersen JE, Hynnekleiv T. Hospital-treated psychosis and suicide in a rural community (1877–2005). Part 2: Genetic founder effects.

Objective: To demonstrate the existence of genetic founder effects in hospital-treated cases of psychosis and self-harm in historical cohorts of a small rural population.
Method: These cohorts consist of named persons born after 1845. The cumulative case registers were linked to the purported pedigrees of three presumed mentally ill founders living in the community in the 17th and 18th centuries. We compared the incidence of psychosis and self-harm in the genetically unexposed population and in three exposed founder populations.
Results: We found a preponderance of organic mental disorders and schizophrenia in the twice-exposed founder population and of other non-organic psychosis and self-harm in the thrice-exposed founder population.
Conclusion: The genetic impact of the founders seems to have affected the incidence rates of severe psychiatric disorders of their descendants in two ways. A founder effect is detected in organic mental disorders and schizophrenia, and it seems to run independently of that detected in affective psychotic disorders and intentional self-harm.

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Key words: cohort study; psychotic disorders; intentional self-harm; incidence study; founder effect

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Both authors declare no conflicts of interest

Significant outcomes:

- Genetic founder effects of psychotic disorders and suicide have been found.
- A genetic based dichotomy is found in psychotic disorders along cognitive and affective lines.
- Some genetic constellations appear to protect against certain severe mental disorders.

Limitations:

- Historical accounts of mental disorder have been taken at face value.
- The study relied on purported kinship.
- The clinical criteria could have been more strictly defined.

Introduction

Epidemiological studies of mental disorders frequently take up issues of geography such as migration (1–3), urban versus rural life styles (4) and regional patterns of distribution (5, 6). This study addresses issues of history (7). In the first paper of this study (8), we performed epidemiological studies of hospital-treated psychosis and acts of intentional self-harm (9) in historical cohorts of a small rural population. We will further pursue the historical perspective. The incidence rates of 86 cases of hospital-treated psychosis, in addition to 19 cases of intentional self-harm (8), are examined in terms of presence or absence of the genes – i.e. the heritable traits – of three presumed mentally ill founders. These founders represent the oldest accounts of presumed mental illness traced within the community. They lived in the community studied in the 17th and 18th centuries (cf. Appendix). We trace their descendants for generations using several genealogical

Table 1. The expansion of the genes of the three founders in the local population from 1665 to 1965

Period	Diagnostic categories	Total population	Unexposed general population	Cases 1846–2005	Once-exposed founder population F1	Cases 1846–2005	Twice-exposed founder population F2	Cases 1846–2005	Thrice-exposed founder population F3	Cases 1846–2005
1665		263	261	–	2	–	0	–	0	–
1723		383	379	–	13	–	2	–	1	–
1762		656	624	–	26	–	5	–	1	–
1846		1212	840	–	329	–	29	–	14	–
1846–1925	F00–F09	2183	770	3	1067	8	167	9	179	2
1846–1946	F20	2580	866	7	1288	15	209	15	217	2
1846–1959	F23.9/F30–F33	2838	909	3	1408	14	235	1	285	7
1846–1965	X60–X84	2920	916	2	1461	10	245	2	298	5

and historical sources (10–16). Their inherited entities – the genes – expanded and influenced the local population (Table 1).

Aim of the study

The aim of the study is to show whether psychosis or intentional self-harm of the founders reappear in their descendants, i.e. to find out if there exist genetic founder effects in psychosis and suicide.

Material and methods

The 1665 populations

The rural community studied consisted of 52 farms in 1665 (Fig. 1). Each farm represented an independent household or a family usually consisting of two or three generations. The head of each household was recorded (10, 11). They were born between 1580 and 1644 (Figs 2–5). Fifty-two households had 263 named persons according to our reconstruction of the 1665 population (Table 1).

The presumed mentally ill founders

F1 was the oldest of the three founders. He was born in a neighbouring community in the first decennium of the 17th century (17). He was referred to as insane in the census of 1665 (10). The two other founders, F2 and F3, were born in the community at later dates (Figs 2–5). We suggest the following diagnostic categorizations, as a priori hypotheses, based on the symptoms and courses of the three founders and of their close genetic relatives as described in the genealogies. F1 had psychotic symptoms compatible with the ones shown in the category of other non-organic psychosis. F2 had a deviant behaviour compatible with that shown in dementia or schizophrenia spectrum disorders. F3 had a violent death suggesting suicide and an affective disorder (cf. Appendix).

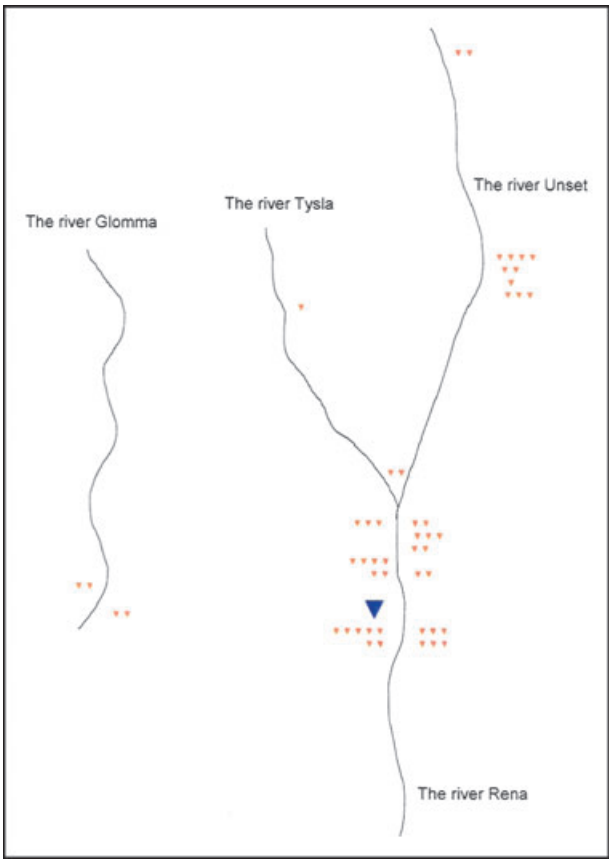

Fig. 1. The geographical distributions of 52 farms or households of the community in the year 1665 [Adapted from S. Sogner (18)]. The community comprised 52 households or farms. F1 was the head of one of the households, here coloured blue. He became insane in 1661 and was deposed. He died in 1678. There is no information of mental illness among the other 51 heads of households, here coloured orange. The other two presumed mentally ill founders, F2 and F3, were born in the community at later dates.

The cases among their descendants

The historical cohorts consisted of named persons born in the community studied after 1845. They descended from 263 persons living in the community in 1665. Twenty-two cases in the diagnostic category of organic mental disorders were recruited

