Am. J. Hum. Genet. 54:864-870, 1994

Evidence for Anticipation in Schizophrenia

Anne S. Bassett* and William G. Honer†

*Department of Psychiatry, University of Toronto, and Genetics Section, Schizophrenia Research Program, Queen Street Mental Health Centre, Toronto; and †Department of Psychiatry, University of British Columbia, Vancouver

Summary

Anticipation, or increasing severity of a disorder across successive generations, is a genetic phenomenon with an identified molecular mechanism: expansion of unstable trinucleotide repeat sequences. This study examined anticipation in familial schizophrenia. Three generations of siblines from the affected side of families selected for unilineal, autosomal dominant-like inheritance of schizophrenia were studied (n = 186). Across generations more subjects were hospitalized with psychotic illness ($P<.0001$), at progressively earlier ages ($P<.0001$), and with increasing severity of illness ($P<.0003$). The results indicate that anticipation is present in familial schizophrenia. These findings support both an active search for unstable trinucleotide repeat sequences in schizophrenia and reconsideration of the genetic model used for linkage studies in this disorder.

Introduction

The clinical observation of anticipation—i.e., inherited illness that becomes more severe across successive generations—has recently been found to have a molecular basis: expanding GC-rich trinucleotide repeat sequence mutations (Harper et al. 1992; Sutherland and Richards 1992). In fragile X syndrome (Verkerk et al. 1991), myotonic dystrophy (Fu et al. 1992), spinobulbar muscular atrophy (Brook et al. 1992), spinocerebellar atrophy type 1 (Orr et al. 1993), and Huntington disease (Huntington's Disease Collaborative Research Group 1993), increasing severity of illness, earlier age at onset, and/or increasing proportion of ill individuals in successive generations are associated with longer trinucleotide expansions. Schizophrenia is another neuropsychiatric disorder that may display this anticipation phenomenon and that therefore may have familial forms caused by an unstable trinucleotide repeat.

Schizophrenia is a severe disorder characterized by social withdrawal and psychotic symptoms, such as delusions and hallucinations. The illness has a variable age at onset, often beginning in early adulthood and resulting in lifelong disabilities in social and occupational functioning. Evidence from family, twin, and adoption studies, including those using reliable diagnostic criteria (Lowing et al. 1983; Kendler et al. 1985), strongly supports a genetic etiology for schizophrenia (Gottesman and Shields 1982). However, the mode of inheritance for schizophrenia is not readily identifiable and is proposed to involve interacting genes (Risch 1990). In families with the illness, reduced penetrance and variable expression are commonly found. Other psychotic disorders, of lesser severity, and schizotypal personality traits such as social isolation, odd communication, and extreme suspiciousness are conditions likely reflecting variable expression of genetic susceptibility to schizophrenia (Gottesman and Shields 1982; Lowing et al. 1983; Kendler et al. 1985). These factors, along with the possibility of genetic heterogeneity and the practical difficulties of studying an illness with a significant suicide rate and suspicious, socially isolated individuals, combine to make schizophrenia a challenging disorder for linkage studies (Bassett 1991). Strategies to overcome these difficulties include focusing on familial schizophrenia where inheritance is consistent with Mendelian patterns, using reliable diagnostic methods, highly polymorphic DNA markers, and lod-score methods that model the complexities of the inheritance. Linkage studies to date, using informative fami-

Received September 13, 1993; accepted for publication December 22, 1993.

Address for correspondence and reprints: Dr. Anne S. Bassett, Schizophrenia Research Program, Queen Street Mental Health Centre, 1001 Queen Street West, Toronto, Ontario M6J 1H4, Canada.

0002-9297/94/5405-0016$02.00

lies and models based on Mendelian inheritance, have yielded significant lod scores but no replicated positive results (Bassett 1991).

