American Journal of Medical Genetics (Neuropsychiatric Genetics) 88:686–693 (1999)

Anticipation in Schizophrenia: A Review and Reconsideration

Melvin G. McInnis,[1]* Francis J. McMahon,[1] Timothy Crow,[2] Christopher A. Ross,[1] and Lynn E. DeLisi[3]

[1]*Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, Maryland*
[2]*University Department of Psychiatry, The Warneford Hospital, Oxford, United Kingdom*
[3]*Department of Psychiatry and Behavioral Sciences, State University of New York at Stony Brook, Stony Brook, New York*

There have been several reports on anticipation and schizophrenia, and the purpose of the present article is to review the literature and present data from an ongoing family study of schizophrenia. The published data find on average a 10-year difference in the age of onset between the parental and offspring generation in family sets that have been ascertained for a genetic linkage study. The biases inherent in such studies include the biases of ascertainment that were described by Penrose [1948]. Several investigators have searched for evidence of enlarged triplet repeats, and some find evidence consistent with expanded triplet repeats, whereas others do not. In any event the phenomenon of anticipation in schizophrenia appears to be consistently found and an explanation is needed. Data are presented from pairwise analyses using intergenerational pairs from 61 pedigrees with schizophrenia showing evidence of anticipation as well as the fertility bias. Anticipation was found in aunt:niece/nephew pairs (14.5 years) but not in uncle:niece/nephew pairs (0.5 years). The sex difference in age of onset was accentuated in uncles versus aunts (8.5 years), present in parents (4.5 years), but absent in the proband generation. Therefore, there appears to be an interaction within families between age of onset and sex that deserves further investigation. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 88:686–693, 1999. © 1999 Wiley-Liss, Inc.

KEY WORDS: anticipation; schizophrenia; genetics; psychiatry; triplet repeats

INTRODUCTION

Anticipation refers to the increasing disease severity in succeeding generations as measured by decreasing age of onset or increase in clinical severity. The term "genetic anticipation" evolved from the study of physical and mental degeneration that began with Morel [1857] in the mid-19th century, who noted that many forms of ill health appeared to become worse in succeeding generations, including psychiatric diseases. Morel considered the environmental influences that might facilitate degeneration, such as poor nutrition and other external forces beyond human control. The "Law of Anticipation" was first introduced as a concept in the context of psychiatric disease in the beginning of this century by Sir Frederick Mott [1910, 1911] who studied 420 parent-offspring pairs in the asylums of London. The diagnostic methods were limited to the general accounts of the keepers of the asylums, and nondescript terms were used in the diagnosis such as "insanity," "chronic alcoholism," and "imbecility." The social and political climate at the time led to a concern over the natural and moral decay of nations [Pick, 1989], a logical consequence of genetic anticipation that led to the acceptance of Mott's work as dogma. For instance, Galton [1909] advocated the establishment of a "genetic card" to be carried by all members of society for comparison with prospective mates to ensure that the stock would improve in quality rather than continuing the downward spiral of decay.

The scientific basis of anticipation was brought into question when Penrose [1948] forcefully argued that the observations of Fleischer [1918] and Bell [1947], consistent with anticipation in myotonic dystrophy, were likely to caused by biases of ascertainment and that anticipation in myotonic dystrophy had no biological basis. The concept did not regain a respectable position in the field of genetics until the study of Howeler

*Correspondence to: Melvin G. McInnis, Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD 21287-7463.

Received 20 October 1998; Accepted 13 April 1999

et al. [1989] demonstrated the presence of anticipation in myotonic dystrophy in a systematically ascertained patient sample. However, the final step in the revival of anticipation only arose with the establishment of the biological mechanism underlying at least some instances of anticipation. The result has been the identification of anticipation in a plethora of human diseases [McInnis, 1996]. Diseases that show anticipation include rheumatoid arthritis [McDermott et al., 1996], nodal osteoarthritis [Wright et al., 1998], Crohn's disease [Bayless et al., 1998], some forms of leukemia [Horwitz et al., 1996], Parkinson's disease [Bonifati et al., 1994], bipolar disorder [McInnis et al., 1993], and many of the neurodegenerative disorders [Wells and Warren, 1998]. It is intriguing that anticipation should be observed in so many unrelated complex disorders. This suggests that they have genetic mechanisms or biases in common. In addition to unstable triplet repeats, common genetic mechanisms may include the additive effects of multiple genes that become concentrated in sibships wherein both parents harbor susceptibility genes (assortative mating).