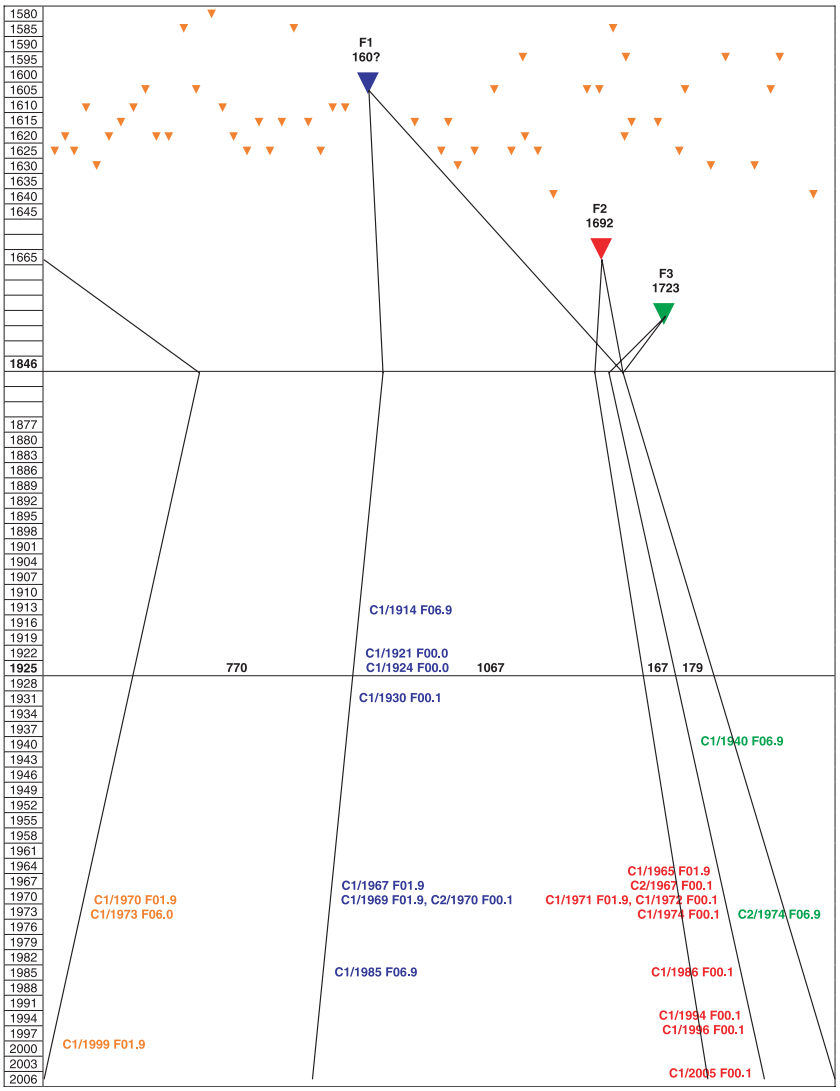

Fig. 2. A graphical representation of 22 cases of organic mental disorders (Tables 2 and 6). It shows the age distributions of 52 heads of the 1665 households (coloured orange), including F1 (coloured blue). They were born between 1580 and 1644. F2 (coloured red) and F3 (coloured green) were born at later dates. The unexposed general population counted 770, the once-exposed founder population 1067, the twice-exposed 167 and the thrice-exposed 179 persons. All were born in the community between 1846 and 1925 (Table 1), and make up the first of four historical cohorts. The unexposed general population generated three hospitalized cases between 1970 and 1999 (coloured orange). The once-exposed founder population generated eight cases between 1914 and 1985 (coloured blue); the twice-exposed nine cases between 1965 and 2005 (coloured red) and the thrice-exposed two cases between 1940 and 1974 (coloured green).

from 2183 persons born in the community between 1846 and 1925. Thirty-nine cases in the category of schizophrenia were recruited from 2580 persons born between 1846 and 1946. Twenty-five cases in the category of other non-organic psychosis were recruited from 2838 persons born between 1846 and 1959. Nineteen cases of intentional self-harm with fatal or near-fatal outcome were recruited from 2920 persons born in the community between 1846 and 1965. Each of these cases was referred to specifically in the first paper (8).

The historical cohorts

The historical cohorts overlap each other. Their different sizes have been determined by the four diagnostic categories mentioned above (9). Each cohort has been divided into one unexposed general population and three exposed founder populations according to the individual genetic relationships to one or more of the three founders. The unexposed general population consisted of gene constellations of a majority of people in the 1665 population. The once-exposed founder population was categorized by adding descendants of F1 to the unexposed general population. The genes of F1 are the only known novelties in the once-exposed founder population. The twice-exposed population was created, by adding descendants of F2 to the once-exposed founder population. The genes of F2 are the only known novelties in the twice-exposed founder population. The thrice-exposed population was created, by adding descendants of F3 to the twice-exposed founder population. The genes of F3 are the only known novelties in the thrice-exposed population (Figs. 2–5).

The procedures

The procedures for diagnostic classifications and incidence estimates were dealt with in the first paper (8). We compared the estimated incidence

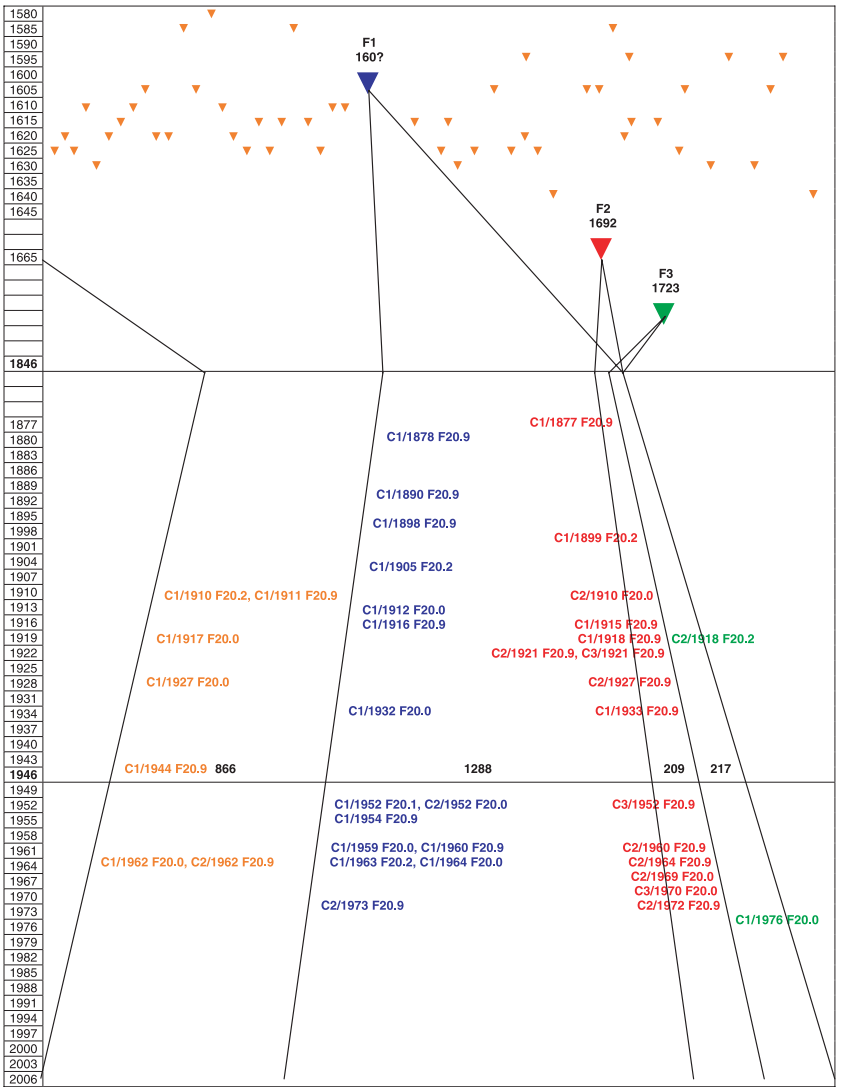

Fig. 3. A graphical representation of 39 cases of schizophrenia (Tables 3 and 6). The unexposed general population counted 866, the once-exposed founder population 1288, the twice-exposed 209 and the thrice-exposed 217 persons. All were born in the community between 1846 and 1946, and make up the second historical cohort. The unexposed general population of the cohort generated seven hospitalized cases between 1910 and 1962 (coloured orange), the once-exposed founder population 15 cases between 1878 and 1973 (coloured blue), the twice-exposed 15 cases between 1877 and 1972 (coloured red) and the thrice-exposed two cases between 1918 and 1976 (coloured green).

rates of organic mental disorders, schizophrenia, other non-organic psychosis and intentional self-harm (9) in the unexposed general population with each of the exposed founder populations. The proportional difference in the number of cases in the unexposed general population was compared with the number of cases in each of the three exposed founder populations in 2 × 2 tables. Chi-quadrate statistical tests were carried out.

