J Med Genet 1994;31:686-689

Anticipation in Swedish families with bipolar affective disorder

Per-Olof Nylander, Christer Engström, Jayanti Chotai, Jan Wahlström, Rolf Adolfsson

Abstract

Anticipation describes an inheritance pattern within a pedigree with an increase in disease severity or decrease in age at onset or both in successive generations. The phenomenon of anticipation has recently been shown to be correlated with the expansion of trinucleotide repeat sequences in different disorders. We have studied differences of age at onset and disease severity between two generations in 14 families with unilinear inheritance of bipolar affective disorder (BPAD).

There was a significant difference in age at onset ($p<0.008$), in episodes per year with ($p<0.006$) and without ($p<0.03$) lithium treatment, and in total episodes per year ($p<0.002$) between generations I and II. Furthermore, there was a highly significant correlation ($p<0.001$) in age at onset between generations I and II. No evidence for specific paternal or maternal inheritance was found.

We found evidence of anticipation and could rule out ascertainment bias or some other artefact. Anticipation is thus an inheritance pattern in BPAD which suggests that the expansion of trinucleotide repeat sequences is a possible mode of inheritance in BPAD.

(J Med Genet 1994;31:686-689)

Bipolar affective disorder (BPAD) is a severe neuropsychiatric disorder with a prevalence of about 1% in the population. Previous family,[1 2] twin,[3] and adoption studies[4] support the hypothesis that genetic transmission is a major aetiological factor in the disease. Linkage analysis has suggested gene localisation to chromosome 11 for BPAD,[5] but further studies have not been able to confirm these results and the results have been inconsistent.[6-8] The mode of inheritance of BPAD is still unknown but the recent demonstration of anticipation in BPAD opens up new possibilities for studying the genetic transmission of this disorder.[9]

Anticipation describes an inheritance pattern within a pedigree with an increase in disease severity or decrease in age at onset or both in successive generations.[10 11] In early clinical studies anticipation was suggested as an inheritance model of psychiatric disorders.[12-14] Anticipation has been found in myotonic dystrophy,[10 15] fragile X syndrome,[16] Huntington's disease,[17-20] amyloidosis,[21] and BPAD.[9] Anticipation has been shown to be directly associated with the expansion of trinucleotide repeats at the disease locus in fragile X syndrome,[22] myotonic dystrophy,[23 24] and Huntington's disease.[17-20]

In this study we have examined 13 two generation unilinear BPAD family pairs and one BPAD family affected in three successive generations, to look for evidence of anticipation. Our results are in agreement with anticipation as an inheritance pattern in pedigrees of BPAD, resulting in an increase in disease severity and a decrease in age at onset in successive generations.

Material and methods

BPAD patients were recruited from the lithium dispensaries at the Psychiatric Clinics of Umeå and Härnösand Hospitals in northern Sweden. Lithium therapy is used as a prophylaxis in BPAD patients, aiming to reduce the frequency and severity of depressive/manic episodes. Its feasibility depends on compliance from the patient. From the register we found that about 25% of these patients fulfilled the DSM-IIIR criteria of BPAD (types I and II). The patient files were checked by OPCRIT,[25] which further confirmed the diagnosis.

Information about the occurrence of psychiatric morbidity in the relatives of these patients was obtained from medical records. In the present study we included only pedigrees with unilinear inheritance of BPAD. Cases of BPAD with other diagnoses in their pedigrees such as schizophrenia, schizoaffective syndrome, unipolar major depression, or unipolar mania were excluded from the study. Altogether we found 14 pedigrees with unilinear inheritance of BPAD, one of these showing three generation inheritance. In five of these pedigrees, one parent and two children each had BPAD.

Anticipation was measured as (1) age at onset and (2) frequency of episodes with and without lithium treatment. The age at onset was defined by the first episode of either depression or mania. Episode frequency was used as a measure of disease severity and its overall value was calculated by the total number of episodes of depression and mania divided by the total number of years from age at onset to death or to the time of investigation. For each person, information was also obtained regarding the episode frequency and the length of time with or without lithium treatment, respectively. This enabled separate estimates of episode frequency either during lithium treatment or when there was no lithium treatment.

Department of Psychiatry, University of Umeå, S-901 85 Umeå, Sweden
P-O Nylander
C Engström
J Chotai
R Adolfsson

Department of Clinical Genetics, University of Umeå, Sweden
P-O Nylander

Department of Clinical Genetics, Gothenborg, Sweden
J Wahlström

Correspondence to Dr Nylander.

