Schizophrenia in the Genetic Isolate of Finland

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We compared the features of schizophrenia in the homogeneous population of Finland (population about 5,000,000) and in an internal isolate in northeastern Finland inhabited in the 1680s by a small group of founders (current population about 18,000) in a register-based epidemiological study. We identified all cases with a diagnosis of schizophrenia in Finland born between 1940–1969 using three national computerized registers and found a total of 267 schizophrenia patients in the internal isolate and 29,124 in Finland. The lifetime prevalence was 2.21% in the internal isolate and 1.21% in Finland, respectively. The age-corrected lifetime risk was 3.2% in the internal isolate and 1.1% in the whole country. The risk of schizophrenia to siblings in the internal isolate was 6.4% (95% confidence interval 0.052, 0.078), 9.1% (95% CI 0.062, 0.130), and 6.8% (95% CI 0.028, 0.135) given 1, 2, or 3 affected siblings, and for all Finland 4.2% (95% CI 0.036, 0.043), 6.4% (95% CI 0.058, 0.071), and 8.7% (95% CI 0.068, 0.107) given 1, 2, or 3, affected siblings, respectively. The mean number of children in schizophrenia families and thus the number of families having at least two affected individuals were clearly higher in the isolate (24.9% vs 9.2%). We did not find any other epidemiological features differing between these two regions. It seems that the family material collected from the internal isolate is a representative subsample from the entire country and hopefully it enables easier identification of at least some predisposing genes for schizophrenia due to its unique population structure. Am. J. Med. Genet. 74:353–360, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: genetic epidemiology; lifetime prevalence; age-corrected lifetime risk; risk for siblings

INTRODUCTION

The process of identifying genes underlying mental disorders faces many difficulties due to complex patterns of inheritance and the strong confounding influence of environmental factors. One way to facilitate the search is to focus the analysis on genetic isolates. In such a setting there may be fewer genes predisposing to a given complex disease than in more mixed populations. Focusing on a highly restricted population may also offer advantages for eventual positional cloning because one may be able to exploit linkage disequilibrium for fine-structure genetic mapping. [Lander and Schork, 1994]. One source of evidence for the accumulation of certain genes is the Finnish Disease Heritage [Norio et al., 1973], which consists of some 30 mostly autosomal-recessive disorders. It provides evidence of a genetic founder effect and subsequent isolation which has resulted in the enrichment of some disease mutations and in a total lack of others in this relatively small population of 5,000,000 inhabitants [Norio, 1981].

The first archaeological evidence of human inhabitants in Finland dates from the last postglacial period, some 11,000 years ago [Edgren, 1992], but the major expansion of the population began only later after a population bottleneck, approximately 3,900 years ago [Sajantila et al., 1996]. Since then, Finland has been isolated for geographic, linguistic, and cultural reasons, and the original relatively small ancestor population slowly invaded the southern and western coastline of the country. The northern and eastern parts of Finland were inhabited later, in the 16th and 17th centuries, and this has resulted in internal isolates inside

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this isolate. We have chosen one internal isolate, a municipality in the northeastern part of Finland, to investigate the genetic epidemiology of schizophrenia.

The municipality was originally populated by the Lapps when the first Finns, some 40 families, moved there in the 1670s from the south. The Finnish population expanded locally; in 1750, when the official registers were established, 1,208 inhabitants were already recorded [Ervasti and Vasari, 1978]. The population increased further and is 18,281 at the present time. There have been several periods when mortality was high due to years with crop failures. However, the population of this municipality has been extremely stable throughout the centuries. People have usually found spouses from the same village and even marriages between people living in northern and southern parts of the same municipality have been rare. Only after World War II has emigration from the municipality increased towards the southern parts of Finland, whereas immigration into the municipality has remained limited.

We performed a nationwide epidemiological survey in Finland to search for differences in the geographical distribution of schizophrenia. We specifically wanted to compare the epidemiological features of schizophrenia in the well-characterized internal isolate with those in the whole population.