SCHIZOPHRENIA AND ANTICIPATION

There have been several studies that have addressed the presence of anticipation in schizophrenia. The first systematic study of anticipation and schizophrenia was done by Penrose [1991]. He collected data on all first admissions to psychiatric hospitals in Ontario, Canada between 1926 and 1943. He organized the data into 13 subgroups of diagnoses and analyzed the data within the diagnoses groups as well as comparing the age of first hospitalization between generations. The not unreasonable assumption was that age of first hospitalization is a measure of age of onset, because the first psychotic episode usually results in hospitalization. Overall, Penrose found the following mean age of first hospitalization: fathers, 53.96 years; mothers, 47.18 years; sons, 33.06 years; and daughters, 35.43 years. While his findings were consistent with genetic anticipation he had already dismissed the notion as a bias of ascertainment [Penrose, 1948].

The study of Penrose was reanalyzed by Bassett and Husted [1997], who found clear evidence of anticipation in the Penrose sample; 88% of 137 pairs showed an intergenerational age of onset difference with a median of 15 years earlier in the younger generation. Including affective disorders in the diagnoses expanded the sample to 331 pairs, and again 88% of pairs showed evidence of anticipation. It is noteworthy that 84% of the affective disorder was in the older generation, suggesting that the phenotype progressed from affective disorder to schizophrenia. This is consistent with the theory of Crow [1990] that affective disorder and schizophrenia are not two separate disorders but are at opposite ends of a continuum.

Bassett and Husted [1997] also evaluated 111 aunt/uncle niece/nephew pairs from the Penrose data to examine the magnitude of the fertility bias. They argue that this removes the bias that results from the selection of parents who are by definition reproductively fit. Nieces and nephews had an age of onset similar to that of the offspring, but the aunts/uncles had an earlier age of onset compared with the parents. This suggested an effect of ascertainment and fertility biases but not enough to account for the anticipation, because 75% of avuncular pairs showed anticipation with a median intergenerational age of onset difference of 8 years. The authors conclude that various biases influence the data set but that anticipation is nonetheless present. The anticipation was significantly greater in early onset offspring of affected fathers (22-year difference) compared with early onset offspring of affected mothers (17 years, $P < 0.01$), however the authors point out that the bias of preferential ascertainment of late onset fathers could have exerted important effects [Husted et al., 1998].

Other work is consistent with the findings of Bassett and Husted [1997]. Asherson et al. [1994] examined the age of onset in 29 families, finding a mean difference of 11.1 years between the older and the younger generation. The affected phenotype included schizophrenia, schizo-affective disorder, and unspecified functional psychosis. The number of intergenerational pairs is not specified nor is it clear if the proband was included in the analyses, an important point because inclusion of the usually severely ill proband tends to enhance the finding of anticipation. There was no evidence of genetic imprinting as offspring of affected mothers had a similar age of onset as offspring of affected fathers. Chotai et al. [1995] studied 19 parent-offspring pairs obtained from 14 two-generation families with schizophrenia. The mean age of onset for the parent generation was 37.3 years and for the offspring generation 20.8 years. The mean difference of 16.5 years supports the presence of anticipation in schizophrenia. Thibaut et al. [1995] studied 26 of 48 schizophrenic families ascertained for a genetic linkage study. The sampling scheme described by McInnis et al. [1993] was used. In the most rigorous sampling scheme of random intergenerational pairs, there was a median difference in age of onset of 11 years, and there was a significant difference in age of onset in all sampling schemes. A significantly shorter interval before onset of illness in younger generations was also apparent by survival analysis. Omitting those offspring in the analysis whose age of onset was younger than the mean age of the transmitting parents at birth of their first child did not affect the findings.

Bassett and Honer [1994] studied first admission to psychiatric hospital with the diagnosis of schizophrenia. This study examined eight extended nonconsanguineous families ascertained for a genetic linkage study. The results were that significantly more individuals were hospitalized with psychosis, the illness appeared to become more severe, and the age of first hospitalization was younger in succeeding generations consistent with genetic anticipation in all families. However, while living subjects were interviewed directly, this study relied on family history information and records for much of the data from older generations.

In a systematically gathered sample (avoiding some of the biases inherent in samples used for linkage studies), Gorwood et al. [1997] examined age of onset in 97

schizophrenic subjects belonging to 24 pedigrees with affected members in at least two generations. The ascertainment was limited to a 1-year period within a limited geographical area of Reunion Island (Indian Ocean). A method of calculating expected age at onset was used that took into consideration the age of interview of the younger subject and the distribution of the age of onset of the parents. The younger generation of patients had a mean corrected age of onset of 21.80 years that was earlier than the predicted age of onset (24.95 years). Both expected and predicted age of onset were significantly different from the age of onset of the parental generation (32.21 years). Excluding the proband and families with bilineal matings and factoring in reduced fertility did not alter the results. No cohort effect, a secular trend towards younger age of onset in succeedingly younger age cohorts, was detected. In a second study Gorwood et al. [1997] analyzed 57 schizophrenic patients who had at least one other schizophrenic in their family belonging to another generation (father/mother, uncle/aunt, son/daughter). The 31 schizophrenic subjects who belonged to the younger generation had a significantly earlier age at onset (24.58 years) compared with the 26 schizophrenic subjects who belonged to the older generation (36.46 years).

