Paternal Transmission and Anticipation in Schizophrenia

Janice Husted¹, Laura E. Scutt², and Anne S. Bassett^{2,3,*}

¹Department of Health Studies and Gerontology, University of Waterloo, Waterloo, Ontario, Canada

²Schizophrenia Research Program, Queen Street Mental Health Centre, Toronto, Ontario, Canada

³Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

Abstract

Recent studies have observed anticipation (earlier age at onset (AAO) or increased disease severity in successive generations) in familial schizophrenia. In other disorders, where the molecular mechanism (repeat expansion) is known, anticipation varies in degree depending on the sex of the transmitting parent. We investigated parental sex effects on anticipation in schizophrenia, using a familial sample of affected two-generation pairs in which anticipation had previously been demonstrated using the median intergenerational difference (MID) in AAO. A Wilcoxon rank sum test for independent samples was used to determine whether MID in AAO was significantly different for paternal and maternal transmission. Results suggested that in a sample of 127 parent-offspring pairs, anticipation was greater with paternal than with maternal transmission (MID = 18 and 14 years, respectively, $P = 0.05$). Paternal effects were strongest in 39 parent-offspring pairs with early-onset offspring (< 21 years) (MID = 22 and 17 years, respectively, for paternal and maternal transmission, $P = 0.01$). However, assessment of the effect of possible selection biases suggests that preferential ascertainment of late-onset fathers may have exerted important effects. While the results support possible paternal effects, further studies are needed to draw firm conclusions about true parent-of-origin effects on anticipation in familial schizophrenia.

Keywords

schizophrenia; anticipation; imprinting; transmission; sex effects

INTRODUCTION

Recent studies have observed anticipation (earlier age at onset (AAO) or increased disease severity in successive generations) in familial schizophrenia [Asherson et al., 1994; Bassett and Honer, 1994; Lesch et al., 1994], consistent with the historical literature [Mott, 1910; Bleuler, 1978]. Findings of significant anticipation in schizophrenia persist even after adjusting for the effects of ascertainment biases, which may simulate anticipation [Gorwood et al., 1996; Bassett and Husted, 1997]. These studies have suggested anticipation as a

*Correspondence to: Dr. Anne S. Bassett, Schizophrenia Research Program, Queen Street Mental Health Centre, 1001 Queen Street West, Toronto, Ontario M6J 1H4, Canada.

mechanism that may contribute to explaining complex modes of inheritance in schizophrenia [Asherson et al., 1994; Bassett and Honer, 1994], a syndrome with variable phenotype involving psychotic symptoms, marked social disabilities, and increased mortality.

In several neuropsychiatric disorders with autosomal-dominant inheritance, anticipation is caused by a dynamic mutation containing cytosine-guanine (CG)-rich trinucleotide repeats (TNR) that can expand in successive generations [Sutherland and Richards, 1995]. Anticipation and the length instability of the associated TNR expansion frequently vary in degree, depending on the sex of the transmitting parent. For instance, paternal transmission is associated with more prominent anticipation of AAO in Huntington disease (HD) [Ranen et al., 1995], spinocerebellar ataxia type I (SCA1) [Jodice et al., 1994], dentatorubral-pallidoluysian atrophy (DRPLA), Machado-Joseph disease (MJD) [Ikeuchi et al., 1996], and adult-onset stages of myotonic dystrophy (DM) [Brunner et al., 1993]. As shown in Table I, the magnitude of these parent-of-origin effects varies from disease to disease.

The observation of parental sex effects on anticipation in other neuropsychiatric disorders raises questions about such effects in schizophrenia. Evidence for the presence of parental sex effects would provide further support for true anticipation in schizophrenia [Ranen et al., 1995] and could help in the search for causal mutations, none of which have yet been identified. Few studies, however, have examined parent-of-origin sex effects on transmission in familial schizophrenia, and sample sizes have been small [Asherson et al., 1994; Bassett and Honer, 1994; Gorwood et al., 1996]. Only one study has reported anticipation of AAO separately for paternal and maternal transmission in schizophrenia [Gorwood et al., 1996]. No evidence for parental sex effects on anticipation was found; however, relatively small numbers of offspring of affected fathers ($n = 24$) and of affected mothers ($n = 19$) may have decreased the power of this study to detect subtle effects. For instance, in HD the detection of subtle paternal anticipation required a large sample of affected parent-offspring pairs ($n = 1,693$) and the investigation of a relatively large subsample of offspring with very young AAO (<21 years) ($n = 169$) to determine significant effects [Ridley et al., 1988].