An overview of all named persons born in a small rural community of south-east Norway between 1580 and 1985 was achieved by using local genealogies (10, 11, 16), historical population censuses (12–15) and an academic thesis in demography (18). We traced the pedigrees of the earliest described cases of presumed mental illness of three named persons in the community. Their pedigrees were pursued in a 'top-down' direction from the 17th and 18th centuries to the present-day population (Table 1). The study comprises totally 12 generations from the oldest founder F1 to the present-day. According to our hypotheses, F1 and F3 had affective disorders with psychotic symptoms, and F2 had dementia (19) or a schizophrenia spectrum disorder (cf. Appendix). These diagnostic judgements were done prior to the division of historical cohorts into one unexposed general population and three exposed founder populations and before the patients in the historical cohorts were diagnosed by the authors (8).

Formal approvals

The National Data Inspectorate, The Board of Health, and The Regional (South) Research Ethics Committee in Norway approved the study.

Results

Organic mental disorders in the elderly in the 1846–1925 cohort

Three of 770 persons in the unexposed general population, eight of 1067 in the once-exposed, nine

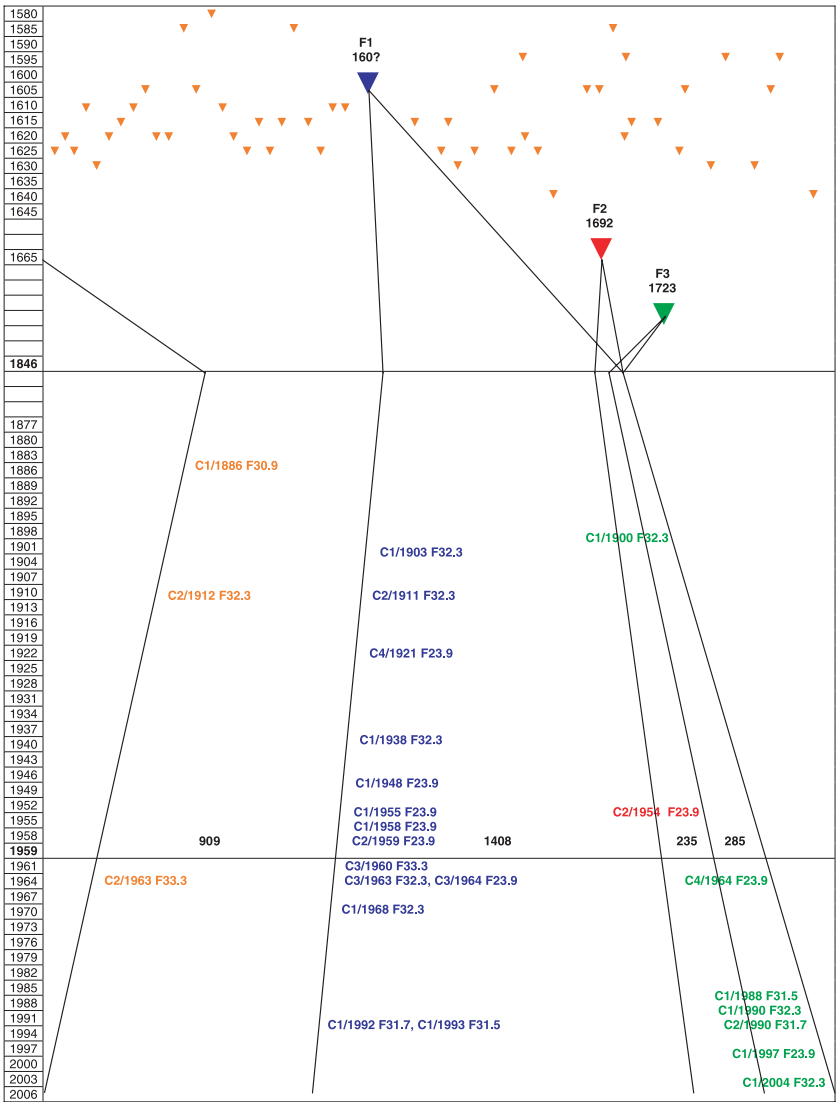

Fig. 4. A graphical representation of 25 cases of other non-organic psychosis (Tables 4 and 6). The unexposed general population counted 909, the once-exposed founder population 1408, the twice-exposed 235 and the thrice-exposed 285 named persons. All were born in the community between 1846 and 1959, and make up the third historical cohort. The unexposed general population of the cohort generated three hospitalized cases between 1886 and 1963 (coloured orange), the once-exposed founder population 14 cases between 1903 and 1993 (coloured blue), the twice-exposed just one case in 1954 (coloured red) and the thrice-exposed seven cases between 1900 and 2004 (coloured green).

of 167 in the twice-exposed and two of 179 in the thrice-exposed founder populations were hospitalized in this diagnostic category between 1914 and 2005 (Fig. 2). This generates incidence rates of 0.06, 0.12, 0.90 and 0.19 per 1000, respectively (Table 2). The rate of organic mental disorders was statistically significant solely in the twice-exposed founder population, when the unexposed general population was compared with each exposed founder population ($\chi^2 = 23.39$; $P < 0.001$; d.f. = 1).

Schizophrenia in the 1846–1946 cohort

Seven of 866 persons in the unexposed general population, 15 of 1288 in the once-exposed, 15 of 209 in the twice-exposed and two of 217 in the thrice-exposed founder population were hospitalized in this diagnostic category between 1877 and 1976 (Fig. 3). This generates incidence rates of 0.13, 0.18, 1.16 and 0.15 per 1000, respectively (Table 3). The rate of schizophrenia was statistically significant solely in the twice-exposed population, when the unexposed general population was compared with each exposed founder population ($\chi^2 = 29.76$; $P < 0.001$; d.f. = 1).

Other non-organic psychosis in the 1846–1959 cohort

Three of 909 named persons in the unexposed general population, 14 of 1408 in the once-exposed, only one of 235 in the twice-exposed and seven of 285 in the thrice-exposed founder population were hospitalized in this category between 1886 and 2004 (Fig. 4). This generates incidence rates of 0.05, 0.16, 0.07 and 0.39, per 1000, respectively (Table 4). The rate of other non-organic psychosis was statistically significant solely in the thrice-exposed population, when the unexposed general population was compared with each exposed