Johnson et al. [1997] reported evidence of anticipation in schizophrenic families identified through the National Institute of Mental Health Genetics Initiative. Families were included that had at least two affected members in successive generations and were not bilineal. Affectation diagnoses included schizophrenia, schizo-affective disorder-depressed, and psychosis not otherwise specified. Three indices of age of onset were used and included age of first psychotic symptoms, age of first psychiatric treatment, and age of first hospitalization. Disease severity was measured by several different indices consisting of the number of hospitalizations and global ratings of positive and negative symptom severity as measured on standardized rating scales. The four sampling schemes suggested by McInnis et al. [1993] were tested. Anticipation was demonstrated for age of onset, regardless of the index or sampling scheme used. Anticipation was not detected for disease severity. Analyses that took into account drug use and diminished fecundity did not affect the results. Ohara et al. [1997b] studied two generations of 49 schizophrenics from 24 families and examined age of onset, numbers hospitalized, diagnostic subclasses of schizophrenia, amounts of antipsychotic medication, positive symptoms, negative symptoms, treatment resistance, and clinical courser ratings, between the two generations. The age of onset was significantly lower in the offspring generation, although there was no difference in the severity between the two generations. The negative symptom scores and clinical course scores in the offspring generation for paternal transmission were significantly higher than those for maternal transmission.

There have been several other studies that have found evidence of anticipation in schizophrenia. Beckmann et al. [1996] studied 139 probands with DSM-III-R schizophrenia, 83 of whom met the criteria of Leonhard [1957] for periodic catatonia and 56 met criteria for systemic catatonia. The authors reported homogeneity of psychosis in the pedigrees identified through a proband with periodic catatonia with direct evidence of vertical transmission and anticipation. Valero et al. [1998] studied 56 schizophrenic pedigrees including 25 with apparently unilineal transmission. Two-thirds of the parent-offspring pairs showed evidence of anticipation, the reason was because of the older age of onset of the parent, and there was no evidence of anticipation in pairs with early onset parents, suggesting a floor effect on age of onset. There was no evidence of a particular subtype of schizophrenia associated with anticipation. No evidence of the cohort effect was found when a group of sporadic (no family history) cases of schizophrenia were analyzed for evidence of decreasing age of onset in younger cohorts. Similarly, Yaw et al. [1996] found overall evidence of anticipation but in the subset of families with early onset parents there was no consistent evidence of anticipation. Heiden et al. [1999] sampled 15 families identified for linkage studies in schizophrenia. Age at onset was significantly earlier in the proband's generation (21.6 ± 6.6 years) compared with the parents (40.2 ± 9.2 years) ($P = 0.0001$). The authors excluded a potential birth cohort effect by investigating a control sample consisting of two nonoverlapping birth cohorts of patients with schizophrenia. Age at onset between the two groups of the control sample did not differ. Anticipation has been reported in Japanese pedigrees [Imamura et al., 1998].

Studies of schizophrenia, with the caveat that complete elimination of ascertainment bias may be impossible, consistently demonstrate a younger age of onset in succeeding generations. In addition, it is clear that a fertility bias exists as affected individuals are less likely to procreate if they are affected at an early age. The general consensus is that it is likely that a subset of families exist wherein anticipation occurs. No evidence of the cohort effect has been reported, and there appears to be an imprinting effect with more severe disorder on inheritance from an affected father [Husted et al., 1998]. We report here an additional analysis of a large schizophrenia cohort with unilineal inheritance that examines the presence of anticipation in schizophrenia.

SUBJECTS AND METHODS

A large registry of families has been identified from the USA and UK with at least two full sibs with the DSM-III-R diagnosis of schizophrenia or schizoaffective disorder. The ascertainment is described elsewhere [DeLisi et al., 1994b]. Briefly, there were two main sources for families: 1) a cohort of cases receiving medical care at a district hospital in northwest London and 2) a USA national survey registry of families identified from treatment centers within a New York-county area (Suffolk county) through clinician referrals and advertisements throughout the USA. After complete description of the study to the subjects, written informed consent was obtained.