The objective of the current study was to investigate parent-of-origin sex effects on anticipation in schizophrenia using a familial sample of affected two-generation pairs in which anticipation had previously been demonstrated [Bassett and Husted, 1997]. In this study we assumed that parental sex effects on anticipation in schizophrenia would be large enough to be observed despite factors complicating all genetic studies of schizophrenia, i.e., decreased reproductive fitness, especially in males [Bassett et al., 1996], and likely locus heterogeneity.

PATIENTS AND METHODS

Penrose Archival Data

Samples used in the current study were drawn from archival data collected for Lionel Penrose's study entitled "Survey of Cases of Familial Mental Illness" [Penrose, 1991], which was published posthumously [Crow, 1991]. Subject recruitment and assessment have been described in detail elsewhere [Bassett and Husted, 1997]. Briefly, Penrose ascertained a large representative sample of familial mental illness by surveying all individuals who had

been admitted to Ontario psychiatric hospitals between 1926–1944, reviewing their medical records, and identifying those with one or more family members who had ever been hospitalized with a mental illness or who had committed suicide. The total sample, comprising approximately 10% of the total psychiatric inpatient population in Ontario, consisted of 7,339 individuals from 3,109 families. For each individual in the sample, Penrose recorded information on diagnostic category, year of birth, year of first psychiatric hospitalization, and how the individual was related to the relative(s) in the data set (e.g., father, daughter, niece). Penrose used the medical chart diagnoses to form 13 broad categories of mental illness, with the majority of individuals in the sample being diagnosed with either schizophrenia (30.8%) or affective disorder (29.8%). In our previous study [Bassett and Husted, 1997], we addressed concerns about the heterogeneity within Penrose's 13 diagnostic categories by examining the original chart diagnosis with Penrose's recorded diagnosis in a subset of the sample ($n = 2,176$). This comparison showed that approximately 94% of subjects in the schizophrenia category had diagnoses of schizophrenia alone or schizophrenia of the catatonic, paranoid, hebephrenic, or mentally defective type. In the affective disorder category, 99.0% of subjects had depressive, manic, manic-depressive, melancholic, or schizoaffective diagnoses. Other findings suggested that the diagnostic categorization of severe psychiatric illnesses was comparable to that of contemporary studies [Crow, 1991]. These included a similar proportion of subjects with schizophrenia and affective disorders in the total sample, separate diagnostic categories for medical disorders, and an earlier median AAO for schizophrenia (31 years) than for affective disorder (44 years).

For the current study we used two samples (I and II) of affected relative pairs after excluding families with bilineal transmission [Bassett and Husted, 1997]. In the cases where there were two or more affected pairs per family (8.6% of sample I and 23.9% of sample II), a single pair per family was randomly selected. Because the diagnosis of schizophrenia after age 60 years is relatively rare [Gorwood et al., 1996], we felt less confident about the validity of the diagnosis in this subgroup. Therefore, families with a member who had a very late AAO (> 60 years) ($n = 10$, sample I; $n = 10$, sample II) were excluded.

Pairs were formed using one relative from the parental generation (parent or aunt/uncle) and one from the index generation (offspring or niece/nephew). Sample I, consisting of 127 parent-offspring pairs with schizophrenia, permitted a direct test of the hypothesis of parental sex effects on anticipation as measured by a generational difference in AAO, which was defined as age at first psychiatric hospitalization. Although only an approximation of AAO of illness, age at first psychiatric hospitalization provides a reliable estimate of the AAO of acute and serious psychiatric symptoms of major mental disorders such as schizophrenia [DeLisi, 1992; Beiser et al., 1993]. In addition, it has been shown that age at first treatment is highly correlated with age at first diagnosis, defined as the age at which patients first met DSM-III-R diagnostic criteria for schizophrenia based on medical records and interviews [Gorwood et al., 1996]. Sample II consisted of 92 aunt/uncle-niece/nephew pairs in which both members were diagnosed with schizophrenia and transmitting parents were unaffected (not hospitalized). This sample permitted an assessment of parental sex effects on anticipation where confounding influences of reduced reproductive fitness and environmental adversity resulting from parent's affected status were minimized.