**MATERIALS AND METHODS**

Three registers were used to identify all probands with a diagnosis of schizophrenia. The National Hospital Discharge Register was established in 1968. All admission and discharge dates and primary diagnoses for inpatient stays at public and private facilities are indexed in this register. In addition, we used two registers of the Social Insurance Institution of Finland, i.e., the Pension Register and the Free Medicine Register. The Pension Register indexes beginning and ending dates and primary diagnosis justifying disability pensions. The Free Medicine Register indexes primary diagnoses for state-subsidized medications.

All three registers have been computerized since 1968. Before 1987 the International Classification of Diseases, Version 8 (ICD-8) descriptions were used as a basis for diagnosis. Thereafter, psychiatric diagnoses have been coded according to the Finnish version of ICD-9 [Kuoppasalmi et al., 1989], using the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Version III Revised (DSM-III-R).

In the registers of the Social Insurance Institute only the first three digits of the diagnostic codes are recorded. Therefore, we identified probands having a "295" diagnosis according to the ICD-8 numbering scheme. This means that schizophreniform disorder, schizoaffective disorder, and ICD-8 simple and latent schizophrenia diagnoses are included in our definition of schizophrenia.

Probands born between 1940–1969 were included in this study, since it was possible to reliably identify first-degree relatives of these patients. Also, inclusion of probands born earlier than 1940 would have introduced a bias because of changes in diagnostic systems and treatment over time.

In a sample of 73 probands born in the internal isolate, the validity of the register diagnosis of schizophrenia was studied. Sixty-two of them had a register diagnosis (DSM-III-R) of schizophrenia (295.10, 295.20, 295.30, 295.60, and 295.90), and 11 had a schizophrenia spectrum diagnosis (295.40, 295.70, 301.20, and 301.22). Original case-notes from psychiatric hospitals and also from outpatient clinics in problematic cases were collected. Based on the clinical information, a DSM-III-R checklist [Tienari et al. 1993] was filled out by a junior researcher (T. Mäkipyrö) trained for diagnostic assessment. In this checklist, the DSM-III-R criteria of schizophrenia and schizophrenia spectrum diagnoses were condensed, as were the main criteria for exclusion. The Operational Criteria Checklist for Psychotic Illness was also completed, and the associated OPCRIT program [McGuffin et al., 1991] used to yield diagnosis according to DSM-III-R criteria. Finally, two senior researchers (M. Isohanni and J. Moring) made a consensus best-estimate diagnosis based on all available information.

Fifty-four of the 62 cases having a register diagnosis of schizophrenia fulfilled DSM-III-R criteria for schizophrenia. Four were rediagnosed as suffering from schizoaffective disorder, 1 from delusional disorder, 1 from schizoid personality disorder, and 2 from psychotic depression. Two of the 11 cases with schizophrenia spectrum diagnoses fulfilled DSM-III-R criteria for schizophrenia, while 3 were diagnosed as having schizoaffective disorder, 1 as having schizophreniform disorder, 1 as having schizoid personality disorder, 1 as having schizotypal personality disorder, 1 as having psychotic depression, 1 as having bipolar I disorder, and 1 as having brief psychotic disorder.

Lifetime prevalence was determined as the number of probands who had ever had a diagnosis of schizophrenia living in a particular area divided by the total population living in the same area. Because of the constraints on years of birth and diagnosis imposed by our ascertainment, and the difference in age structure of the population between the internal isolate and the rest of Finland, an age-adjusted lifetime "risk" was computed as follows: for each year of birth there was a range of possible ages of onset (defined here as time of first schizophrenia-related hospitalization). We counted the number of individuals \( K(x, y) \) born in each year \( X \) (between 1940–1969) who were diagnosed at age \( Y \) (where \( X + Y \) was between 1974–1991, i.e., the range of our diagnostic time frame), and the number of individuals \( N(x, y) \) born in each year \( X \) who could have had onset at age \( Y \) (i.e., if \( X + Y \) is not between 1974–1991, then \( N(x, y) = 0 \); otherwise it is just the number of individuals born in year \( X \)). From this, we computed the probability of a first hospitalization at each age \( Y \) as:

\[
\phi_Y = \frac{\sum_{X = \min(1940, 1974)}^{1991 - Y} K(x, y)}{\sum_{X = \min(1940, 1974)}^{1991 - Y} N(x, y)}
\]