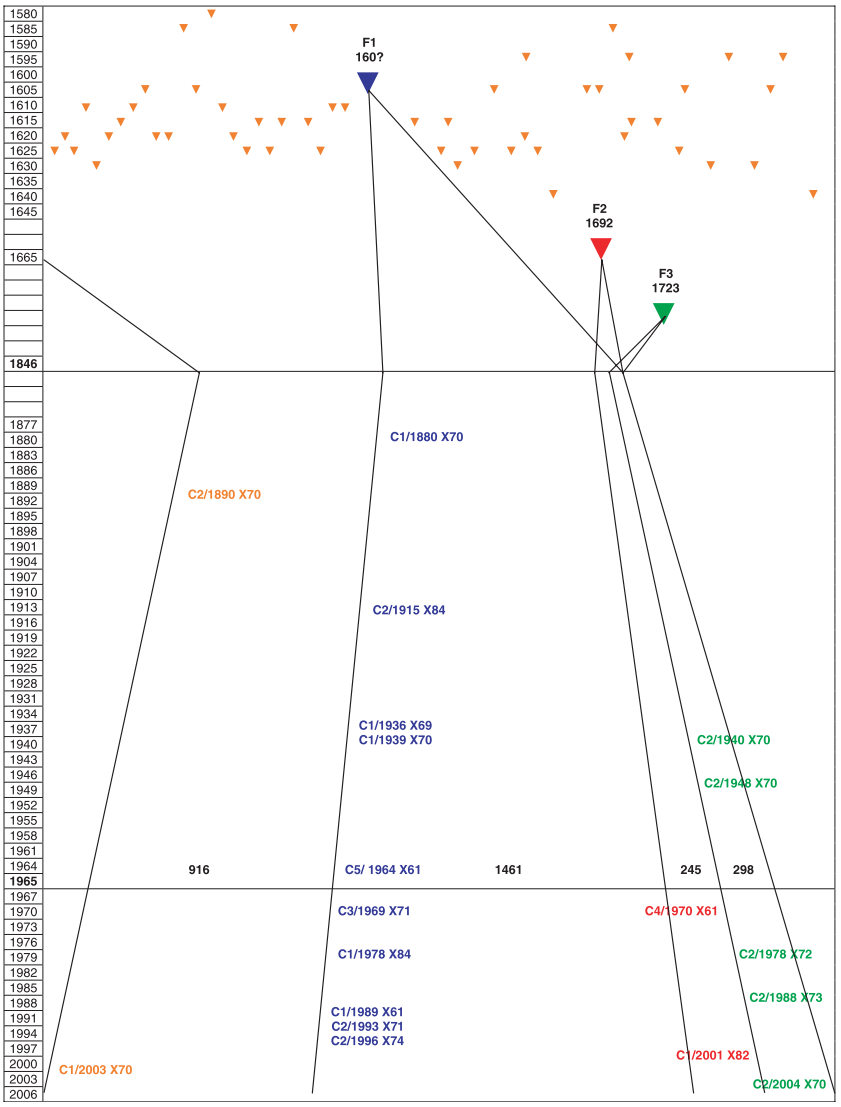

Fig. 5. A graphical representation of 19 cases of intentional self-harm with fatal or near-fatal outcome (Table 5). The unexposed general population counted 916, the once-exposed founder population 1461, the twice-exposed 245 and the thrice-exposed 298 named persons. All were born in the community between 1846 and 1965, and make up the fourth historical cohort. The unexposed general population of the cohort generated two cases of intentional self-harm between 1890 and 2003 (coloured orange). The once-exposed founder population generated 10 cases with fatal or near-fatal outcome between 1880 and 2003 (coloured blue) The twice-exposed population generated two cases between 1970 and 2001 (coloured red), and the thrice-exposed population generated five cases with fatal or near-fatal outcome between 1900 and 2004 (coloured green).

population ($\chi^2 = 10.33$; $P < 0.01$; d.f. = 1). It approached statistical significance in the once-exposed founder population ($\chi^2 = 3.55$; $P > 0.05$; d.f. = 1).

Intentional self-harm with fatal or near-fatal outcome in the 1846–1965 cohort

There were two cases of intentional self-harm among 916 persons in the unexposed general population; 10 among 1461 identified persons in the once-exposed; two among 245 in the twice-exposed and five among 298 in the thrice-exposed population in this category between 1880 and 2004 (Fig. 5). This generates a rate of 3.5, 10.9, 13.0 and 26.8 per 100 000 respectively (Table 5). The rate of intentional self-harm was statistically significant solely in the thrice-exposed population, when the unexposed general population was compared with each exposed founder population ($\chi^2 = 7.18$; $P < 0.01$; d.f. = 1).

Discussion

One may easily dispute the sources and details of the historical and clinical premises, but we pursued the study as if the hypothetical a priori diagnoses were correct. The proposed psychiatric diagnoses of the founders, the trustworthiness of the purported genetic relationships and the soundness of the hospital diagnoses may be considered as our model assumption. They are basic, but independent of other validity claims of the present study. We connected input variables with output variables (20). The input variables are our psychiatric diagnosis assumptions of the founders and their genetic relatives (cf. Appendix). The output variables consist of the 86 cases of hospital-treated psychosis (Tables 2–4) or their original diagnoses at last discharge (21). Nine of them were revised (8). We have added 19 cases of intentional self-harm to the hospital-treated psychosis (Table 5).

Table 2. The incidence per 1000 of organic mental disorder in the presence or absence of, the genes of the three founders (specification of gender has been omitted in this and other tables due to confidentiality)

No.	Case id.	Age at first admission/final discharge	Number of stays	Year of final discharge	The original hospital diagnoses at final discharge	Final ICD-10 diagnosis	F1	F2	F3
01	C1/1970	72/72	1	1970	Psychosis arteriosclerotica	F01.9	–	–	–
02	C1/1973	86/86	1	1973	Reactive psychosis*	F06.0*	–	–	–
03	C1/1999	78/78	1	1999	Vascular dementia	F01.9	–	–	–
Incidence per 1000 in the unexposed general population: [3/(770 × 59.99)] × 1000 = 0.06495 = 0.06									
01	C1/1914	48/55	1	1921	Vitium organie cerebri	F06.9	+	–	–
02	C1/1921	62/62	1	1921	Dementia senilis	F00.1	+	–	–
03	C1/1924	62/67	1	1929	Dementia senilis	F00.1	+	–	–
04	C1/1930	69/71	1	1932	Dementia senilis	F00.1	+	–	–
05	C1/1967	76/76	1	1967	Psychosis arteriosclerotica	F01.9	+	–	–
06	C1/1969	66/68	3	1971	Psychosis arteriosclerotica	F01.9	+	–	–
07	C2/1970	75/75	1	1970	Psychosis senilis	F00.1	+	–	–
08	C1/1985	88/88	1	1985	Psychosis cum morbo infectionis	F06.9	+	–	–
Incidence per 1000 in the once-exposed founder population: [8/(1067 × 59.99)] × 1000 = 0.12498 = 0.12									
01	C1/1965	79/79	1	1965	Psychosis arteriosclerotica	F01.9	+	+	–
02	C2/1967	83/83	1	1967	Psychosis senilis	F00.1	+	+	–
03	C1/1971	78/79	2	1972	Psychosis arteriosclerotica	F01.9	+	+	–
04	C1/1972	76/78	2	1974	Psychosis senilis	F00.1	+	+	–
05	C1/1974	89/89	1	1974	Dementia senilis	F00.1	+	+	–
06	C1/1986	69/70	2	1987	Dementia senilis	F00.1	+	+	–
07	C1/1994	91/91	1	1994	Dementia in Alzheimer's disease	F00.1	+	+	–
08	C1/1996	73/73	1	1996	Dementia in Alzheimer's disease	F00.0	+	+	–
09	C1/2005	80/80	1	2005	Dementia in Alzheimer's disease	F00.1	+	+	–
Incidence per 1000 in the twice-exposed founder population: [9/(167 × 59.99)] × 1000 = 0.89835 = 0.90									
01	C1/1940	66/66	1	1940	Psychosis *ex vitio* cerebri	F06.9	+	+	+
02	C2/1974	61/61	1	1979	Psychosis e morbis cerebri aliis	F06.9	+	+	+
Incidence per 1000 in the thrice-exposed founder population: [2/(179 × 59.99)] × 1000 = 0.18626 = 0.19									
Incidence per 1000 in the total population: [22/(2180 × 59.99)] × 1000 = 0.16822 = 0.17									

*Revised by the authors.

The original hospital diagnoses were finally expressed in broad categories according to the diagnostic criteria of the ICD-10 (9). All cases of hospital-treated psychosis and intentional self-harm in the historical cohorts can be traced back to the persons in the heads of households in the 1665 population. They are designated by orange triangles in Figs 2–5. They make up the background scenery of the present-day population. They are the most recent common ancestors (MRCAs) of identified persons of the historical cohorts. Chang has calculated that 80% of the people who lived on the earth 20 to 35 generations ago are the ancestors of all people living today (22). The oldest founder F1 is the MRCA about two-thirds of the named persons in the historical cohorts after 12 generations (Table 1; Figs 2–5). Long-distant ancestry and the very definition of genetic founder effect may defend a choice of using a categorical approach. The absence or presence of the genes of one or more of the three founders seemingly decides the psychiatric diagnosis of their descendants (Tables 1–6). Mayr defined founder effect as 'the establishment of a new population by a few original founders, which carry only a small fraction of the total variation of the parental population' (23). Tiny fractions of the total variations of the parent population seem to the psychiatric diagnoses in their distant descendants. These fractions act apparently in a non-Mendelian all-or-nothing manner.