Received 28 September 1993
Revised version accepted for publication 19 April 1994

Table 1 Sex, year of birth, age at onset, episodes per year with and without lithium treatment, and total episodes per year in 14 families with bipolar affective disorder

Family	*Generation*	*Sex*	*Year of birth*	*Age at onset (y)*	*Episodes/year no lithium*	*Episodes/year lithium*	*Total episodes/year*
1	I	F	1932	30	0·1	–	0·1
	II	M	1952	32	1·0	1·0	1·0
	II	F	1953	21	1·3	0·5	0·8
2	I	F	1928	30	0·3	0·0	0·2
	II	F	1955	18	0·6	2·0	0·9
3	I	M	1940	25	1·5	0·5	0·7
	II	M	1974	18	1·0	–	1·0
4	I	F	1917	35	0·1	0·1	0·1
	II	M	1941	31	1·0	0·4	0·4
5	I	M	1911	52	0·4	–	0·4
	II	M	1946	37	1·3	0·7	0·9
6	I	F	1927	49	0·6	–	0·6
	II	F	1948	36	?	?	2·0
7	I	F	1926	34	0·6	0·1	0·4
	II	F	1950	14	0·6	0·2	0·4
8	I	F	1927	38	1·0	0·0	0·1
	II	F	1952	23	3·0	0·1	0·2
	II	M	1954	21	0·5	1·0	0·6
9	I	F	1901	33	0·2	–	0·2
	II	F	1935	29	0·3	0·6	0·5
	III	M	1958	23	1·0	1·4	1·3
10	I	M	1921	34	0·4	–	0·4
	II	M	1950	22	0·2	0·0	0·2
	II	M	1956	22	0·4	–	0·4
11	I	F	1892	50	0·4	–	0·4
	II	F	1913	44	0·5	0·8	0·7
12	I	M	1921	47	0·5	0·0	0·2
	II	F	1948	36	?	?	0·5
	II	M	1953	22	?	?	0·4
13	I	M	1936	20	0·4	0·0	0·3
	II	M	1973	15	2·5	–	2·5
14	I	M	1915	21	0·7	0·0	0·4
	II	M	1946	16	0·6	–	0·6
	II	F	1952	20	0·4	–	0·4

F = female, M = male, ? = unknown, – = no treatment with lithium

Table 2 Episodes per year in generations I and II with and without lithium treatment

Treatment	*Generation*	*No*	*Episodes per year*		
			Range	*Mean (SD)*	*p*
No lithium	I	15	0·1–1·5	0·50 (0·36)	
	II	17	0·2–3·0	0·95 (0·76)	<0·03
With lithium	I	9	0·0–0·6	0·14 (0·23)	
	II	12	0·0–2·0	0·72 (0·57)	<0·006
Total	I	15	0·1–0·7	0·33 (0·18)	
	II	20	0·2–2·5	0·78 (0·58)	<0·002

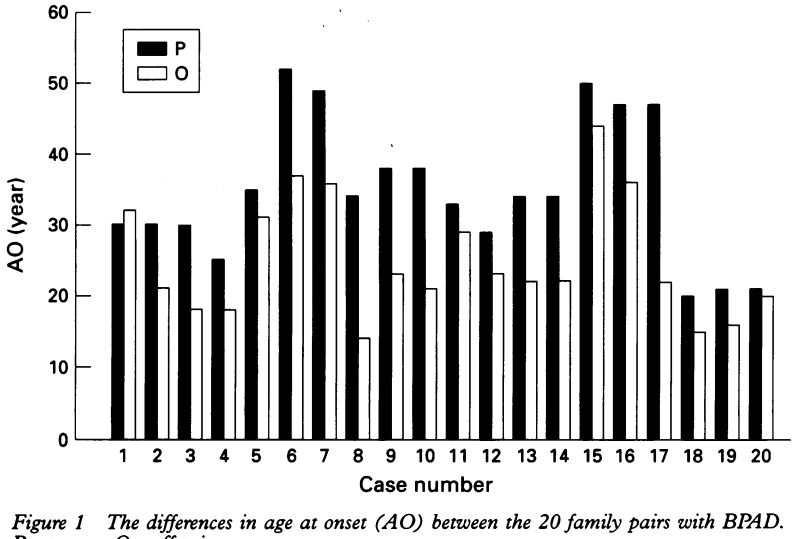

Figure 1 The differences in age at onset (AO) between the 20 family pairs with BPAD. P = parent, O = offspring.

STATISTICAL ANALYSIS

The three generation family was broken up into two generation pairs, so the person in the middle generation appeared once as a parent and once as a child. For comparing generation I and generation II, the Wilcoxon rank sum test for independent samples was used to test for statistical significance. To investigate paternal or maternal inheritance and for the correlation analyses, however, pairwise comparisons were made within parent-offspring pairs. Each of the five families with two BPAD children were treated as two parent-offspring pairs. Statistical significance was tested by the Wilcoxon rank sum test for pair observations. Correlation analyses were performed by Spearman correlation coefficients. Two tailed p values were used for all tests.

Results

The family data including sex, generation, year of birth, age at onset, total episodes per year, and episodes per year with and without lithium treatment are shown in table 1.