Dynamic modifications of classical patterns of genetic transmission, such as anticipation (Mott 1911) and genomic imprinting (differential expression of genetic material depending on parental origin of the gene and the underlying molecular mechanisms), may explain the complex genetics of schizophrenia and other major mental illnesses (McInnis et al. 1991; Flint 1992). For example, trinucleotide repeats can cause reduced penetrance and variable expression (Caskey et al. 1992; Sutherland and Richards 1992), by existing in a premutation form, by reductions in repeat size, or by somatic mutation in early embryogenesis (Lavedan et al. 1993). The unstable nature of trinucleotide repeats also provides a possible mechanism for the high mutation rates proposed for schizophrenia (Slater and Cowie 1971). If there were evidence of anticipation in schizophrenia, screening for triplet repeat mutations would become a rational option for gene localization studies, and modification of the genetic model used in linkage studies would need to be considered. The current study investigated whether anticipation was present in a familial schizophrenia sample participating in a linkage study.

Subjects and Methods

Subjects were members of eight extended nonconsanguineous families participating in a genetic linkage study of familial schizophrenia. Local psychiatrists identified prospective pedigrees segregating schizophrenia. Families were selected for large size, availability of two or more generations of adults, and apparent unilineal, autosomal dominant–like inheritance of schizophrenia and genetically related disorders. Bilineal families with evidence, from family or collateral history, of schizophrenia or other nonaffective psychotic disorders on both sides were excluded. Further details of the original ascertainment and assessment for the linkage study are described elsewhere (Bassett et al. 1993). Since families were ascertained in their entirety, proband status could be assigned to all affected subjects. Therefore no subjects were excluded from analyses.

Subjects only from the affected side of each family were taken into account, to determine sibling sets (siblines) in the index generation (IG) (n = 13 siblines), parental generation (PG) (n = 10 siblines), and grandparental generation (GG) (n = 8 siblines). The affected side was defined by (1) a parent hospitalized with psychosis (four cases), (2) an aunt/uncle hospitalized with psychosis (four cases), (3) a parent/aunt/uncle with schizotypal traits (seven cases), or (4) a sibship linking two affected nuclear families (six cases in two extended families) (see fig. 1). In two cases in the GG, the affected side could not be determined, and the smaller of the unaffected maternal or paternal siblines was arbitrarily selected. There were three instances of unknown paternity. In two of these cases, the maternal line was affected. In the third case, neither the mother nor her five siblings were affected, and this GG sibline was not included in the analysis.

Family-history information was obtained for each subject from three or more family members by using the Family History–Research Diagnostic Criteria (FH-RDC) method (Andreasen et al. 1977). Genealogical records were used to confirm dates of birth and death. Medical records were searched back to 1866 for evidence of psychiatric hospitalization. Because the subject families originated and seldom moved from a circumscribed region of Canada, and because the one psychiatric hospital available until the 1980s consistently maintained a comprehensive file-card system of recording admissions, virtually complete ascertainment of psychiatric hospitalization was assured. Records were collected for all subjects with a history of psychiatric hospitalization. Living subjects participating in the linkage study were directly interviewed by a psychiatrist (Bassett et al. 1993). Diagnostic folders containing the family history and, if present, medical records and interview data were reviewed independently by two psychiatrists (A.S.B. and W.G.H.), one of whom (W.G.H.) was blind to the pedigree structures. A consensus lifetime Research Diagnostic Criteria (RDC) diagnosis for psychotic disorders, age at first hospitalization for a psychotic illness, and presence of two or more RDC schizotypal traits were recorded. Psychotic disorders included schizophrenia (n = 25), schizoaffective disorder (n = 13; 12 mainly schizophrenic type and 1 other), unspecified functional psychosis (n = 4), mania with psychosis (n = 1), and depression with psychosis (n = 1). Schizophrenia and schizoaffective disorder were approximately equivalent in severity in the current sample (Bassett et al. 1993) and were considered together in the current study. Individuals with psychotic disorders not severe enough to require hospitalization, as well as subjects with schizotypal traits, were combined in a single schizotypal group, because of small numbers in each category.

