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Schizophrenia and birthplace of paternal and maternal grandfather in the Jerusalem perinatal cohort prospective study

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ABSTRACT

Some forms of epigenetic abnormalities transmitted to offspring are manifested in differences in disease incidence that depend on parent-of-origin. To explore whether such phenomena might operate in schizophrenia spectrum disorders, we estimated the relative incidence of these conditions in relation to parent-of-origin by considering the two grandfathers' countries of birth. In a prospective cohort of 88,829 offspring, born in Jerusalem in 1964–76 we identified 637 cases through Israel's psychiatric registry. Relative risks (RR) were estimated for paternal and maternal grandfathers' countries of birth using proportional hazards methods, controlling for parents' ages, low social class and duration of marriage. After adjusting for multiple observations, we found no significant differences between descendants of maternal or paternal grandfathers born in Iraq, Iran, Turkey, Syria, Yemen, Morocco, Algeria, Tunisia, Libya/Egypt, Poland, USSR, Czechoslovakia, Germany or the USA. Those with paternal grandfathers from Romania (RR = 1.9, 95% CI = 1.3–2.8) or Hungary (1.6, 1.0–2.6) showed an increased incidence; however, those with maternal grandfathers from these countries experienced reduced incidence (RR = 0.5, 0.3–0.8 and 0.4, 0.2–0.8). In post-hoc analyses we found that results were similar whether the comparison groups were restricted to descendants of other Europeans or included those from Western Asia and North Africa; and effects of paternal grandfathers from Romania/Hungary were more pronounced in females, while effects of maternal grandfathers from these countries were similar in males and females. These post-hoc "hypothesis-generating" findings lead one to question whether some families with ancestors in Romania or Hungary might carry a variant or mutation at a parentally imprinted locus that is altering susceptibility to schizophrenia. Such a locus, if it exists, might involve the X chromosome.

1. Introduction

There is increasing interest in the hypothesis that epigenetic alterations might contribute to the causes of schizophrenia (Petronis et al., 1999; Crow, 2007; Huang et al., 2007, Crespi, 2008; Isles and Wilkinson, 2008). Epigenetics refers to the changes in gene expression brought about by methylation of DNA and/or by modifications of

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chromatin structure (Keverne and Curley, 2008). Several peculiarities of epigenetics may be relevant to psychosis and other psychiatric conditions. First, certain genes are expressed from only one allele, activation or suppression depending on the parent-of-origin; some such genes are important in growth, development and neuroendocrine function (Wilkinson et al., 2007). Examples include the cluster of parentally imprinted loci on chromosome 15q11–q13 associated with Prader–Willi and Angelman syndromes (Horsthemke and Wagstaff, 2008) and with autism (Dimitropoulos and Schultz, 2007); and those on chromosome 7q21 associated with OCD, alcohol abuse and other psychiatric conditions (Hess et al., 2007). Second, many genes on the X chromosome are epigenetically inactivated in females (Payer and Lee, 2008); diverse loci on the X chromosome are important in brain development (Nguyen and Disteche, 2006) and some may reflect parent-of-origin effects (Davies et al., 2008). Third, genetically vulnerable individuals may be shaped by the social or physical environment at a critical period of fetal life or childhood; such influence may alter the individual's "program" of further development (Szyf et al., 2008). Examples of phenotypes associated with such gene-environment interactions include violent and antisocial personality in males (due to inactivating mutation in X-linked MAO-A combined with abuse in childhood) and affective disorders (due to variants in the 5HTT promoter combined with other stresses in life) (Craig, 2007).

That parentally imprinted loci might be involved in schizophrenia is suggested by the parent-of-origin effects observed in some studies (Crow et al., 1989; Husted et al., 1998; Ohara et al., 1997; Petronis, 2000; Corradi et al., 2005; Francks et al., 2007). To search for evidence of this, we used conventional epidemiologic methods to estimate the risk of schizophrenia in Jews in relation to parent-of-origin, picking parents according to their ancestral geographic origin. To our knowledge, there have been no previous studies taking this approach. Elsewhere, we have reported that for offspring born in this cohort, neither immigration of the parents nor their broad geographic origin affected the incidence of schizophrenia (Corcoran et al., in press).