The rates of psychosis and suicide were considerably lower in the unexposed general population of the historical cohorts than in the country at large (24–27) and in some of the exposed founder populations (Tables 1–6). The rates of organic mental disorders and schizophrenia were exceptionally high in the twice-exposed founder population (Tables 2 and 3). These peaks were highly statistically significant when compared with the corresponding rates in the unexposed general population (Table 6). The peaks were seemingly due to gene constellations containing genes of F2, i.e. the genes of F2 were the only known novelties in the twice-exposed founder population (Figs 2 and 3).

The rates of other non-organic psychosis (Table 4) and intentional self-harm with fatal or near-fatal outcome (Table 5) were high in the thrice-exposed founder population. These peaks were statistically significant when compared with the corresponding rates in the unexposed general population (Table 6). The peaks were seemingly due to gene constellations containing genes of F3,

Table 3. The incidence per 1000 of schizophrenia in the presence or the absence of, the genes of the three founders

No.	Case id.	Age at first admission./final discharge	Number of stays	Year of final discharge	The original hospital diagnoses at final discharge	Final ICD-10 diagnosis	F1	F2	F3
01	C1/1910	18/19	1	1911	Dementia praecox (Catatonia)	F20.2	–	–	–
02	C1/1911	34/37	1	1914	Dementia praecox	F20.9	–	–	–
03	C1/1917	41/57	1	1933	Paranoia*	F20.0	–	–	–
04	C1/1927	57/58	1	1928	Dementia paranoids	F20.0	–	–	–
05	C1/1944	14/14	1	1944	Schizophrenia	F20.9	–	–	–
06	C1/1962	54/66	2	1974	Schizophrenia (Paranoid form)	F20.0	–	–	–
07	C2/1962	50/55	2	1965	Schizophrenia	F20.9	–	–	–
Incidence per 1000 of the unexposed general population: $[7/(866 \times 61.85)] \times 1000 = 0.13$									
01	C1/1878	33/42	2	1887	Dementia	F20.9	+	–	–
02	C1/1890	40/46	2	1896	Dementia	F20.9	+	–	–
03	C1/1898	42/46	1	1902	Alcoholismus chronicus*	F20.9	+	–	–
04	C1/1905	28/31	2	1908	Dementia praecox (Catatonia)	F20.2	+	–	–
05	C1/1912	34/76	2	1955	Schizophrenia (Paranoid)	F20.0	+	–	–
06	C1/1916	34/34	2	1916	Dementia praecox	F20.9	+	–	–
07	C1/1932	28/56	2	1960	Schizophrenia (Paranoid form)	F20.0	+	–	–
08	C1/1952	64/73	1	1963	Schizophrenia (Hebephrenia)	F20.1	+	–	–
09	C2/1952	54/64	2	1962	Schizophrenia (Paranoid form)	F20.0	+	–	–
10	C1/1954	46/64	2	1972	Schizophrenia	F20.9	+	–	–
11	C1/1959	53/63	3	1969	Schizophrenia (Paranoid form)	F20.0	+	–	–
12	C1/1960	54/57	4	1963	Schizophrenia (Paranoid form)	F20.0	+	–	–
13	C1/1963	19/20	4	1964	Psychosis schizo-affectiva*	F20.9	+	–	–
14	C1/1964	49/68	2	1983	Psychosis paranoides*	F20.0	+	–	–
15	C2/1973	40/49	3	1982	Exitatio reactiva*	F20.9	+	–	–
Incidence per 1000 of the once-exposed founder population: $[15/(1288 \times 61.85)] = 0.19$									
01	C1/1877	22/23	1	1878	Dementia	F20.9	+	+	–
02	C1/1899	22/24	1	1901	Mania*	F20.9	+	+	–
03	C2/1910	37/43	1	1916	Dementia paranoids	F20.0	+	+	–
04	C1/1915	35/37	1	1917	Dementia praecox	F20.9	+	+	–
05	C1/1918	22/68	6	1964	Schizophrenia	F20.9	+	+	–
06	C2/1921	40/65	1	1946	Schizophrenia	F20.9	+	+	–
07	C3/1921	38/71	1	1954	Schizophrenia	F20.9	+	+	–
08	C2/1927	36/41	1	1932	Schizophrenia	F20.9	+	+	–
09	C1/1933	32/73	1	1974	Schizophrenia	F20.9	+	+	–
10	C3/1952	34/43	2	1961	Schizophrenia	F20.9	+	+	–
11	C2/1960	26/28	3	1962	Schizophrenia	F20.9	+	+	–
12	C2/1964	41/68	6	1991	Psychosis manio-depressiva*	F20.9	+	+	–
13	C2/1969	27/49	6	1991	Schizophrenia (Paranoid form)	F20.0	+	+	–
14	C3/1970	59/78	2	1989	Schizophrenia (Paranoid form)	F20.0	+	+	–
15	C2/1972	26/45	9	1991	Schizophrenia	F20.9	+	+	–
Incidence per 1000 of the twice-exposed founder population: $[15/(209 \times 61.85)] \times 1000 = 1.16$									
01	C2/1918	24/27	1	1921	Dementia praecox (Catatonia)	F20.2	+	+	+
02	C1/1976	33/61	32	2004	Schizophrenia (Paranoid form)	F20.0	+	+	+
Incidence per 1000 of the thrice-exposed founder population: $[2/(217 \times 61.85)] \times 1000 = 0.15$									
Incidence per 1000 of the total population: $[39/(2580 \times 61.85)] \times 1000 = 0.24$									

*Revised by the authors.

i.e. the genes of F3 were the only known novelties in the thrice-exposed population (Figs 4 and 5).

This outcome reveals presence of two, not one, different genetic effects. The genetic constitution containing genes of F2 are associated with both organic mental disorders and schizophrenia (Tables 1 and 2). Statistically significant proportions of first admissions of both diagnostic categories can be traced back to F2. This person is the MRCA of hospital-treated patients in both organic mental disorders and schizophrenia. He is their common founder. These two diagnostic categories are normally not clinically linked today. A categorical link between the two was more obvious a 100 years ago, when the diagnostic terms dementia senilis and praecox were in frequent use (Tables 1 and 2). The core meaning of the historical term dementia was cognitive failure, chronic behavioural disturbances and psychosocial incompetence occurring at any age (19). There exist indications of a possible genetic association between organic mental disorders and schizophrenia (28). Organic mental disorders imply cognitive disturbances. The cognitive disturbance in schizophrenia have been observed for a long time (29) and supported during recent years in several studies (30). We are well aware of the fact that cognitive disturbances have been found in bipolar disorders (31), but it remains unclear whether these disturbances existed before disease onset, as in schizophrenia (30, 32). The

Table 4. The incidence per 1000 of other non-organic psychosis in the presence or the absence of, the genes of the three founders