Of the 209 subjects in the affected siblines, 23 were excluded from the analyses. One IG subject had not attained the age of 15 years, considered a minimum age

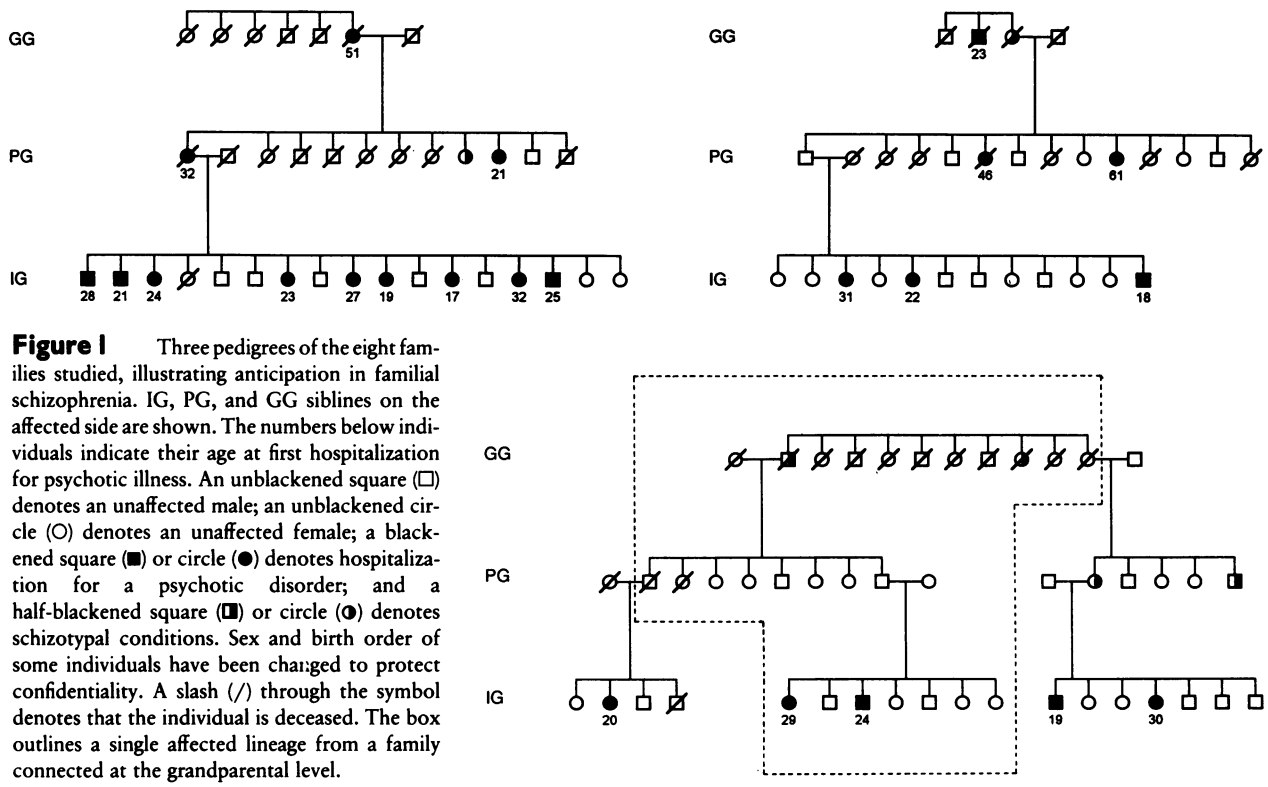

Figure 1 Three pedigrees of the eight families studied, illustrating anticipation in familial schizophrenia. IG, PG, and GG siblines on the affected side are shown. The numbers below individuals indicate their age at first hospitalization for psychotic illness. An unblackened square (□) denotes an unaffected male; an unblackened circle (○) denotes an unaffected female; a blackened square (■) or circle (●) denotes hospitalization for a psychotic disorder; and a half-blackened square (◧) or circle (◑) denotes schizotypal conditions. Sex and birth order of some individuals have been changed to protect confidentiality. A slash (/) through the symbol denotes that the individual is deceased. The box outlines a single affected lineage from a family connected at the grandparental level.