Then, the age-corrected “lifetime risk” was computed
as $\phi = \sum \phi_Y$. We tested for any differences in age of onset as a function of year of birth by maximum likelihood methods, and found absolutely no evidence for any differences, and thus treating each year of birth as if their age of onset density function is the same seems justified. It is acknowledged that there may be some slight understimation of the overall "lifetime risk," as some individuals might become affected at ages outside the range of admissible values given our time frame (i.e., at ages over 51), but this number is likely to be very small, and will add only a small amount to these estimated lifetime risks. The resulting estimated age-of-onset functions, $\phi_Y$, are shown graphically in Figure 3, separately for the internal isolate and for the remainder of Finland. This "age-corrected lifetime risk," $\phi$, was calculated based on the data from Hospital Discharge Register for people born between 1940–1969 who had had their first hospital admission between 1974–1991. Only years after 1974 were looked at, since the National Hospital Discharge Register was founded in 1968, and after that there was a 6-year period when the number of first hospitalizations was not stably recorded. The mean age at first hospitalization for schizophrenia was 23.5 years for males and 25.0 years for females (SD, 6.4) and 28.6 years for females (SD, 6.5), and in all Finland 27.7 years for males (SD, 6.5) and 28.4 years for females (SD, 7.0). This was considered as the age of onset (Fig. 3). If the first hospitalization is calculated only for the cohort born between 1950–1959 in order to avoid the birth cohort bias of the Hospital Discharge Register, the respective mean age at first hospitalization was 23.5 years for males and 25.0 years for females in the internal isolate, and 25.2 years for males and 23.7 years for females in all Finland. The mean number of hospitalizations for schizophrenia in the internal isolate was 7.5 for males (SD, 7.4) and 7.1 for females (SD, 10.5) and in all Finland 6.1 for males (SD, 7.4) and 6.0 for females (SD, 7.1) (Table II).

RESULTS

We found a total of 267 schizophrenia patients born between 1940–1969 in the internal isolate (population 18,281) and 29,124 in Finland (population 4,998,478). The lifetime prevalence of schizophrenia in all municipalities ($n = 455$) of Finland could be determined and is shown in Figure 2. Prevalence was unevenly distributed, varying from 0.000–0.039. The internal isolate is located in a region with high prevalence in eastern Finland, as indicated in the map (Fig. 2).

The lifetime prevalence for affected males and females in the internal isolate was 2.49% and 1.93%, respectively, and in all Finland 1.28% and 1.14%, respectively. There was a sex difference in prevalence in both samples, but the difference was statistically significant only in the sample from the entire country ($\chi^2 = 81.88$, df = 1, $P < 0.0000001$), and not in the internal isolate ($\chi^2 = 2.58$, df = 1, $P = 0.11$). The total prevalence was 2.21% in the internal isolate and 1.21% in Finland, thus being 1.8 times higher in the isolate ($\chi^2 = 63.67$, df = 1, $P < 0.0000001$). The age-corrected lifetime risk for affected males and females in the internal isolate was 3.9% and 2.4%, respectively, and in Finland 1.3% and 1.0%, respectively. The total age-corrected lifetime risk for schizophrenia was 3.2% in the internal isolate and 1.1% in the rest of Finland ($\chi^2 = 285.64$, df = 33, $P < 0.00000001$). Here again we also found significant evidence for sex difference only in the sample from the entire country ($\chi^2 = 285.74$, df = 33, $P < 0.00000001$).