Analyses

Since the distribution of AAO was asymmetrical (Fig. 1), we used the median to compare AAO between the parental and offspring generations within each sample [Bassett and Husted, 1997]. We first determined anticipation of AAO by subtracting offspring generation AAO from parental generation AAO for each pair. The Wilcoxon sign-rank paired-sample test was used to determine whether pairwise intergenerational AAO differences were significantly >0 , testing the null hypothesis of no anticipation. To examine whether there was a parental sex effect on anticipation, we used the Wilcoxon rank sum test for independent samples to determine whether pairwise intergenerational AAO differences were significantly different for paternal and maternal transmission. In addition, to assess the effect of preferential selection of late-onset fathers, we examined parental sex effects on anticipation in early-AAO (< 34 years) parents. Our definition of early and late AAO is consistent with that used by Penrose and with mean AAO values for first-admission schizophrenia samples in 1943 [Penrose, 1991; Bassett and Husted, 1997]. Consistent with the HD literature, we also investigated parental sex effects in very young-onset offspring, defined as offspring with AAO < 21 years. All analyses were performed using the SAS System for Windows, Release 6.11 (Cary, North Carolina).

RESULTS

Sex Effects of Affected Transmitting Parents on Anticipation

Of the 127 parent-offspring pairs with schizophrenia in sample I, 39 pairs had an affected father and 88 had an affected mother (Table II). This ratio is consistent with male reproductive fitness, which is about half that of females with schizophrenia [Bassett et al., 1996]. Ninety-five percent of paternally transmitted pairs and 84% of maternally transmitted pairs showed anticipation, with significant median intergenerational AAO differences of 18 and 14 years, respectively (Table II). Figure 2 shows the distribution of anticipation. There was an abnormal skew for paternal transmission (-0.37) and for maternal transmission (-0.40). The median AAO was 40 years for the parental generation (fathers and mothers) and 24 years for the offspring generation. These values bracket the mean AAO of 34 years observed in a random sample of first admissions in Ontario in 1943 [Penrose, 1991], and likely reflect the effects of ascertaining affected parent-offspring pairs [Bassett and Husted, 1997]. There were no significant sex differences in median AAO within generations (see Table II).

As shown in Table II, anticipation was significantly greater in paternal transmission than maternal transmission (Wilcoxon two-sample Z statistic = 1.93, $P = 0.05$). Further analyses revealed that the sex of offspring (son or daughter) did not modify the observed paternal effect on anticipation (data not shown). A similar pattern of results was observed when the diagnosis was broadened to include one affected relative with either schizophrenia or a major affective disorder, a related group of illnesses that forms the major differential diagnosis for schizophrenia ($n = 289$ parent-offspring pairs; data not shown). The subgroup analysis of early-AAO parents (< 34 years) (Table II), however, showed no significant difference in anticipation between paternal and maternal transmission. A paternal effect on anticipation remained in the larger sub-sample of late-AAO parents (> 34 years) (median

anticipation = 20 years and 16 years for paternal and maternal transmission, respectively; Wilcoxon two-sample Z statistic = 1.88, $P = 0.06$), suggesting late-onset fathers as a major source of the effect.

Early-Onset Offspring (≤ 21 Years) and Sex Effects of Transmitting Parents on Anticipation