All participants were evaluated by a trained clinician. Subjects were interviewed using a modified SADS

TABLE I. Diagnoses and Age of Onset Per Generation

Diagnosis	Grandparent *n*	G1* *n* (median age of onset)	G2** *n*	Total
Schizophrenia	4 (28.5)	17 (18)	79 (18)	100 (18)
Schizoaffective disorder	1 (31)	2 (29)	50 (18)	56 (18)
Bipolar disorder	0	10 (29.5)	2 (19.5)	12 (28)
Psychosis NOS	2 (13.5)	16 (30)	3 (16)	21 (26)
Schizotypal personality disorder	1 (25)	5 (29)	4 (16.5)	10 (25)
Major depression	2 (28)	36 (29)	17 (20)	55 (25)
Total	10	89	155	254

*G1 Indicates the parental generation.
**G2 Indicates the offspring generation.

(Schedule for Affective Disorders and Schizophrenia) structured format. Clinical information was obtained from multiple sources when available by direct structured interviews of all available individuals, from a reliable relative (usually parent) who lived in the same household with the individual during the onset of their illness, and from other relatives if needed. Where there was disparity, a decision was made by the investigator collecting data as to the most reliable informant. Those investigators gathering the information were not aware of the hypothesis being tested or the phenomenon of "anticipation."

For this study only, those families that showed no evidence of bilineality were included, i.e., the disease was only identified in one parental line and evidence of the illness was present in a second-degree relative. Sixty-one families met those criteria. Age at first onset of psychosis was used as the age at onset of disease. The median age of onset was examined for parents and offspring and for sibs of parents and their same-sex niece or nephew. In this study there was no identifiable proband, the family with multiple affected individuals was ascertained as a unit. The sample is described in Table I.

ANALYSES

Onset age was compared among all affected members of the parental generation (G1) and the offspring's generation (G2) by using life-table analyses and the Gehan's Generalized Wilcoxon test. Pairwise analyses were performed using the nonparametric Wilcoxon statistic as the age at onset data showed highly non-Gaussian distributions. These analyses parallel our previous analysis of anticipation in bipolar affective disorder [McInnis et al., 1993].

The analyses were done on two diagnostic groups according to the diagnosis of the pair member from the previous generation: 1) schizophrenia, schizo-affective disorder, and psychosis—not otherwise specified and 2) schizophrenia, schizo-affective disorder, psychosis—not otherwise specified and schizotypal personality disorder. All affected family members were included in the analyses.

The two diagnostic groups were stratified by the nature of the relationship of the pairs: 1) transmitting (parent-child) and 2) nontransmitting (aunt/uncle-niece/nephew). Both were stratified according to sex. This approach was taken in view of the differences in anticipation in known trinucleotide-repeat diseases being affected by sex of the affected parent [The Huntington's Disease Collaborative Research Group, 1993] and because sex specific age at onset differences in schizophrenia are well documented [Gottesman, 1991].

RESULTS

Tables I and II describe the total family sample stratified according to generational membership and relationship to the younger generation.

Life-Tables Analysis

Figure 1 shows survival to affected status in those families wherein the parents have a diagnosis of schizophrenia, schizo-affective disorder, or psychosis NOS (not otherwise specified). As a group, the G2 experienced a significantly earlier onset compared with G1 (Gehan's Wilcoxon statistic = 4.4; $P = 0.00001$). The significance increased marginally when the schizotypal personality disorder diagnosis was included.

Pairwise Comparisons

Table III shows the pairwise comparisons for the transmitting and the nontransmitting pairs as well as the median age at onset difference between the pairs. There is a significant pairwise difference between generations in transmitting and nontransmitting pairs across all diagnostic subgroups (as characterized by the diagnosis of the elder pair member). Examining all 101 transmitting and nontransmitting pairs wherein the elder pair member is schizophrenic, schizo-affective, or psychosis NOS (i.e., diagnostic subgroup I), there is a median age at onset difference of 8 years. The differ-

TABLE II. Sex and Age of Onset (All Diagnoses)

	Grandparent	G1	G2	Total
	(median age at onset - all diagnoses)			
All males	5 (15)	38 (21)	112 (18)	155 (19)
All females	5 (28)	51 (29)	43 (18)	99 (22)
Total	10 (26.5)	89 (28)	155 (18)	254 (19.5)
Fathers	1 (28)	15 (30)		16 (30)
Mothers	1 (12)	25 (35)		26 (34.5)
Aunts	4 (27)	26 (27)		30 (27.5)
Uncles	4 (23)	23 (19)		27 (19)
Offspring		6 (13)	155 (18)	161 (18)