of risk for psychotic illness (Gottesman and Shields 1982). Five subjects (2 PG and 3 GG) had moved, and collateral information was insufficient to determine hospitalization status; and 17 subjects (3 IG, 5 PG, and 9 GG) died before the age of 40 years. Thirteen died in infancy or childhood, two in war, one in an accident at work, and one of unknown cause; none were suicides. Most new cases of schizophrenia may be expected before age 40 years (Gottesman and Shields 1982). Data on the remaining 186 subjects were examined for anticipation, in three ways. First, the rates of hospitalization for psychotic disorders and the rates of schizotypal conditions were compared across generations by using χ^2 analyses. Second, to assess severity of illness, subjects were assigned the following ratings: hospitalized with schizophrenia or schizoaffective disorders—3; hospitalized with other psychotic disorders—2; schizotypal—1; and unaffected—0. Means for each generation were compared using the one-way analysis of variance (ANOVA), including correction for multiple tests of significance with the Student-Newman-Keuls procedure. Third, age at first hospitalization for psychosis was assessed using the life-table method of survival analysis for 1-year intervals. Homogeneity of survival curves over the generations was examined using the Wilcoxon test. The analysis was performed assuming (1) no differential mortality between affected and unaffected and (2) hospitalization rates independent of chronological time (e.g., 1920 vs. 1970). Observations ended at the subject's current age or age at death. Covariates tested were sex and transmission patterns (maternal/paternal).

Results

Demographic characteristics of the sample and results indicating anticipation are presented in table 1. As for other illnesses demonstrating anticipation, expression of illness varied between members of a sibship (fig. 1).

Rates and Distribution of Illness

There were significantly more subjects hospitalized for psychosis across successive generations ($\chi^2 = 16.84$, $P<.0001$, 2 df). Most had schizophrenia or schizoaffective disorders (IG, $n = 30$; PG, $n = 8$; and GG, $n = 0$). Of the six subjects with less severe disorders—unspecified functional psychosis ($n = 4$), psychotic mania ($n = 1$), or psychotic depression ($n = 1$)—four were in PG or GG. Subjects with the least severe illnesses (schizotypal con-

Table 1

Characteristics of the Sample, by Generation (n = 186)

	IG	PG	GG
Total no. of subjects (females)	86 (38)	62 (24)	38 (21)
Mean size of sibline (SD)	6.61 (4.27)	6.20 (3.61)	5.43 (4.20)
Mean age of living[a] (SD)	40.61 (8.74)	65.55 (12.96)	71.80 (8.26)
Mean age at death[b] (SD)	44.25 (3.20)	57.15 (14.58)	77.35 (9.34)
Mean age at first hospitalization (SD)	26.16 (8.28)	34.00 (17.28)	41.33 (15.89)
Subjects hospitalized for psychotic illness	32 (37.21%)	9 (14.52%)	3 (7.89%)
Subjects with schizotypal conditions	8 (9.30%)	8 (12.90%)	8 (21.05%)

[a] No. of living subjects: IG, 82; PG, 42; and GG, 10.

[b] No. of dead subjects with known age at death: IG, 4; PG, 20; and GG, 20. Eight other GG subjects had ages at death that were less precisely known, e.g., "in their 70s." The mean shown did not change significantly when these subjects were included using estimated ages at death.

ditions) were twice as common in the GG as in the IG (21.05% vs. 9.30%); however, across the three generations, the result was not significant (χ^2 = 3.24, P = .20, 2 df). When these subjects with schizotypal conditions were included with hospitalized subjects, there were still significantly more affected subjects in the youngest generation (χ^2 = 6.86, P = .032, 2 df).