Of the 127 pairs with schizophrenia in sample I, 39 pairs had an affected offspring with very young AAO (≤ 21 years) (Table II). The proportion of very early-AAO offspring of affected fathers (38.5%) and of affected mothers (27.3%) did not differ significantly (chi-square statistic = 1.59, $df = 1$, $P = 0.21$). Among the very early-AAO offspring, AAO ranged from 16–21 for paternal transmission and 13–21 for maternal transmission; AAO for fathers ranged from 29–56, and AAO for mothers ranged from 22–47. Anticipation was significantly greater with paternal transmission than with maternal transmission in very early-AAO offspring (see Table II). However, the median AAO of fathers of very early-onset offspring was significantly older than that of mothers (40 years vs. 35 years, Wilcoxon two-sample Z statistic = 2.88, $P = 0.004$). To attempt to adjust for this difference in parental AAO, we examined parental sex effects on anticipation in parents with an AAO ≤ 40 years (8 fathers and 19 mothers) and in parents with an AAO >40 years (7 fathers and 5 mothers). In both subgroups, median anticipation was 4–5 years greater with paternal transmission than with maternal transmission; however, the observed paternal effect was not statistically significant in either group, probably due to small sample sizes.

Sex Effects of Unaffected Transmitting Parents on Anticipation

In sample II, consisting of 92 aunt/uncle-niece/nephew pairs with schizophrenia, there were 37 pairs with paternal transmission, and 55 pairs with maternal transmission (Table II). The paternal:maternal transmission ratio of 2:3 is consistent with a degree of reduced reproductive fitness previously observed in men who did not have schizophrenia but who were at increased risk of being gene carriers [Bassett et al., 1996]. Seventy-eight percent of paternally transmitted pairs and 71% of maternally transmitted pairs showed anticipation. As reported previously, the overall magnitude of anticipation was less than that for parent-offspring pairs [Bassett and Husted, 1997] owing to a reduced role of ascertainment bias in the aunt/uncle-niece/nephew sample. In this sample, median anticipation was not significantly greater for paternal than maternal transmission (see Table II). This finding did not change when the sex of the offspring generation (niece/nephew) was taken into consideration or when the sex of both the paternal and offspring generations were simultaneously controlled for in the analyses (e.g., paternal aunt-nephew pairs compared with maternal aunt-nephew pairs; data not shown). In a subsample selected for very early-AAO nieces/nephews (≤ 21 years), median anticipation was 14 years and 9.5 years, respectively, for paternal ($n = 9$) and maternal ($n = 16$) transmission, a nonsignificant difference (Wilcoxon two-sample Z statistic = 0.85, $P = 0.40$).

DISCUSSION

Parental sex effects on anticipation have been observed for several diseases which involve a dynamic mutation containing CG-rich trinucleotide repeats (TNR) [Sutherland and Richards, 1995]. In schizophrenia, evidence for parental sex effects would provide further

support for the observed anticipation being a true phenomenon with a comparable molecular genetic basis [Ranen et al., 1995]. As observed in past studies [Asherson et al., 1994; Lesch et al., 1994; Gorwood et al., 1996; Bassett and Husted, 1997], results from the current study suggest that anticipation in schizophrenia is present in transmission from both sexes. This study is, however, the first to report significantly greater anticipation with paternal transmission than maternal transmission, in a relatively large sample of parent-offspring pairs with schizophrenia. The paternal-maternal differences in anticipation of AAO were subtle, in the range of 4–5 years, which could explain absence of the finding in smaller samples [Gorwood et al., 1996]. As in HD [Ridley et al., 1988], paternal effects were strongest in a subgroup of the sample with very early-onset offspring (< 21 years). Anticipation differences were of the same magnitude but not significant in a small subsample of very early-onset nieces and nephews. Compared to single major locus disorders with anticipation (Table I), the results appear to be most consistent with DM, DRPLA, and MJD, and less so with HD, where significant anticipation is a phenomenon restricted to paternal transmission [Ridley et al., 1988; Ranen et al., 1995]. The results are also consistent in direction with a recent study of bipolar I disorder [Grigoriou-Serbanescu et al., 1997], a major psychotic disorder where anticipation has previously been reported [McInnis et al., 1993].