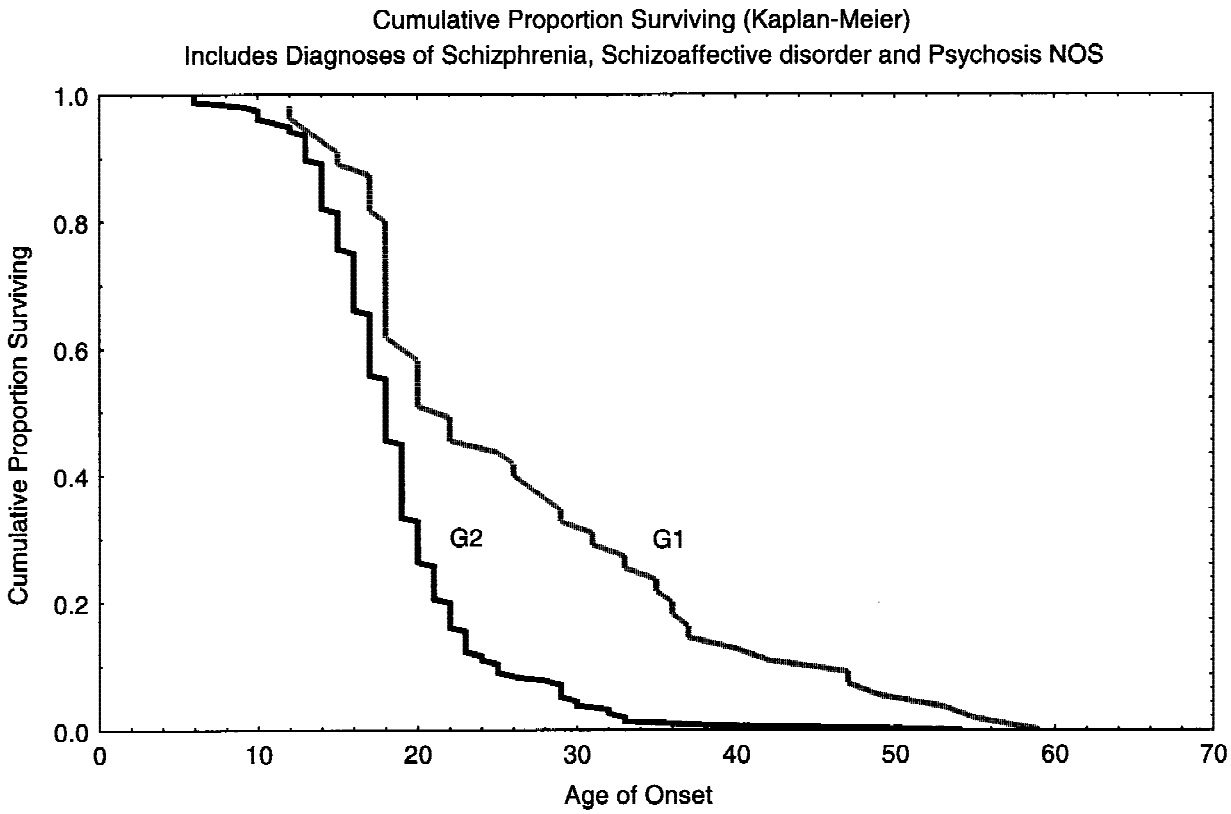

Fig. 1. Cumulative survival to first episode of schizophrenia, schizo-affective disorder, or psychosis not otherwise specified of affected individuals in the parental group (G1) and the offspring group (G2).

ence is primarily in the transmitting pairs wherein the difference is 14.5 years.

Table IV shows the pairwise comparisons for mothers and fathers, both of whom show a significant difference across all diagnostic subgroups. In 18 mother-offspring pairs (mother with psychotic diagnosis, i.e., subgroup I), there was a median age at onset difference of 15.5 years. In 18 father-offspring pairs, subgroup I, the median age at onset difference was 11 years.

Table V shows the comparisons of pairs of 1) uncles to nieces or nephews, 2) uncles to nephews, 3) aunts to nieces or nephews, and 4) aunts to nieces. In diagnostic subgroup I there was no significant difference between uncles and nieces or nephews (Wilcoxon matched pairs; $Z = 0.882$; $P = 0.38$), and the median age at onset difference was 0.5 years. Comparing just uncles and nephews or aunts and nieces did not affect the significance level. There was a significant difference in comparing aunts of the same diagnostic subgroup with nephews and/or nieces; the median age at onset difference was 9–14.5 years.

DISCUSSION

In this study, we report data with apparent support of the presence of anticipation in families with schizophrenia. The median age at onset of the affected offspring was significantly lower (>13 years) than that of the affected parent. However, the data can be explained in terms of ascertainment and fertility biases. A less biased test of the hypothesis compares affected avuncular pairs and is less sensitive to the fertility bias. The evidence of anticipation when comparing all nontransmitting (avuncular) pairs was attributable entirely to the comparison of aunts to nieces and/or nephews (9 years). Further support of the existence of a fertility effect is that only 12 (all currently unaffected) of 57 affected aunts and uncles have offspring.