No.	Case id.	Age at first admission final discharge	Number of stays	Year of final discharge	The original hospital diagnoses at final discharge	Final ICD-10 diagnosis	F1	F2	F3
01	C1/1886	19/19	1	1886	Mania	F30.9	–	–	–
02	C2/1912	16/16	1	1912	Melancholia	F32.3	–	–	–
03	C2/1963	71/73	2	1965	Neurosis depressiva*	F33.3	–	–	–
Incidence per 1000 in unexposed general population: [3/(909 × 62.56)] × 1000 = 0.05									
01	C1/1903	32/32	1	1903	Melancholia	F32.3	+	–	–
02	C2/1911	62/62	1	1911	Melancholia	F32.3	+	–	–
03	C4/1921	46/46	1	1921	Amentia	F23.9	+	–	–
04	C1/1938	64/65	1	1939	Psychosis manio-melancholica	F32.3	+	–	–
05	C1/1948	33/59	6	1974	Psychosis *ex constitutione*	F23.9	+	–	–
06	C1/1955	50/55	3	1960	Psychosis *ex constitutione*	F23.9	+	–	–
07	C1/1958	38/38	1	1958	Psychosis *ex constitutione*	F23.9	+	–	–
08	C2/1959	18/18	1	1959	Psychosis *ex constitutione*	F23.9	+	–	–
09	C3/1960	44/72	5	1988	Psychosis reactiva depressiva	F32.3	+	–	–
10	C3/1963	70/70	1	1963	Melancholia involutiva	F32.3	+	–	–
11	C4/1964	30/30	2	1964	Psychosis paranoides	F23.9	+	–	–
12	C1/1968	61/61	1	1968	Psychosis reactiva depressiva	F32.3	+	–	–
13	C1/1992	36/43	4	1999	Bipolar affective disorder	F31.7	+	–	–
14	C1/1993	49/49	1	1993	Bipolar affective disorder	F31.5	+	–	–
Incidence per 1000 in the once-exposed founder population: [14/(1408 × 62.56)] × 1000 = 0.16									
01	C2/1954	46/46	1	1954	Psychosis *ex constitutione*	F23.9	+	+	–
Incidence per 1000 in the twice-exposed founder population: [1/(235 × 62.56)] × 1000 = 0.07									
01	C1/1900	32/32	1	1900	Melancholia	F32.3	+	+	+
02	C5/1964	18/23	3	1969	Psychosis *ex constitutione*	F23.9	+	+	+
03	C1/1988	29/39	3	1998	Bipolar affective disorder	F31.5	+	+	+
04	C1/1990	83/83	1	1990	Psychosis reactiva depressiva	F32.3	+	+	+
05	C2/1990	51/53	3	1992	Bipolar affective disorder	F31.7	+	+	+
06	C1/1997	40/40	1	1997	Acute paranoid psychosis	F23.9	+	+	+
07	C1/2004	51/51	1	2004	Depressive episode with psychosis	F32.3	+	+	+
Incidence per 1000 in the thrice-exposed founder population: [7/(285 × 62.56)] × 1000 = 0.39									
Incidence per 1000 in the total population: [25/(2838 × 62.56)] × 1000 = 0.14									

*Revised by the authors.

Table 5. The incidence per 100 000 of intentional self-harm with fatal or near-fatal outcome is shown in the presence or absence of the genes of the three founders

No.	Case id./year of self-harm	Age at self-harm	ICD-10 codes	Outcome	Sources	F1	F2	F3
01	C1/1890	39	X70	Fatal	Nygaard (44)	–	–	–
02	C1/2003	39	X70	Fatal	Patient record of relatives	–	–	–
The unexposed general population: [2/(916 × 62.66)] × 100 000 = 3.5								
The median national rate of suicide per 100 000 for the period 1890–2003: 8.7								
01	C1/1880	33	X70	Fatal	Nygaard (44)	+	–	–
02	C1/1915	39	X84	Fatal	Bull (11)	+	–	–
03	C1/1936	29	X69	Fatal	Patient record of relatives	+	–	–
04	C1/1939	30	X70	Fatal	Patient record of relatives	+	–	–
05	C1/1964	20	X61	Fatal	Patient record of relatives	+	–	–
06	C1/1969	63	X71	Fatal	Patient record of relatives	+	–	–
07	C1/1978	48	X84	Fatal	Patient record of relatives	+	–	–
08	C1/1989	73	X61	Fatal	Our patient record	+	–	–
09	C1/1993	48	X71	Fatal	Patient record of relatives	+	–	–
10	C2/1996	31	X74	Near-fatal	Patient record	+	–	–
The once-exposed founder population: [10/(1461 × 62.66)] × 100 000 = 10.9								
The median national rate of suicide per 100 000 for the period 1880–1993: 10.1								
01	C1/1970	17	X61	Fatal	Patient record of relatives	+	+	–
02	C1/1999	45	X82	Fatal	Our patient record	+	+	–
The twice-exposed founder population: [2/(245 × 62.66)] × 100 000 = 13.0								
The median national rate of suicide per 100 000 for the period 1970–1999: 10.8								
01	C1/1940	44	X70	Fatal	Patient recorfd of relatives	+	+	+
02	C1/1948	31	X70	Fatal	Patient record of relatives	+	+	+
03	C2/1978	46	X72	Fatal	Patient record of relatives	+	+	+
04	C1/1988	78	X73	Fatal	Our patient record	+	+	+
05	C2/2004	47	X70	Near-fatal	Our patient record	+	+	+
The thrice-exposed founder population: [5/(298 × 62.66)] × 100 000 = 26.8								
The median national rate of suicide per 100 000 for the period 1940–1988: 12.0								

Table 6. Proportional differences between the number of cases (*n*) and the size of the subpopulations (*M*) are estimated in four diagnostic categories

Subpopulations/diagnostic categories	Number of cases (*n*)	Size of the sub-populations (*M*)	χ^2 with Yates' corrections	*P*-values	d.f.
Organic mental disorders 1846–1925					
Unexposed general population versus	3	770			
1. Once-exposed founder population	8	1067	1.41	ns	1
2. Twice-exposed founder population	9	167	23.39	$P < 0.001$	1
3. Thrice-exposed founder population	2	176	0.84	ns	1
Sum	22	2180			
Schizophrenia 1845–1946					
Unexposed general population versus	7	866			
1. Once-exposed founder population	15	1288	0.76	ns	1
2. Twice-exposed founder population	15	209	29.91	$P < 0.001$	1
3. Thrice-exposed founder population	2	217	0.75	ns	1
Sum	39	2580			
Other non-organic psychotic disorders 1846–1959					
Unexposed general population versus	3	909			
1. Once-exposed founder population	14	1408	3.55	ns	1
2. Twice-exposed founder population	1	236	0.27	ns	1
3. Thrice-exposed founder population	7	285	10.33	$P < 0.01$	1
Sum	24	2838			
Intentional self-harm 1846–1965					
Unexposed general population versus	2	916			
1. Once-exposed founder population	10	1461	2.69	ns	1
2. Twice-exposed founder population	2	245	0.89	ns	1
3. Thrice-exposed founder population	5	298	7.18	$P < 0.01$	1
Sum	17	2920			

The unexposed general population is compared with each of the three exposed founder populations. Statistical significance estimated by χ^2 with Yates' correction.

results from this material suggest a genetic link between organic mental disorders and schizophrenia.

The genetic makeup containing genes of F3 are associated with other non-organic psychosis and intentional self-harm (Tables 4 and 5). Statistically significant proportions of these cases can be traced back to F3, who is the most recent common ancestor of all these cases. This index person is their common founder. A clinical association between mood disorders and suicide is well established (33, 34). The outcome of this study suggests an additional genetic link between other non-organic psychosis and possible suicide.

In this material, gene constellations confined to the twice-exposed founder population, in which the genes of F2 constituted the known novelties, may be interpreted as resilience factors in the development of other non-organic psychosis and intentional self-harm (Figs 2 and 3). And vice versa, gene constellations confined to the thrice-exposed founder population, in which the genes of F3 constituted the single known novelties, may act protective in the development of organic mental disorders and schizophrenia. Effects of gene constellations involving the two founders seem to be antithetical. Gene constellations of the twice-exposed population seem to result in cognitive disturbances. Gene constellations in the thrice-exposed population seem to result in emotional disorders. Both constellations may act reciprocally, as resilience factors.

Chang (22) has traced pedigrees of a two-parent model backwards from a hypothetical present-day population into the distant past in his quest for the MRCAs. Humans have two parents, four grandparents, etc., and the growth of our ancestors is close to exponential as we trace them back in time. This is true for anybody's ancestor and there must soon be an overlap between the ancestors of two more randomly chosen individuals. In simplified models, which assume random mating, the average number of generations has been estimated (22, 35) to be around $\log_2(n)$, where n is the population size. So if, e.g. the present-day population were to consist of 1000 people, the average number back to the universal ancestor would be $\log_2(1000)$ – about 10 generations (36). The size of the historical cohorts of this study varies from 2180 to 2920 individuals. The endogamy within the cohorts was considerable (11). F1 became the common ancestor of about two-thirds of the persons born after 1845 in the historical cohorts. There are totally 12 generations from F1 to the present-day population (Figs 2–5).