The mean age at first hospitalization for schizophrenia in the internal isolate was 27.9 years for males (SD, 6.4) and 28.6 years for females (SD, 6.5), and in all Finland 27.7 years for males (SD, 6.5) and 28.4 years for females (SD, 7.0). This was considered as the age of onset (Fig. 3). If the first hospitalization is calculated only for the cohort born between 1950–1959 in order to avoid the birth cohort bias of the Hospital Discharge Register, the respective mean age at first hospitalization was 23.5 years for males and 25.0 years for females in the internal isolate, and 25.2 years for males and 23.7 years for females in all Finland. The mean number of hospitalizations for schizophrenia in the internal isolate was 7.5 for males (SD, 9.1) and 7.1 for females (SD, 10.5) and in all Finland 6.1 for males (SD, 7.4) and 5.8 for females (SD, 7.1) (Table II).

The mean number of children in nuclear families with schizophrenia cases was 5.13 (SD, 2.75) in the internal isolate and 3.39 (SD, 1.95) in all Finland. In the internal isolate there was a total of 365 families with 1 or more affected family members, 91 families (24.9%) with 2 or more affected family members, 25 families (6.8%) with 3 or more affected family mem-
with a well-established population history to see whether the prevalence rates are higher in the isolate within Finland, and to test if the isolated population can be efficiently used in the search for predisposing genes for schizophrenia.

We used three nationwide registers, the National Hospital Discharge Register, the Pension Register, and the Free Medicine Register, in order to find all treated cases of schizophrenia. The Pension Register and the Free Medicine Register are reliable because disability pensions and free medications are paid according to the information they contain. The reliability of the Hospital Discharge Register has been studied and found to be excellent: about 95% of hospital discharges are reported to the register, and the diagnostic codes are transferred accurately from medical records to the register [Keskimäki and Aro, 1991; Aro et al., 1995].

We studied the validity of the register diagnoses in a sample of cases from the internal isolate. Fifty-four (87.1%) out of 62 patients having a schizophrenia diagnosis in the registers fulfilled DSM-III-R criteria for schizophrenia, and 2 (18.2%) out of 11 cases with a spectrum diagnoses received a schizophrenia diagnosis according to DSM-III-R. Thus, according to this study the validity is good.

Two other studies of the reliability of diagnosis in the National Hospital Discharge Register have been made. Pakaslahti [1987a,b] compared routine hospital diagnoses with diagnoses obtained by using the PSE-CATEGO system in all consecutive first admissions to the two mental hospitals in Helsinki during one calendar year, 1981 (n = 297). Schizophrenia accounted for 18.8% of hospital diagnoses but 35.0% of PSE-CATEGO diagnoses. Pakaslahti [1987a,b] concluded that there appears to be a tendency in clinical practice to underdiagnose schizophrenia. Isohanni et al. [1997] investigated all entries to the Hospital Discharge Register for a sample based upon the Northern Finland 1966 Birth Cohort. Their diagnostic validation process was identical to the one used in our study. Out of 563 subjects having a register diagnosis indicating a psychiatric illness, they did not find any false-positive diagnoses.

### Validity of the Registers

Our goal was to compare the genetic epidemiology of schizophrenia in Finland and in one internal isolate with a well-established population history to see whether large family sizes in the isolate. However, no significant differences could be recorded in the proportion of families having affected individuals in two samples, once there are enough affected sibs to be reasonably sure the gene(s) are segregating in the family.

The proportion of families having at least 2 affected individuals was clearly higher in the isolate (24.9%) than in all Finland (9.2%), which is mainly due to larger family sizes in the isolate. However, no significant differences could be recorded in the proportion of families having affected individuals in two generations. In the isolate 8.2%, and in all Finland 7.3%, of the schizophrenia families had schizophrenic patients in two generations. In the internal isolate, 4.4% of individuals in the parental generation and 24.7% of individuals in the offsprings’ generation were affected, and in Finland, 4.2% and 32.3%, were affected, respectively.