TABLE III. Pairwise Analyses

	Transmitting pairs			Nontransmitting pairs		
Diagnosis* of the pair member of the earlier generation	*n*	Onset difference (years)	*P* value	*n*	Onset difference (years)	*P* value
1, 2, and 4	36	14.5	<0.0001	65	2	0.0012
1, 2, 4, and 5	49	13	<0.0001	66	2	0.002

*Numbers correspond to diagnoses in Table I.

TABLE IV. Transmitting Pairs: Breakdown Between Mother and Father

Diagnosis* (parent)	Fathers - offspring			Mothers - offspring		
	n	Onset difference (years)	*P* value	*n*	Onset difference (years)	*P* value
1, 2, and 4	18	11	0.0004	18	15.5	0.0002
1, 2, 4, and 5	23	8	0.0004	26	14.5	<0.0001

*Numbers correspond to diagnoses in Table I.

The remaining biases of ascertainment as reported by Penrose [1948] in his original criticism of the finding of anticipation in myotonic dystrophy are undoubtedly present to some degree and include preferential ascertainment, caused by severity of disease, in the childhood generation and preferential bias of ascertainment of families with simultaneous onset in parent and child. These biases apply to these data, but as with myotonic dystrophy the significance of these biases will only be resolved with identification of the gene(s). There are some biases that may be considered unique to schizophrenia. Being a parent despite having schizophrenia might suggest that one has a relatively milder form of schizophrenia. It is perhaps less likely that a family with a parent of young age of onset will be ascertained as 1) young affected individuals may be less likely to develop intimate relationships or marry and 2) if male and has children, it is probably less likely for him to maintain a relationship with the mother and remain available for study. In addition the older generation has already gone through the age of risk for developing schizophrenia, whereas other sibs in successive generations have not. It is theoretically possible that, if these families were followed for another 10–20 years through the risk period, later ages of onset of illness would be recorded. There is no evidence that a systematic bias caused by forgetting of past episodes (memory bias) is present as there are several individuals in the older generation with early age of onset.

Sex Effect

It has been well documented that the age of onset of schizophrenia is lower for males than females [Gottesman, 1991]. Overall the data presented here support this observation; median age of onset for males is 19 years and for females is 22 years. However, uncles show a median age of onset of 19 years, whereas aunts at onset are 27.5 years, fathers 30 years, and mothers 34.5 years. The median age of onset of uncles is almost the same as that for their nieces and nephews (18 years). Interestingly there is no difference in the median age of onset for males and females in the proband generation (G2). Within multiplex families, females have been found to have an earlier age of onset [DeLisi et al., 1994a]. These findings suggest that within families there is an interaction between sex, generation, and age of onset. One possible interpretation is that there is an interaction between an unstable autosomal locus and an effect (such as epistasis or imprinting) from the sex chromosomes. Another possible interpretation is that the primary locus is itself on the sex chromosomes and is influenced by imprinting or X inactivation. A locus in a region of X-Y homology has been suggested, and some linkage evidence supports it [Laval et al., 1998].

In his survey of cases of familial mental illness, Penrose [1991] calculated correlation coefficients for first admission ages between affected relative pairs (see Table 15 of Penrose [1991]). He wrote "The association between mother and son, +0.440, is higher than that between other types of parental pairs and the father-son association, +0.302, is the lowest in this group. Amongst the three sib-sib coefficients, brother-sister pairs have the lowest value. For uncles, aunts, nephews and nieces, the coefficient with the highest value, +0.480, belongs to the maternal uncle and nephew relationship and the lowest coefficient, 0.144, belongs to paternal aunt and nephew. These findings are in keeping with what would be expected if one or more of the genetic factors which modify age of onset were sex-linked, that is to say, carried on the X chromosome." Perhaps this conclusion deserves reconsideration in the light of what is now known about anticipation, X-Y linkage, and the phenomenon of X inactivation.

Expanding Triplet Repeats

The presence of anticipation in schizophrenia leads to the hypothesis that expanding triplet repeats may underlie the genetic susceptibility. Studies using the repeat expansion detection method (RED) [Schalling et al., 1993] have suggested that CAG/CTG repeat expansions may be associated with schizophrenia, however there have been no reports of expanded RED products passing from parent to offspring. O'Donovan et al. [1995] found an increase in the number of enlarged CAG repeats in schizophrenic subjects compared with controls but found no association between age of onset and repeat length but found a larger repeat length in affected females compared with affected males, leading to the suggestion that an expanded repeat might exist on the X chromosome. Similarly, Morris [1995] found longer repeats in female subjects with schizophrenics. In an analysis of 152 schizophrenic and 143 bipolar