Because of the possibility of compounded error with families being connected at the parental or grandparental level, analyses were rerun with a single affected lineage from each of the seven kindreds that had data from all three generations, with the largest siblines being selected (see fig. 1). The same results were found using this subsample of 151 subjects, for both hospitalization rates (χ^2 = 12.30, P<.002, 2 df) and hospitalization plus schizotypal rates (χ^2 = 9.46, P<.009, 2 df). Excluding subjects who died before age 40 or moved away (n = 22) could have influenced the study's findings, since most were in the two senior generations. When results with these subjects and with penetrance estimated maximally at 100% were considered, so that one-half (n = 11) would have been hospitalized with psychotic disorders, the results for hospitalization rates would still have remained significant (χ^2 = 10.02, P<.01, 2 df). Data were also reanalyzed examining the effect that increasing hospitalization rates over time would have on the results. Secular trends of hospitalization rates for specific illnesses were not available. Therefore, arbitrary increases were tested, by adding 100% more subjects (n = 3) to the hospitalized GG group and 50% more (n = 4.5) to the PG group. Under these conditions, a significant increase in the rate of psychosis requiring hospitalization would continue to be present over the generations (χ^2 = 7.75, P<.05, 2 df).

Severity of Illness

Means for four-point severity-of-illness ratings for the three generations were as follows: IG (n = 86), 1.19; PG (n = 62), 0.58; and GG (n = 38), 0.37. Severity of illness significantly increased over the generations (F = 8.39, 2 df, P = .0003). Pairwise comparisons using the Student-Newman-Keuls test revealed that the significant difference was between the IG and the PG and GG. PG and GG severity means were not significantly different from each other.

Age at First Hospitalization

The survival curve (fig. 2) shows that subjects were first hospitalized for psychosis at progressively younger ages, across generations (χ^2 = 26.76, P = .0001, 2 df). Sex of subject was not a significant covariate to generation, for age at first hospitalization (increment χ^2 = 0.40, P = .53, 1 df). All of the GG and most (68%) of the PG subjects had achieved an age of 55 years or more, by which time they would have been virtually through the age at risk for schizophrenia (Gottesman and Shields 1982).

Imprinting

There were equal rates of maternal and paternal transmission (six and seven cases, respectively) from the PG to the IG. The mean age at first hospitalization for maternal transmission (PG to IG) was 25.00 years (SD 5.94 years), and that for paternal transmission was 27.64 years (SD 10.63 years), a nonsignificant difference (t = .83, P = .41). Grandparental to parental transmission was predominantly maternal (seven of nine cases), with one unknown and only one example of paternal transmission. Sex of transmitting parent was not a sig-

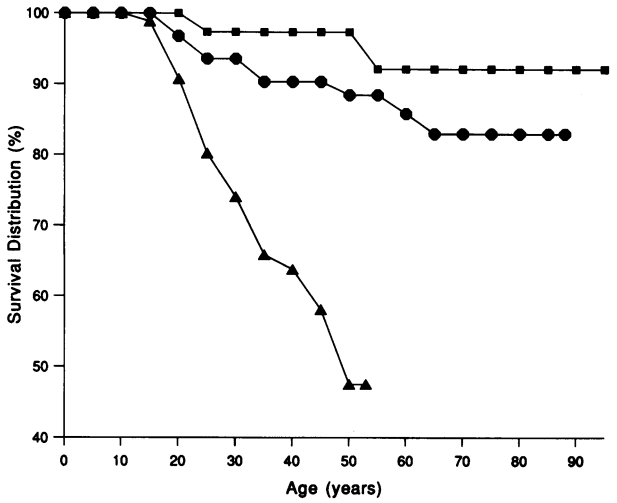

Figure 2 Survival curves for age at first hospitalization for psychotic illness, comparing IG (▲), PG (●), and GG (■). Annual percent surviving without hospitalization is plotted for every 5th year. Observation of individuals ended at their age of death or, if they were living, at their current age.

nificant covariate in the survival analysis examining age at first hospitalization (increment $\chi^2 = 0.32$, $P = .57$, 2 df).