2. Methods

In 1964–76, the Jerusalem Perinatal Study surveyed all 92,408 births to mothers resident in Western (Israeli) Jerusalem. Items abstracted from the birth certificate included demographic information on the parents and both grandfathers; these were supplemented with data abstracted from medical records, interviews and surveillance of pediatric inpatients. The methods, characteristics of the population, tracing and verification have been described in detail (Davies et al., 1969; Harlap et al., 1977, 2007; Malaspina et al., 2001). The cohort was linked to Israel's national Psychiatric Registry of persons hospitalized for psychiatric conditions. This registry, established in 1950, receives information from multiple sources, including inpatient wards in psychiatric and general hospitals, and psychiatric day-care facilities. Diagnoses of psychoses have been validated (Weiser et al., 2005). Because the data base was prepared by government employees as a pilot/preliminary study, schizophrenia was defined broadly, taking schizophrenia-related diagnostic codes F20-F29 (ICD-10) at discharge, hereafter termed "schizophrenia". The date of onset was taken as the date of the first admission episode in the registry. Names, identity numbers and other identifying information were removed and the anonymous file was analyzed collaboratively in New York and Israel. The study was approved by the Institutional Review Boards Hadassah Medical Center, Jerusalem, New York University Medical Center and Columbia University Medical Center, New York, and exempted from the requirement for informed consent.

2.1. Countries of origin

Offspring were classified according to the countries of birth of grandfathers, as recorded on the birth notification. No information was available on grandmothers or on associations within families. The coding system used in the Jerusalem Perinatal Study was the one used by the Israel government in the mid-1960s; this did not provide individual codes for the separate components of the former Soviet Union. Similarly, our study cannot separate Kurdish Jews, who at that time made up a substantial but unknown proportion of Jerusalem's immigrants from Iraq, from other Jews from Iraq, Iran, Syria or Turkey.

2.2. Data analysis

We used SAS® version 9.1 to analyze the data, studying time to diagnosis with Kaplan–Meyer and proportional hazards methods. Offspring were followed from birth until date of diagnosis, death or censoring (December 31, 1997); the survivors were then aged 21–33. Results are given as relative risks (RR, i.e. hazard ratios) and 95% confidence intervals, relative to a stated comparison group. Unless otherwise mentioned, the *p*-values refer to raw, two-tailed tests. To limit the probability of false discovery, we arbitrarily restricted the countries for analysis to those for which there were at least 1000 offspring with either a maternal or a paternal grandfather born there. In addition, we present adjusted *p*-values, calculated both by Hochberg's (Hochberg, 1988) modification of the Bonferroni method and by the method of Benjamini and Hochberg (Benjamini, 1995). Proportional hazards assumptions were verified by inspecting log-negative log plots and by testing each variable (coded 0, 1) as a time-dependent variable constructed from its product with the length of follow-up. Variables included in the models were those we found to be significantly related both to broad ethnic groups (unadjusted $p<.05$) and to schizophrenia and/or variables that altered the crude estimates of relative risks for ethnic groups by at least 10%. Included were paternal age (treated as a continuous variable, in deviations from the mean (age 31) with unknowns (0.8%) being assigned to the mean); duration of marriage (1.7% unknowns were assigned to the mean (5 years)); and a series of dichotomies coded 1 (if present) or 0 (if absent) for maternal age (30–34, 35+ versus younger); sex (male); and lower paternal social class at birth based on our previously described classification of occupations (Harlap et al., 1977). Other variables tested, but not included in the final models, were categories of religion, parents' status as immigrants or Israeli-born; the immigrants' broad areas of origin (Western Asia, North Africa or Europe/America), rural versus urban