If this simplified mathematical model of the coalescent theory [$\log_2(n)$] were to be used, it would be senseless to speak of the presence of genetic founder effects. If we trace the history of the genome, not the genes, recombination would

complicate matters; this genetic 'shuffling' ensures that each child does not inherit exactly the same genomic information as its siblings, and means that the genealogical relationships of different genome segments can be different. Thus, genetic recombination and consanguinity makes the difference between the simplified mathematical model of the coalescent theory, and the existence of genetic founder effects in real life. There might be relevant links to molecular biological discoveries, phenomena as stretches of DNA – jumping genes – that move around the genome.

We have traced pedigrees of three presumed mentally ill founders downwards from a known 17th century rural population to the present-day in our quest for genetic founder effects (Table 1; Figs 2–5). According to this model, the oldest founder F1 may have had a psychotic disorder in a broad category of other non-organic psychosis. We found a genetic founder effect approaching statistical significance ($\chi^2 = 3.55$; $P > 0.05$; d.f. = 1) in the category of other non-organic psychosis among his descendants in the once-exposed a population of the cohort (Tables 4 and 6; Fig. 4). According to this diagnostic model, F2 had a schizophrenia spectrum disorder and F3 had a violent death and he may have had an affective disorder. The distance from F2 and F3 to the present-day population is about 10 generations and the genetic founder effects were more outspoken. We have found genetic founders effects ($\chi^2 = 23.39$; $P < 0.001$; d.f. = 1) and ($\chi^2 = 29.76$; $P < 0.001$; d.f. = 1) in cognitive disturbances among descendants of F2 (Tables 2, 3 and 6; Figs 2 and 3). We also have found genetic founder effects ($\chi^2 = 10.33$; $P < 0.01$; d.f. = 1) and ($\chi^2 = 7.18$; $P < 0.01$; d.f. = 1) in emotional disorders among descendants of F3 (Tables 4–6; Figs 4 and 5).

Cases of both cognitive disturbances and emotional disorders did occur in the unexposed general population. Cases of cognitive disturbance did occur in the once- and the thrice-exposed founder populations, where emotional disorders were the most prominent (Tables 2 and 4). And vice versa, cases of emotional disorders did occur in the twice-exposed population, where cognitive disturbances were the most prominent (Table 2). These cases may be reminiscent of affected founders living in the area prior to the recorded history, i.e. before 1665 (Table 1).

There are clinical traditions for grouping unipolar and bipolar disorders with psychotic episodes together with acute and transient psychosis under the heading other non-organic psychosis. Acute and transient psychosis mainly affects females with onset throughout adult life. They have an acute or abrupt onset. Their onset is only rarely dependent on acute severe stress. Their active periods of psychosis are very short. They respond well to antipsychotic drugs, and consequently have favourable outcome in spite of the fact that they are frequently recurrent. By grouping the phenotypes of uni/bipolar, and acute/transient psychosis together, we maintain for this material the original Kraepelinian dichotomy (37). The outcome here suggests a division of severe mental disorders along cognitive and emotional lines. This dichotomy has been challenged for a long time, but there still exist observations that support the existence of such a dichotomy (38), including various recent neurobiological results (39–41).

Tiny proportions of genome of the three founders, not necessarily expressed in the parental generation, seem to have tilted the balance from relative mental health to severe psychiatric illness in the descendants. It is not inconceivable that the balance can be tilted in the opposite direction, i.e. from severe mental illness to relative mental health as seen in the apparently sudden decline in the incidence of schizophrenia in the first paper of this study (8). Molecular biology has provided various ideas for possible mechanisms (42), which fall outside the scope of this paper. Finally, we should add that it has not escaped our notice that this material invites us to carry on with a more quantitative approach regarding inbreeding, through traditional kinship coefficient calculations (43).

Acknowledgements

The authors are grateful to professor Ulrik Fredrik Malt for continuous support, and for various forms of support to clinical heads Berit Bakkemo and Martin Rolstad, professor Per Farup, advisor Unni Aaboen, professor Per Sundby and psychiatric nurse Frode Birkelund. Thanks also to professor Nils Retterstøl, psychiatric consultants John E. Berg and Morten Juell for critical reading of earlier versions of the manuscript.

The study has been financially supported by The University of Oslo, The Norwegian Research Council, EU's Biomed 1 and 2 programme, Innlandet Hospital Trust, as well as donations from Solveig og Johan P. Sommers stiftelse and Josef og Haldis Andresens legat.

References

1. Mortensen PB, Pedersen CB, Westergaard T et al. Effects of family history and place and season of birth on the risk of schizophrenia. N Engl J Med 1999;**340**:603–608.
2. Zolkowska K, Cantor-Graae E, Mcneil TF. Increased rates of psychosis among immigrants to Sweden: is migration a risk factor for psychosis? Psychol Med 2001;**31**:669–678.
3. Cantor-Graae E, Bøcker Pedersen C, Mcneil TF, Mortensen PB. Migration as a risk factor for schizophrenia: a Danish