Discussion

The results suggest that familial schizophrenia exhibits anticipation. All of the families studied showed this phenomenon, manifest as increasing rates of hospitalized psychotic illness, worsening severity of illness, and/or earlier age at onset, across successive generations (fig. 1). These findings are consistent with differences in rates of hospitalization and age-at-onset data for parent-child pairs in studies of schizophrenia over the century (Mott 1910; Kay 1963; Penrose 1971; Decina et al. 1991). In each of these studies, rates of hospitalization for psychosis were lower for antecedent generations, and age at onset for parents was significantly later than that for offspring. Investigations of ancestors and extended families also support these findings (Karlsson 1966; Odegaard 1972; Wetterberg and Farmer 1991). As well, less severe psychotic illnesses (e.g., affective disorders) are consistently more common in the generation antecedent to schizophrenic probands (Slater and Cowie 1971; Bleuler 1978). These results complement reported morbid risk of schizophrenia for parents, which is almost half that for siblings (Gottesman and Shields 1982). While alternative reasons, including selection biases such as reduced fertility in earlier-onset schizophrenia, have been proposed to explain these clinical observations, they are all consistent with the phenomenon of anticipation in schizophrenia.

In contrast, findings from the current study are only suggestive of sex-specific differences in the transmission of schizophrenia. However, the possibility of an excess maternal over paternal transmission in schizophrenia is consistent with trends found both recently by others (Sharma et al. 1993) and in studies of large data sets in the older literature (Penrose 1971; Slater and Cowie 1971). Fertility may be especially low in male patients with schizophrenia (Gottesman and Shields 1982), and in the current study this could be the reason for the high rate of maternal transmission from the GG lines to the PG lines. If this were the case, however, one would have expected predominantly maternal inheritance from the PG to the IG lines; but maternal and paternal rates were equal. Comparable transmission patterns have been found to be due to greater variation of trinucleotide repeat length after female meiosis in myotonic dystrophy (Lavedan et al. 1993). The effect may be subtle, requiring larger samples to demonstrate imprinting in schizophrenia.

There are several possible biases that can explain results that indicate anticipation (Penrose 1948). First, subjects could have died before expressing the mutation. However, all of the GG and most of the PG lived beyond age 55 years. Also, significantly different hospitalization rates across generations remained in the current study, even when half of those who had moved or died before age 40 years were assigned affected status. Second, reduced fertility of individuals with earlier onset of schizophrenia could cause preferential ascertainment of parents with later onset. This bias should be minimized in the current study, because (1) few parents were affected with psychosis and (2) siblines were large in all three generations, providing multiple opportunities for detection of affecteds, regardless of their fertility. Third, subjects in the IG could have been too young to yet express a late-onset form of psychosis, which would attenuate the age-at-onset findings. Since one-half of the subjects in the IG were over age 40 years, most were beyond the period of highest risk. Even if more new cases of psychosis subsequently arose, this would most likely occur in the IG and would only serve to strengthen the present study's findings with respect to differential rates of illness.

In contrast to major depression (Gershon et al. 1987), there is no evidence for a cohort effect in schizophrenia. However, secular trends, such as improved detec-

tion, that could, over time, lead to higher hospitalization rates and/or younger age at first hospitalization for psychosis are important to consider, since these could have influenced the principal findings of the current study. In the literature (Mott 1910; Kay 1963; Penrose 1971; Decina et al. 1991), examination of ages at first hospitalization did not reveal secular trends to younger age over the century. In the current study, arbitrary increases in hospitalization incidence assigned to the PG or GG did not change the observation of anticipation. Specific factors that may influence secular trends in hospitalization, including drug abuse and psychosocial stressors, do not appear to have played a role in the sample studied. Only three hospitalized subjects in the IG had a history of stimulant or hallucinogen use, drugs that may in some cases precipitate a psychotic illness. On the basis of direct interviews, it appeared that psychosocial stressors endured by PG and GG, such as the World Wars and Great Depression, were more severe than those faced by the IG.

Another possibility is that the family-history method tends to underestimate rates of psychiatric disturbance, particularly in relatives who are dead or less known (Andreasen et al. 1977). The consequence could be that actual rates for schizotypal traits could be higher than those found, particularly for PG and GG. However, results for severe illness requiring hospitalization would remain unchanged. Another factor that could have compounded errors in the PG and GG was the use of IG siblines connected at the parental or grandparental level. However, both the fact that results remained the same when only one ascending line from each kindred was examined and the fact that at least 13 affected siblines had resulted from eight originating GG lines support the finding of anticipation.