TABLE V. Nontransmitting Pairs

Diagnosis* (uncle or aunt)	Uncles:nephews			Uncles:nieces/nephews			Aunts:nieces/nephews			Aunts:nieces		
	n	onset difference (years)	*P*	*n*	onset difference (years)	*P*	*n*	onset difference (years)	*P*	*n*	onset difference (years)	*P*
1, 2, and 4	18	0	0.67	28	0.5	0.38	37	9	<0.0001	10	14.5	0.009
1, 2, 4, and 5	18	0	0.67	28	0.5	0.38	38	7.5	0.001	10	14.5	0.009

*Numbers correspond to diagnoses in Table I.

patients and matched controls including 62 probands (41 bipolar and 21 schizophrenic) with DNA from affected parents, O'Donovan et al. [1996] continued to demonstrate a shift towards longer RED products in both schizophrenia and bipolar disorder. However, no size difference was apparent in parent-offspring pairs, the shift in the patient groups was equal for males and females, and there was no correlation between age of onset and repeat length. There have been several studies that have not shown any evidence of enlarged CAG repeat containing alleles [Schurhoff et al., 1997; Vincent et al., 1996, 1998; Ohara et al., 1997a; Bengel et al., 1998; Li et al., 1998].

CONCLUSION

Our findings are comparable with published reports that suggest the presence of anticipation in pedigrees with schizophrenia. It is still possible that a fertility bias accounts for these findings. An alternative explanation is that the appearance of anticipation is because of the accumulation of many genes that becomes concentrated in a sibship because of assortative mating. However, our data also demonstrate an effect of sex on the affected phenotype that varies depending on generational membership or position in the pedigree. This suggests either an effect of imprinting on an autosomal locus or of inactivation/imprinting of a sex chromosomal locus. Further investigation of the sex by generation interaction within families may lead to an understanding of the so far unexplained sex difference in age of onset in schizophrenia.

REFERENCES

Asherson P, Walsh C, Williams J, et al. 1994. Imprinting and anticipation: are they relevant to genetic studies of schizophrenia? Br J Psychiatry 164:619–624.

Bassett AS, Honer WG. 1994. Evidence for anticipation in Schizophrenia. Am J Hum Genet 54:864–870.

Bassett AS, Husted J. 1997. Anticipation or ascertainment bias in schizophrenia: Penrose's familial mental illness sample. Am J Hum Genet 60:630–637.

Bayless TM, Picco MF, LaBuda MC. 1998. Genetic anticipation in Crohn's disease. Am J Gastroenterology 93:2322–2325.

Beckmann H, Franzek E, Stober G. 1996. Genetic heterogeneity in catatonic schizophrenia: a family study. Am J Med Genet 67:289–300.

Bell J. 1947. Dystrophia myotonica and allied diseases. In: Pearson K, editor. London: DuLaw. p 343.

Bengel D, Balling U, Stober G, Heils A, Li SH, Ross CA, Jungkunz G, Franzek E, Beckmann H, Riederer P, Lesch KP. 1998. Distribution of the B33 CTG repeat polymorphism in a subtype of schizophrenia. Eur Arch Psychiatry Clin Neurosci 248:78–81.

Bonifati V, Vanacore N, Meco G. 1994. Anticipation of onset age in familial Parkinson's disease. Neurology 44:1978–1979.

Chotai J, Engstrom C, Ekholm B, Son BM, Adolfsson R, Nylander PO. 1995. Anticipation in Swedish families with schizophrenia. Psychiatr Genet 5:181–186.

Crow TJ. 1990. The continuum of psychosis and its genetic origins: the sixty-fifth Maudsley lecture. Br J Psychiatry 156:788–797.

DeLisi LE, Bass N, Boccio A, Shields G, Morganti C. 1994a. Age of onset in familial schizophrenia. Arch Gen Psychiatry 51:334–335.

DeLisi LE, Devoto M, Lofthouse R, et al. 1994b. Search for linkage to schizophrenia on the X and Y chromosomes. Am J Med Genet 54:113–121.

Fleischer B. 1918. Uber myotonische dystrophie mit katarakt: eine heriditare, familiare degeneration. Archiv Ophthalmologie 96:91–133.

Galton F. 1909. Essays in eugenics. London: The Eugenics Education Society.

Gorwood P, Leboyer M, Falissard B, Rouillon F, Jay M, Feingold J. 1997. Further epidemiological evidence for anticipation in schizophrenia. Biomed Pharmacother 51:376–380.

Gottesman II. 1991. Schizophrenia genesis: the origins of madness, ed. 1. New York: W.H. Freeman.

Heiden A, Willinger U, Scharfetter J, et al. 1999. Anticipation in schizophrenia. Schizophr Res 35:25–32.

Horwitz M, Goode EL, Jarvik GP. 1996. Anticipation in familial leukemia. Am J Hum Genet 59:990–998.