population-based cohort study. Br J Psychiatry 2004;**182**:117–122.
4. Allardyce J, Boydell J, van Os J et al. Comparison of the incidence of schizophrenia in rural Dumfries and Galloway and urban Camberwell. Br J Psychiatry 2001;**179**:335–339.
5. Haukaa J, Suvisaari J, Varilo T, Lonnqvist J. Regional variations in the incidence of schizophrenia in Finland: a study of birth cohorts born from 1950 to 1969. Psychol Med 2001;**31**:1045–1053.
6. Schelin EM, Munk-Jørgensen P, Olesen AV, Gerlach J. Regional differences in schizophrenia incidence in Denmark. Acta Psychiatr Scand 2000;**101**:293–299.
7. Karlsson JL. Inheritance of schizophrenia. Acta Psychiatr Scand 1974;**50**(suppl. 247):1–116.
8. Andersen JE, Hynnekleiv T. Hospital treated psychosis and suicide in a rural community (1877–2005). Part 1. Incidence rates. Acta Psychiatr Scand, 2007;**116**(suppl. 436): 6–19.
9. World Health Organization/Statens Helsetilsyn. ICD-10: Den internasjonale statistiske klassifikasjon av sykdommer og beslektede helseproblemer.(The ICD-10: The international statistical classification of diseases and related health problems, Norwegian Board of Health Supervision). Oslo: Elanders forlag, 1998.
10. Riksarkivet. Sogneprestenes manntall 1664–1666. Hedmark. Øvre Rendal. (Enrollment of the vicars 1664–1666.) Hedmark. Øvre Rendal. Oslo. Riksarkivet, 2007.
11. Bull JB. Øvre Rendal: gardenes og slektenes historie. (Øvre Rendal: the farms and the genealogies). Oslo: Gyldendal Norsk Forlag, 1940.
12. Arkivverket. Folketellinga for 1801 Reendahlen. (The population census of 1801 for Rendalen). Bergen: Digitalarkivet. Available at: http://digitalarkivet.uib.no/cgi-win/wc/webcens.exe?slag=n&filename=arkivverket/ft1801/f10432&spraak (3 October 2007).
13. Registreringssentralen for historiske data. Folketellinga 1865 for 0432 Rendalen. (The population census of 1865 for Rendalen). Tromsø: Universitetet i Tromsø, 1987.
14. Registreringssentralen for historiske data. Folketellinga 1875 for 0432 Rendal. (The population census of 1875 for Rendalen). Tromsø: Universitetet i Tromsø, 1987.
15. Registreringssentralen for historiske data. Folketellinga 1900 for 0433 Øvre Rendal. (The population census of 1900 for Øvre Rendal). Tromsø: Universitetet i Tromsø, 1987.
16. Lindtoft K. Øvre Rendal: gardenes og slektenes historie. (Øvre Rendal: the farms and the genealogies). Øvre Rendal: Bygdebokkomiteen, 1989.
17. Bang AC. Den norske kirkes geistlighed i reformationsaarhundredet (1536–1600): biografiske, kulturhistoriske og kirkehistoriske oplysninger. (The clergies of the Norwegian church during the century of reformation (1536–1600): biographical, cultural and church historical information). Kristiania: Cammermeyer, 1897.
18. Sogner S. Folkevekst og flytting. En historisk demografisk studie i 1700 årenes Øst-Norge. (Population growth and migration. A historical demographic study of Eastern Norway in the eighteenth century. English summary.) Oslo: Universitetsforlaget, 1979.
19. Berrios GE. Dementia during the seventeenth and eighteenth centuries: a conceptual history. Psychol Med 1987;**17**:829–837.
20. Diamond JM. Collapse. How societies choose to fail or survive. London: Allan Lane, 2005:18.
21. Kendell RE, Malcolm DE, Adams W. The problem of detecting changes in the incidence of schizophrenia. Br J Psychiatry 1993;**162**:212–218.
22. Chang JT. Recent common ancestors of all present-day individuals. Adv Appl Probab 1999;**31**:1002–1026.
23. Diamond JM, Rotter JI. Observing the founder effect in human evolution. Nature 1987;**329**:105–106.
24. Ødegaard Ø. A statistical investigation of the incidence of mental disorders in Norway. Psychiatr Q 1946;**20**:381–399.
25. Jablensky A. Epidemiology of schizophrenia. In: Gelder MG, Lòpez-Ibor JJ, Andreasen N, eds. The new Oxford textbook of psychiatry. Oxford: Oxford University Press, 2000:585–599.
26. Retterstøl N. Selvmord (Suicide). Oslo: Universitetetsforlaget, 1990.
27. Statistics Norway. Table 8, published 21 June 2006. Suicide and suicide rates per 100.000 according to gender and age. 1951–2004. Avilable at: http://www.ssb.no/emner/03/01/10/dodsarsak/tab-2006-06-01-08.html (3 October 2007).
28. Go RC, Perry RT, Wiener H et al. Neuroreguline-1 polymorphism in late onset Alzheimer's disease families with psychoses. Am J Med Genet B Neuropsychiatr Genet 2005;**139**:28–32.
29. Kasanin JS, ed. Language and thought in schizophrenia: collected papers presented at the meeting of the American Psychiatric Association, May 12, 1939 Chicago, Illinois. New York: WW Norton & Company, 1964.
30. Reichberg A, Davidson M. Cognitive functioning before or at the onset of the first episode. in: Sharma T, Harvey PD, eds. The early course of schizophrenia. Oxford: Oxford University Press, 2006:41–55.
31. Torrent C, Martinez-Aran A, Daban C et al. Cognitive impairment in bipolar II disorder. Br J Psychiatry 2006;**189**:254–259.
32. Tuulio-Henrikson A, Partonen T, Suvisaari J et al. Age at onset and cognitive functioning in schizophrenia. Br J Psychiatry 2004;**184**:215–219.
33. Krupinski M, Fischer A, Grohmann R et al. Risk factors for suicides of inpatients with depressive psychoses. Eur Arch Psychiatr Clin Neurosci 1998;**248**:141–147.
34. Schneider B, Philipp M, Muller MJ. Psychopathological predictors of suicide in patients with major depression during a 5 year follow up. Eur Psychiatry 2001;**16**:283–288.
35. Rhode DLT, Olson S, Chang JT. Modelling the recent common ancestry of all living humans. Nature 2004;**431**:562–566.
36. Hein J. Pedigrees of all humanity. Nature 2004;**431**:518–519.
37. Marneros A. Beyond the Kraepelinian dichotomy: acute and transient psychotic disorders and the necessity for clinical differentiation. Br J Psychiatry 2006;**189**:1–2.
38. Saugstad LF. Kraeplin's dichotomy is true: contrasting brain dysfunction at the extremes of human growth and maturation. Excitability, the fundamental property of nervous tissue, is affected. World J Biol Psychiatry 2007; 1–18.
39. Posner MI, Rueda MR. Mental chronometry in the study of individual and group differences. J Clin Exp Neuropsychol 2002;**24**:968–976.
40. Benes FM, Matazilevich D, Burke RE et al. The expression of proapoptosis genes is increased in bipolar disorder, but not in schizophrenia. Mol Psychiatry 2006;**3**:241–251.
41. Benes FM, LIM B, Matzilevich D, Walsh JP. Regulation of the GABA cell phenotype in hippocampus of schizophrenics and bipolars. Proc Natl Acad Sci U S A 2007;**12**:104.

42. Pearson H. Genetics: What is a gene? Nature 2006;**441**:398–401.
43. Vogel F, Motulsky AG. Human genetics. Berlin/Heidelberg: Springer, 1997:550–551.
44. Nygaard L. Preliminary historical notes, Oslo, 1994.

Appendix

The three founders (F1, F2, F3), their immediate descendants and the diagnostic hypotheses

F1

Historical information. F1 is the oldest of the three founders. He was of Pomeranian descent. He was born some time between 1592 and 1622, when his German-born father was a protestant vicar in a neighbouring community (44). F1 was married and had only one son born in 1656 (11). Later, his son became the sheriff of the local community. F1 became insane and deposed in 1661 (11). His great grandson also became insane. F1 was insane (10), but lived in the local community with his wife and their then 9-year-old son in 1665 (Figs 1–5). He died there in 1676 (11).

Clinical considerations. F1 must have become psychotic at a mature age, which makes schizophrenia to appear as an unlikely diagnosis. Contributory factors to this exclusion diagnosis are the fact that he was educated and married and had a son before the onset of his disease. F1 must have had some standing in the local community. His son became the local sheriff and probably inherited his standing in the community.

The diagnostic hypothesis: Other non-organic psychosis.

F2

Historical information. F2 was a local farmer. He was born in 1692 (11). He was married and had 10 children, of whom only one grew up to have a family of his own. The other nine died, some as small children and others as young unmarried adults. One of his unmarried daughters died in a catatonic spell at 30 years of age. His brother killed his fiancée. He was sentenced to death, but evaded justice by fleeing to Sweden (11). A great grandson of F2 was arrested for vagrancy and a few named descendants of F2 were according to both local genealogies (11), and national population censuses of the 19th century (13–15), either categorized as insane, incapacitated or illiterate. F2 himself was brought to court at 32 years of age for deviant behaviour (11).

Clinical considerations. F2 was brought to court at an early age and must have been a poor caretaker. We have no direct information of psychosis in his case. One of his daughters probably died of catatonia and other descendants of the 19th century were characterized as insane. The behaviour of F2, his brother and descendants of F2 reflect cognitive failures, behavioural disturbances and psychosocial incompetence, which is the very *historical* definition of the diagnosis of dementia (19), which preceded the term of dementia praecox. Similar behaviour was not displayed in any of their ancestors in the 1665 population (11–15).

The diagnostic hypothesis: Schizophrenia spectrum disorder.

F3

Historical information. F3 was son of a clergyman. He was born in 1723 and died in a fire with his 90-years-old mother in 1767 (11). His mother was a well-to-do woman of English descent. Her great grandfather migrated to Trondheim, Norway, from Yorkshire in the 16th century (45). F2 married a local girl the very year before his violent death. He had one daughter born in 1766. His mothers' aunt committed suicide in a spell of madness in 1680s (45). F2 himself was characterized as 'less worthy' (11).

Clinical considerations. F3 came from a wealthy family. All his siblings did well in life. Characterized as 'less worthy', he stayed with his mother and married late. A family history of suicide and insanity raises the question of an extended suicide in the case of the violent death of F3 and his mother; although an accident cannot be ruled out.

The diagnostic hypothesis: Depressive episode and suicide.