A limitation that is important to consider in studies of common illnesses is the potential for assortative mating to cause an apparently increased prevalence of illness in offspring. This possibility was minimized by selecting unilineal pedigrees with no evidence of schizophrenia or related disorders in the married-in person, their siblings, or parents. Although individuals marrying in could have been nonexpressing carriers of the disorder with nonexpressing close relatives, the likelihood appears small that assortative mating could account for the results in the current study. Because the families studied were selected because of their autosomal dominant-like inheritance and large sibships, the results may not be generalizable to schizophrenia in the general population, although they are consistent with observations from large population-based samples (Penrose 1971; Bleuler 1978). Also, the schizophrenia in the subject families may be a particularly severe form, which could exaggerate the findings. However, the mean age at onset for the IG is similar to others' results (Mott 1911; Gottesman and Shields 1982; Decina et al. 1991; Sharma et al. 1993). Data on specific symptom patterns suggest that the familial schizophrenia in the present families is comparable in nature and in severity to samples drawn from the general population (Bassett et al. 1993).

Despite the possible biases and limitations, the weight of evidence from both the current investigation and the literature is consistent with the finding of anticipation in familial schizophrenia. Other families with schizophrenia should be examined for anticipation and possible accompanying maternal imprinting phenomena, to confirm the current study's findings. Although published pedigrees consistently show evidence of anticipation (Karlsson 1966; Wetterberg and Farmer 1991), complete ascertainment of other large kindreds with contemporary reliable diagnostic assessments would be useful. However, the most exciting possibilities—and the confirmation of the clinical observations of the current study—lie in the search for expanding trinucleotide repeats and other DNA sequence mutations in schizophrenia. New methods becoming available to detect these mutations (Orr et al. 1993; Schalling et al. 1993) will complement and may accelerate the search for pathological genes in linkage studies. In addition, the current study has implications for the genetic model used in linkage studies. Parameters, particularly penetrance, which would vary according to generation, may need to be modified to reflect the effects of anticipation and possibly imprinting. In the light of clinical evidence for anticipation, these strategies represent real promise for deciphering the genetics of schizophrenia.

Acknowledgments

The authors are grateful to the families for their cooperation; to J. McAlduff, R.N., and A. Bury, B.A., for invaluable assistance; and to N. Risch, Ph.D., for comments on the manuscript. This work was supported in part by funding from the Scottish Rite Schizophrenia Research Program, Ian Douglas Bebensee Foundation, Ontario Mental Health Foundation, and Medical Research Council of Canada.

References

Andreasen N, Endicott J, Spitzer R, Winokur G (1977) The family history method using diagnostic criteria: reliability and validity. Arch Gen Psychiatry 34:1228–1235

Bassett AS (1991) Linkage analysis of schizophrenia: challenges and promise. Soc Biol 38:189–196

Bassett AS, Collins EJ, Nuttall S, Honer WG (1993) Positive and negative symptoms in families with schizophrenia. Schizophr Res 11:9–19

Bleuler M (1978) The schizophrenic disorders: long-term patient and family studies. Yale University Press, New Haven

Brook JD, McCurrach ME, Harley HG, Buckler AJ, Church D, Aburatani H, Hunter K, et al (1992) Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3′ end of a transcript encoding a protein kinase family member. Cell 68:799–808

Caskey CT, Pizzuti A, Fu Y, Fenwick RG Jr, Nelson DL (1992) Triplet repeat mutations in human disease. Science 256:784–788

Decina P, Mukherjee S, Lucas L, Linder J, Horwath E (1991) Patterns of illness in parent-child pairs both hospitalized for either schizophrenia or a major mood disorder. Psychiatry Res 39:81–87

Flint J (1992) Implications of genomic imprinting for psychiatric genetics. Psychol Med 22:5–10

