

Genetic Approaches to Mental Disorders



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Preface



The American Psychopathological Association (APPA) has served as a prominent venue for deliberations on psychiatric genetics since this field's modern origins in the United States, that is, since Franz Kallmann's papers, particularly those presented at APPA meetings and published in its proceedings between 1945 and 1966. These included his work on twin and family studies of manic-depressive illness and schizophrenia, which were the major studies in this field until his death in 1965.

Historically, the landmark study on genetic transmission of major psychiatric illness is the series of papers on adopted-away schizophrenic patients and normal subjects in Denmark published by Seymour Kety, who is a past president of the APPA, and his colleagues, starting nearly 30 years ago. Kety's Hoch Award paper, delivered to the APPA in 1972, is one of the important papers in this series. The proceedings of that meeting, published in 1975 (Fieve et al. 1975), include some of the most widely read and cited papers in psychiatric genetics, including papers on genetic factors in schizophrenia, manic-depressive disorder, sociopathy, and alcoholism, as well as some of the initial genetic linkage studies in manic-depressive illness.

Many researchers in psychiatric genetics have been attempting since then to advance from epidemiological findings to a biological one, namely, the demonstration that a particular gene plays a role in vulnerability to a psychiatric disorder, such as schizophrenia, manic-depressive illness, panic disorder, or substance abuse. At this time, there is optimism among investigators, fueled by advances in genotyping methods, virtually complete genetic linkage maps of the human genome, advances in mathematical analysis of linkage and association in complex disorders, and the numerous epidemiological and diagnostic studies that have served to define the prevalences of systematically diagnosed psychiatric illnesses in the population and in relatives of patients.

Nonetheless, there have been disappointments. Linkage to schizophrenia on chromosome 5 and to manic-depressive illness on chromo-

somes X and 11 were followed by failures of replication in the original pedigrees or in other sampled pedigrees. Although we cannot explain how these disappointments occurred, we investigators have all matured through them. We can confidently state that the particular disappointments of nonreplication in the same data set are unlikely to recur, since positive data on linkage will no longer be acceptable without saturating the chromosomal region with markers, so that every observed meiosis is informative, and the region is scanned for a considerable distance. We have also come to the position that there is often an unquantifiable error margin in some of our experiments, because the model of genetic transmission is unknown prior to linkage and association marker studies. We are thus forced to rely on replication rather than significance levels alone to validate any finding.

It is with a sense of tempered optimism, then, that we present this volume, the proceedings of the 82nd annual meeting of the American Psychopathological Association, to our colleagues in psychiatry and in genetics. We hope that the reader is as pleased as we are with the cogency and timeliness of the contributions of our colleagues and that our optimism is soon confirmed by experimental results.

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Reference

Fieve RR, Rosenthal D, Brill H (eds): Genetic Research in Psychiatry: Proceedings of the 63rd annual meeting of the American Psychopathological Association. Baltimore, MD, Johns Hopkins University Press, 1975

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