Although the findings in the sample of parent-offspring pairs are suggestive of paternal transmission effects on anticipation in schizophrenia, they require cautious interpretation. Several alternate explanations should be considered. One plausible explanation is that the slightly greater anticipation in father-offspring pairs vs. mother-offspring pairs may arise from uncontrolled ascertainment biases. Specifically, the significant paternal effect in parent-offspring pairs may be a result of preferential selection of late-AAO fathers, because reduced reproductive fitness in men with severe, early-AAO illness led to their exclusion from study. This possibility is suggested by the absence of a significant paternal transmission effect in both the aunt/uncle-niece/nephew sample, where reproductive fitness biases were less, and in the subgroup of parents with early AAO (< 34 years), although the sample size of father-offspring pairs was small ($n = 7$). However, preferential ascertainment of late-AAO fathers does not appear to explain results for the very young AAO offspring subsample, where there was a 4–5-year difference in anticipation of AAO, whether parents had an AAO that was younger or older than the parental median.

Another possibility is that if assortative mating occurs more frequently among affected fathers than affected mothers with schizophrenia, this could lead to the finding of slightly greater anticipation for paternal transmission. However, there is some evidence suggesting that the frequency of assortative mating is relatively rare and, when present, tends to be more frequent in affected mothers [Gottesman and Shields, 1976]. This, along with the inclusion of only unilineal families in the current study, argues against assortative mating explaining the results. A third possibility is that the sex of the affected parent influenced the likelihood of hospitalization, and therefore entry in the sample. Men may be more likely to be hospitalized than women of equal disease severity because of differences in social expectations and symptom expression between the sexes [Goldstein and Tsuang, 1990]. If this were the case, anticipation in maternal transmission may have been underestimated. While this form of ascertainment bias was unmeasured, the vast majority of individuals with

a serious psychotic disorder are hospitalized, minimizing the influence of this particular bias [Link and Dohrenwend, 1980]. Alternately, gender may influence the timing of hospitalization, particularly for late-AAO cases. However, there is no evidence to suggest that late-AAO males experience a delayed hospitalization compared with late-AAO females. A fourth limitation relates to our measure of anticipation. The current study did not investigate parental sex effects on disease severity across generations. This may be important, since there is conflicting evidence with respect to parental sex effects on genetic risk of schizophrenia. Past studies have reported that offspring of affected mothers have a higher risk of schizophrenia than the offspring of affected fathers; however, other studies found no such maternal effect [Gottesman and Shields, 1976].

Finally, since two-generation families were studied, results of this study would likely apply to familial schizophrenia with an inheritance pattern consistent with autosomal-dominant transmission and would not pertain to all schizophrenia in the general population. Notably, the results are not consistent with either X-linked or mitochondrial transmission, which have been suggested for bipolar disorder [Gelernter, 1995; McMahon et al., 1995]. The nonsignificant results for parent-of-origin effects on anticipation in aunt/uncle-niece/nephew pairs may be compatible with oligogenic inheritance, which is likely to be the most common mode of inheritance in schizophrenia, and with genetic heterogeneity. Also, intrafamilial variability of AAO has been observed in other anticipating disorders [Howeler et al., 1989], and this may have been another factor in the differing results between the aunt/uncle-niece/nephew and the parent-offspring samples.

If paternal transmission were truly associated with greater anticipation for familial schizophrenia with autosomal-dominant-like inheritance, what implications could this have for the molecular genetics of schizophrenia? First, the finding would strengthen the evidence for genetic anticipation in schizophrenia and the possibility that unstable (TNR) mutation mechanisms may play a role in etiology. Second, the similarity to some aspects of anticipation in DRPLA, MJD, and DM suggests that the mechanisms proposed for those disorders [Brunner et al., 1993; Ikeuchi et al., 1996] may be more applicable to schizophrenia than those implicated in other anticipating disorders. If adult-onset DM were used as a model for familial schizophrenia, unaffected obligate carriers may be more likely to be male than female [Brunner et al., 1993], and the chance of finding large changes in repeat size would be maximized by examining father-offspring pairs. There is also a possible relationship between mechanisms for anticipation and those proposed for genomic imprinting, or monoparental methylation, which causes gene inactivation [John and Surani, 1996]. The possibility that mechanisms related to imprinting may be acting in schizophrenia is intriguing [Flint, 1992], particularly given the likelihood that imprinted genes may play a key role in regulating development of both the brain and behavior [Keverne et al., 1996].