Fu Y-H, Pizzuti A, Fenwick RG Jr, King J, Rajnarayan S, Dunne PW, Dubel J, et al (1992) An unstable triplet repeat in a gene related to myotonic muscular dystrophy. Science 255:1256–1258

Gershon ES, Hamovit JH, Guroff JJ, Nurnberger JI (1987) Birth-cohort changes in manic and depressive disorders in relatives of bipolar and schizoaffective patients. Arch Gen Psychiatry 44:314–319

Gottesman II, Shields J (1982) Schizophrenia: the epigenetic puzzle. Cambridge University Press, Cambridge

Harper PS, Harley HG, Reardon W, Shaw DJ (1992) Anticipation in myotonic dystrophy: new light on an old problem. Am J Hum Genet 51:10–16

Huntington's Disease Collaborative Research Group (1993) A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 72:971–983

Karlsson JL (1966) The biologic basis of schizophrenia. Charles C Thomas, Springfield, IL

Kay DWK (1963) Late paraphrenia and its bearing on the aetiology of schizophrenia. Acta Psychiatr Scand 39:159–169

Kendler KS, Gruenberg AM, Tsuang MT (1985) Psychiatric illness in first-degree relatives of schizophrenic and surgical control patients. Arch Gen Psychiatry 42:770–779

Lavedan C, Hofmann-Radvanyi H, Shelbourne P, Rabes J-P, Duros C, Savoy D, Dehaupas I, et al (1993) Myotonic dystrophy: size- and sex-dependent dynamics of CTG meiotic instability, and somatic mosaicism. Am J Hum Genet 52:875–883

Lowing PA, Mirsky AF, Pereira R (1983) The inheritance of schizophrenia spectrum disorders: a reanalysis of the Danish adoption study data. Am J Psychiatry 140:1167–1171

McInnis MG, McMahon FJ, Chase GA, Simpson SG, Ross CA, DePaulo JR Jr (1991) Anticipation in bipolar affective disorder. Am J Hum Genet 53:385–390

Mott FW (1910) Hereditary aspects of nervous and mental diseases. Br Med J 2:1013–1020

——— (1911) Heredity and insanity. Lancet 3:1251–1259

Odegaard O (1972) The multifactorial theory of inheritance in predisposition to schizophrenia. In: Kaplan AR (ed) Genetic factors in schizophrenia. Charles C Thomas, Springfield, IL, pp 256–275

Orr HT, Chung M, Banfi S, Kwiatkowski TJ Jr, Servadio A, Beaudet AL, McCall AE, et al (1993) Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. Nature Genet 4:221–226

Penrose LS (1948) The problem of anticipation in pedigrees of dystrophia myotonica. Ann Eugenics 14:125–132

——— (1971) Critical survey of schizophrenia genetics. In: Howells JG (ed) Modern perspectives in world psychiatry. Oliver & Boyd, Edinburgh, pp 3–19

Risch N (1990) Linkage strategies for genetically complex traits. I. Multilocus traits. Am J Hum Genet 46:222–228

Schalling M, Hudson TJ, Buetow KH, Housman DE (1993) Direct detection of novel expanded trinucleotide repeats in the human genome. Nature Genet 4:135–139

Sharma T, Brynjolfsson J, Butler R, Read T, Murphy P, Sigmundsson T, Petursson H, et al (1993) Genomic imprinting in the Icelandic/British schizophrenia study: preliminary results. Schizophr Res 9:124–125

Slater E, Cowie V (1971) The genetics of mental disorders. Oxford University Press, London

Sutherland GR, Richards RI (1992) Anticipation legitimized: unstable DNA to the rescue. Am J Hum Genet 51:7–9

Verkerk AJMH, Pieretti M, Sutcliffe JS, Fu Y-H, Kuhl DPA, Pizzuti A, Reiner O, et al (1991) Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. Cell 65:905–914

Wetterberg L, Farmer AE (1991) Clinical polydiagnostic studies in a large Swedish pedigree with schizophrenia. Eur Arch Psychiatry Clin Neurosci 240:188–190