### DISCUSSION

#### Validity of the Registers

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### TABLE I. Number of Siblings in Schizophrenic Families in the Internal Isolate and in All Finland

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schizophrenia cases: all 37 cases having a register diagnosis of schizophrenia also received a schizophrenia diagnosis according to DSM-III-R criteria. However, Isohanni et al. [1997] found 34 additional cases of schizophrenia, who most frequently had a register diagnosis of schizophreniform or other psychoses. These studies do not, of course, cover the whole of Finland or all of our study period. Nevertheless, they do not give us reason to assume that there are many false-positive schizophrenia cases in the Hospital Discharge Register.

When interpreting the results, it must be borne in mind that we used a broad definition of schizophrenia, including schizophreniform and schizoaffective psychoses, which are often considered to belong to spectrum disorders, and not to core schizophrenia. On the other hand, we probably missed some cases who never sought treatment. We only studied patients born between 1940-1969, who were 22-51 years old in 1991, which makes comparisons with other studies difficult. Some studies used different kinds of age-correction methods to take into account different population structures. Since we knew that the population in the internal isolate is younger than the whole population, we also calculated an age-corrected lifetime risk for schizophrenia. The age-corrected lifetime risk was clearly higher than the lifetime prevalence in the isolate, whereas the age-corrected lifetime risk and the lifetime prevalence were almost identical in the whole country.
Prevalence of Schizophrenia

We found high prevalence of schizophrenia in northern and eastern Finland, especially in rural areas (Fig. 2), as opposed to some previous studies [reviewed in Freeman, 1994]. The validation of possible mechanisms such as migration, social drift, or viral infections remains elusive. Interestingly, an unequal distribution of etiologically relevant genetic and environmental factors has also been proposed as an explanation of vastly differing regional prevalence figures of schizophrenia in Ireland [Youssef et al., 1991].

The prevalence of schizophrenia in the whole country was similar to that reported in earlier studies in Finland. In the Mini Finland Health Survey, the prevalence of schizophrenia was 1.3% for both men and women. Regionally, schizophrenia was found to be most frequent in rural areas and least frequent in densely populated southwestern and southern Finland [Lehtinen et al., 1990]. In a previous Finnish study a prevalence rate of 1.5% was obtained in a study population of 1,000 people in 1971. After the 16-year follow-up of this sample, the age-adjusted prevalence rate in schizophrenia was 2.3% for men and 0.4% for women [Väisänen, 1975; Lehtinen et al., 1993].

When compared to the prevalence of schizophrenia found elsewhere in the world, it seems that in Finland the prevalence is higher. In a review of over 70 prevalence studies from 1948–1987, the lowest reported rate was 0.3 per 1,000 among the Amish population in the US, and the highest was 17.0 per 1,000 in a restudy of an isolate population in northern Sweden. It was also suggested that there could be a possible north–south gradient in the distribution of the disease [Torrey, 1987]. In the Swedish study [Böök et al. 1978], the prevalence in the northern isolate was about three times higher than in the entire country, similar to our results in the present study. It therefore seems that there are small areas at least in northern Europe where the prevalence of schizophrenia is higher than the national average. These regions have been isolated for several hundred years and high prevalence might be due to enrichment of genes predisposing to schizophrenia.

New studies have also yielded lower prevalence rates than in Finland [Helgason and Magnusson, 1989; Bojholm and Strömgren, 1989; Dilling et al., 1989; Goldacre et al., 1994]. In the National Comorbidity study the lifetime prevalence of schizophrenia was 1.1% by computer algorithm but only 0.15% based on clinician diagnoses [Kendler et al., 1996]. The latter was, however, interpreted only as a plausible lower limit because in the number of cases the diagnostician was confident about the presence of nonaffective psychosis, but information was lacking to enable a more specific diagnosis. The lifetime prevalence of all nonaffective psychoses was 0.7% based on clinician diagnoses.