In summary, the current study is unique in that it investigated parental sex effects on anticipation using a relatively large and representative sample of familial schizophrenia. While the findings in the affected parent-offspring sample are suggestive of a paternal effect on anticipation in familial schizophrenia, it is unclear to what extent the observed phenomenon reflects a true parental sex effect or ascertainment bias. Further studies of parental sex effects on anticipation, using large samples and measures of both disease

severity and AAO, are clearly warranted. However, it is likely that conclusive evidence concerning parental sex effects on genetic anticipation will evolve only from identifying disease-causing mutations and investigating the molecular mechanisms of anticipation in schizophrenia.

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Fig. 1.

Histograms of age at onset (AAO) for parents (black bars) and offspring (white bars) in sample I ($n = 127$). AAO values are grouped into 5-year cohorts for both the paternally transmitted pairs ($n = 39$) and the maternally transmitted pairs ($n = 88$). Median, mean, and mode, respectively, for AAO of subjects were as follows: fathers (top, black bars): 41.0, 42.6 ($SD = 9.9$), and 36.0; offspring of fathers (top, white bars): 23, 26.2 ($SD = 8.7$), and 17; mothers (bottom, black bars): 39, 39.6 ($SD = 8.7$), and 35; offspring of mothers (bottom, white bars): 25, 27.4 ($SD = 9.1$), and 22.

Fig. 2.

Histograms of anticipation of AAO data (median intergenerational difference in 10-year groups) for 127 parent-offspring pairs with schizophrenia. Frequency of distribution (top) and percentage of cases (bottom) for paternal (black bars) and maternal (white bars) transmission are shown.

TABLE I
Parental Sex Effects on Anticipation of AAO for Selected Autosomal-Dominant Diseases

	<u>Huntington's disease^d</u>		<u>Dentatorubralpallidoluysian atrophy^b</u>		<u>Machado-Joseph disease^b</u>		<u>Myotonic dystrophy^c</u>	
	Paternal	Maternal	Paternal	Maternal	Paternal	Maternal	Paternal	Maternal
Anticipation in years (SD)	6.73 (9.2)	1.35 (8.49)	25.6 (2.4)	14.0 (4.0)	15.4 (2.5)	6.9 (2.0)	30	27
TNR instability	Paternal > maternal		Paternal > maternal		Paternal > maternal		Paternal > maternal ^d	

^aRidley et al., 1988; Ranen et al., 1995.
^bIkeuchi et al., 1996.
^cLopez de Munain et al., 1994.
^dWith paternal transmission, instability increases but the rate of transmission decreases with increasing TNR size; transmission of congenital DM is almost exclusively maternal.

TABLE II

Parental Sex Effects on Anticipation in Schizophrenia

Median AAO (years)	Sample I: Affected parents						Sample II: unaffected parents all niece/ nephews	
	Subgroup analyses							
	All offspring		Early AAO parents (34 years)		Very early onset offspring (21 years)			
	Paternal (n = 39)	Maternal (n = 88)	Paternal (n = 7)	Maternal (n = 24)	Paternal (n = 15)	Maternal (n = 24)	Paternal (n = 37)	Maternal (n = 55)
Parental generation ^a	41	39	29	31	40 ^b	35	35	32
Offspring generation ^a	23	25	23	23.5	19	18.5	25	24
Anticipation ^c	18 [*]	14 [*]	6 ^{***}	6 ^{**}	22 [*]	17 [*]	9 [*]	7 [*]
Paternal vs. maternal difference in anticipation ^d	Z = 1.93 (<i>P</i> = 0.05)		Z = 0.50 (<i>P</i> = 0.62)		Z = 2.50 (<i>P</i> = 0.01)		Z = 0.90 (<i>P</i> = 0.37)	

^aNo significant differences found between paternal and maternal AAO for both the parental and offspring generations (Wilcoxon two-sample statistic), except as indicated in next footnote.

^bZ = 2.88 (P = 0.004).

^cMedian years of anticipation. The corresponding Wilcoxon matched-pairs sign-rank statistic, showing significance level of difference in median AAO from 0 (null hypothesis), is indicated in the next three footnotes.

^dWilcoxon two-sample Z-statistic showing significance of difference in anticipation between paternal and maternal transmission.

^{*}P = 0.0001.

^{**}P = 0.0335.

^{***}P = 0.50.