Howeler CJ, Busch HFM, Geraedts JPM, Niermeijer MF, Staal A. 1989. Anticipation in myotonic dystrophy: fact or fiction? Brain 112:779–797.

Husted J, Scutt LE, Bassett AS. 1998. Paternal transmission and anticipation in schizophrenia. Am J Med Genet 81:156–162.

Imamura A, Honda S, Nakane Y, et al. 1998. Anticipation in Japanese families with schizophrenia. J Hum Genet 43:217–223.

Johnson JE, Cleary J, Ahsan H, et al. 1997. Anticipation in schizophrenia, biology or bias. Am J Med Genet 74:275–280.

Laval SH, Dann JC, Butler RJ, et al. 1998. Evidence for linkage to psychosis and cerebral asymmetry (relative hand skill) on the X chromosome. Am J Med Genet 81:420–427.

Leonhard K. 1957. Aufteilung der endogenen psychosen. Berlin: Akademie-Verlag.

Li T, Vallada HP, Liu XH, et al. 1998. Analysis of CAG/CTG Repeat size in Chinese subjects with schizophrenia and bipolar affective disorder using the repeat expansion detection method. Biol Psychiatry 44:1160–1165.

McDermott E, Khan MA, Deighton C. 1996. Further evidence for genetic anticipation in familial rheumatoid arthritis. Ann Rheum Dis 55:475–477.

McInnis MG. 1996. Anticipation: an old idea in new genes. Am J Hum Genet 59:973–979.

McInnis MG, McMahon FJ, Chase G, Simpson SG, Ross CA, DePaulo JR Jr. 1993. Anticipation in bipolar affective disorder. Am J Hum Genet 53:385–390.

Morel BA. 1857. Traite des degenerescences, ed. 1. Paris: J.B. Bailliere.

Morris AG, Gaitonde E, Mckenna PJ, Mollon JD, Hunt DM. 1995. CAG repeat expansions and schizophrenia: association with disease in females and early age-at-onset. Hum Mol Genet 4:1957–1961.

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

Mott FW. 1911. A lecture on heredity and insanity. Lancet 1:1251–1259.

O'Donovan MC, Guy C, Craddock N, et al. 1995. Expanded CAG repeats in schizophrenia and bipolar disorder. Nat Genet 10:380–381.

O'Donovan MC, Guy C, Craddock N, et al. 1996. Confirmation of association between expanded CAG/CTG repeats and both schizophrenia and bipolar disorder. Psychol Med 26:1145–1153.

Ohara K, Tani K, Tsukamoto T, et al. 1997a. Exclusion of five trinucleotide repeat (CAG and CCG) expansions in 17 families with schizophrenia. Biol Psychiatry 42:756–759.

Ohara K, Xu HD, Mori N, Suzuki Y, Xu DS, Wang ZC. 1997b. Anticipation and imprinting in schizophrenia. Biol Psychiatry 42:760–766.

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

Penrose LS. 1991. Survey of cases of familial mental illness. Eur Arch Psychiatr Neurol Sci 240:315–324.

Pick D. 1989. Faces of degeneration. Cambridge: Cambridge University Press.

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

Schurhoff F, Stevanin G, Trottier Y, et al. 1997. A preliminary study on early onset schizophrenia and bipolar disorder: large polyglutamine expansions are not involved. Psychiatry Res 72:141–144.

The 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.

Thibaut F, Martinez M, Petit M, Jay M, Campion D. 1995. Further evidence for anticipation in schizophrenia. Psychiatry Res 59:25–33.

Valero J, Martorell L, Marine J, Vilella A, Labad A. 1998. Anticipation and imprinting in Spanish families with schizophrenia. Acta Psychiatrica Scandinavica 97:343–350.

Vincent JB, Kalsi G, Klempan T, Tatuch Y, Sherrington R, Breschel TS, McInnis MG, Brynjolfsson J, Petursson H, Gurling HM, Gottesman II, Torrey EF, Petronis A, Kennedy JL. 1998. No evidence of expansion of CAG or GAA repeats in schizophrenia families and monozygotic twins. Hum Genet 103:41–47.

Vincent JB, Klempan T, Parikh SS, et al. 1996. Frequency analysis of large CAG/CTG trinucleotide repeats in schizophrenia and bipolar affective disorder. Mol Psychiatry 1:141–148.

Wells RD, Warren ST. 1998. Genetic instabilities and hereditary neurological diseases. New York: Academic Press.

Wright GD, Regan M, Deighton CM, Wallis G, Doherty M. 1998. Evidence for genetic anticipation in nodal osteoarthritis. Ann Rheum Dis 57: 524–526.

Yaw J, Myles-Worsley M, Hoff M, et al. 1996. Anticipation in multiplex schizophrenia pedigrees. Psychiatr Genetics 6:7–11.