As in many other recent studies reviewed earlier, we found a higher prevalence for males than for females in the whole country. Age at first hospitalization did not differ significantly between males and females either in the internal isolate or in the whole country, and neither did the number of hospitalizations. Two recent Finnish incidence studies did not find significant sex differences in the incidence of DSM-III schizophrenia [Salokangas, 1993] or psychotic disorders in general [Lehtinen et al. 1996], but the sample sizes were small, with 186 schizophrenia cases in the former and 44 psychotic cases in the latter. The incidence study of schizophrenia did not find significant differences in age at onset, either [Salokangas, 1993]. It seems that the course of schizophrenia measured by age at onset and number of hospitalizations is similar in males and females in Finland. The findings concerning age at onset are contradictory to many earlier studies but are similar to the findings in Ireland [Kendler and Walsh, 1995].

Risk of Schizophrenia to Siblings

The risk of schizophrenia for a sibling of an affected individual in Finland seems to be in the same range as in other populations. Kendler and Diehl [1995] reanalyzed the 11 most recent family studies and found that the risk for schizophrenia in first-degree relatives varied from a low of 1.4% to a high of 8.9%. They concluded that there might be true population differences in the risk for schizophrenia in relatives of schizophrenic probands. On average, the first-degree relatives of schizophrenic probands had a risk for schizophrenia 5–10-fold higher than that found in the relatives of control probands.

For the whole of Finland, the risk to remaining siblings increased, the higher the number of siblings with schizophrenia. In the isolate we did not see this, which might be due to the fact that the family size is larger there, so that the probability of these families having...
young healthy siblings still at risk of getting the disease is higher. Also, the number of families having more than 3 affected children was small. Increase in risk with birth order has been associated with external factors such as respiratory viral infections. They are frequently brought into the home by young children, and individuals whose second and third trimesters of fetal life coincide with an epidemic of influenza have a greater risk of schizophrenia later in life. Having siblings 3–4 years older has been associated with a significantly increased risk of schizophrenia [Sham et al., 1993].

Applications to Molecular Genetic Analyses

We did not find any differences in severity of disease between the internal isolate and the whole country when we looked at age of first hospitalization or number of hospitalizations. The differences in lifetime prevalence and age-corrected lifetime risk seem to be due to genetic or environmental factors, and not due to the different natures of the disease, and the internal isolate may well be regarded as a representative study population when trying to identify genes predisposing to schizophrenia.

The recent history of the internal isolate shows that the majority of cases of schizophrenia in the modern population can be linked together into extended pedigrees through the registers extending back to 1680. We are currently tracing the ancestors of these families to find out the precise relationships between individual families. The structure of these extended pedigrees, however, shows that the disease trait is transmitted in complex multilinear patterns, making the sample ineffective for gene detection through traditional pedigree analyses. However, if we assume that the majority of cases have descended from a common ancestor, genes might be amenable to isolation through the analysis of linkage disequilibrium in affected individuals. Also, in case of recessive genes, the consanguinity of families probably resulted in enrichment of certain predisposing genes. Nikali et al. [1995] earlier demonstrated the feasibility of this technique in the case of a recessively inherited subtype of hereditary ataxia belonging to the Finnish disease heritage. The focus was assigned by random screening using the DNA of only 4 affected individuals.

On the other hand, the entire country represents a relatively homogeneous population, with still much greater homogeneity in the genes predisposing to schizophrenia than to be expected from present-day mixed populations elsewhere. However, since the predisposing genes for schizophrenia must be quite common, even in this isolated population more than a single ancestral genetic defect should be expected. The presence of an extensive network of diagnostic and population registers has led to the detection of a large number of multiplex nuclear pedigrees with a mixture of affected and healthy individuals from the entire country, and hopefully the relative isolation of the Finnish population will allow for a more simple detection of at least some major genes contributing to the etiology of schizophrenia in Finland.

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REFERENCES


