ORIGINAL ARTICLE

Severe Mental Disorders in Offspring With 2 Psychiatrically Ill Parents

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Background: Studies of couples of psychiatric patients with children allow us to calculate the effects of double predispositions on morbid risk in the offspring, which is of interest for molecular genetic research and for genetic counseling.

Objective: To determine the risks in offspring of receiving a diagnosis of schizophrenia, bipolar disorder, unipolar depressive disorder, or any diagnosis from parents who both have received a diagnosis of schizophrenia or bipolar disorder.

Design: National register-based cohort study.

Setting: Denmark.

Participants: A population-based cohort of 2.7 million persons born in Denmark, alive in 1968 or born later than 1968, with a register link to their mother and father and aged 10 years or older in 2007.

Main Outcome Measure: Risk of schizophrenia or bipolar disorder, calculated as cumulative incidences by age 52 years.

Results: The risk of schizophrenia in 270 offspring of 196 parent couples who were both admitted to a psychiatric facility with a diagnosis of schizophrenia was 27.3% (increasing to 39.2% when schizophrenia-related disorders were included) compared with 7.0% in 13 878 offspring from 8006 couples with only 1 parent ever admitted for schizophrenia and 0.86% in 2 239 551 offspring of 1 080 030 couples with neither parent ever admitted. The risk of bipolar disorder was 24.9% in 146 offspring of 83 parent couples who were ever admitted with bipolar disorder (increasing to 36.0% when unipolar depressive disorder was included) compared with 4.4% in 23 152 offspring from 11 995 couples with only 1 parent ever admitted and 0.48% in 2 239 553 offspring of 1 080 030 couples with neither parent ever admitted. Risks of schizophrenia and bipolar disorder in offspring of couples with 1 parent with schizophrenia and the other with bipolar disorder were 15.6% and 11.7%, respectively. The maximal risks of any psychiatric disorders in the offspring of parents both with schizophrenia or both with bipolar disorder were 67.5% and 44.2%, respectively.

Conclusions: Derived risks may be informative for counseling. Patterns of transmission may support evolving assumptions about genetic overlap for traditional categories.

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GENETICALLY ORIENTED studies of offspring of 2 psychiatric patients followed into adulthood represent a super-high-risk strategy compared with studies of children with only 1 affected parent. The dual-mating study permits calculating the effects of double predispositions on the lifetime morbid risk (age-corrected) in the offspring of couples with the same or different mental disorders. Such risks will be of use to genetic counselors to inform personal decisions with regard to marriage, family formation, adoption, and health insurance planning. Studies of the outcome in the offspring of parents with homotypic disorders, eg, schizophrenia × schizophrenia and bipolar affective disorder × bipolar affective disorder, may elucidate modes of transmission and possible genetic heterogeneity.[1,2] Matings between those with heterotypic disorders, eg, schizophrenia × bipolar disorder, may reveal the presence and risk of possible spectrum interforms or other atypical forms of parental criterion diagnoses in the offspring[3,4] and may be of interest to researchers intrigued by the overlap in offspring phenotypes between schizophrenia and bipolar affective disorder.[5-7]

Infrequent psychiatric dual-mating studies during the last century have relied on case histories of small clinical samples. They were all central European studies with diagnostic evaluations based on the German and Swiss concepts of Kraepelin and Bleuler, which are quite similar to the descriptions from the *International Classification of Diseases, Eighth Revision (ICD-8)* and *International Classification of Diseases, Ninth Revision (ICD-9)*.[8,9] Morbid risks (ie, age-corrected) of schizophrenia in offspring of 2 schizophrenic parents varied between 28% and 58% in 8 studies (on average, 48% in pooled data). Risk of manic-depressive disorder in offspring of 2 such