In generation I (n = 15) the range for birth year was 1892–1940 and for age at onset 20–52 years. The corresponding figures for generation II (n = 20) were 1913–1974 and 14–44 years, respectively. The mean age at onset was 35·1 (SD 10·3) in generation I and 25·0 (SD 8·4) in generation II. There was a significant difference ($p<0·008$) in age at onset (10·1 years) between generations I and II.

The number of episodes per year in generations I and II, with and without lithium treatment, can be seen in table 2. A significantly higher frequency ($p<0·002$) of total episodes per year was found in generation II (0·78, SD 0·58) compared with generation I (0·33, SD 0·18). There were also significant differences in episodes per year with ($p<0·006$) and without ($p<0·03$) lithium treatment between generations I and II, with the highest frequencies in generation II.

The distribution of the age at onset (AO) for the 20 parent-offspring pairs can be seen in fig 1. Anticipation (age at onset in parent minus

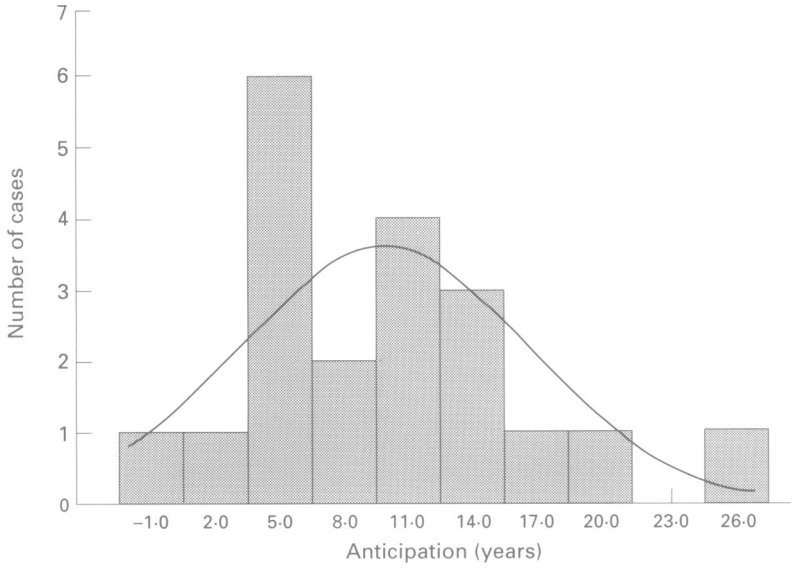

Figure 2 Distribution of anticipation (age at onset in parent minus age at onset in offspring) of 20 cases with BPAD. A normal distribution curve is plotted.

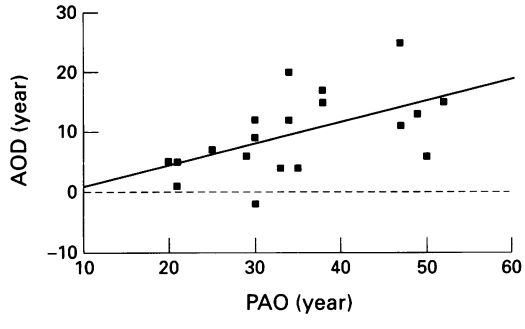

Figure 3 Regression analyses between anticipation (age at onset in parent minus age at onset in offspring, AOD) and parental age at onset (PAO).

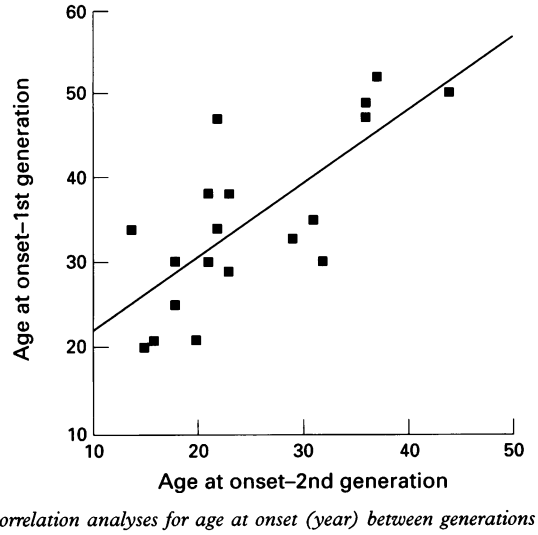

Figure 4 Correlation analyses for age at onset (year) between generations I and II.

Table 3 Paternal and maternal inheritance of bipolar affective disorder: age at onset

Generation pair	*No*	*Age at onset*			
		Range (y)	*Mean (SD)*	*Diff*	*p*
Father–offspring	9				
Father		20–52	33·4 (12·6)		
Offspring		15–37	23·1 (8·0)	10·3 (7·0)	<0·008
Mother–offspring	11				
Mother		30–50	36·0 (7·4)		
Offspring		14–44	26·5 (8·8)	9·5 (6·6)	<0·005
Father–son	7				
Father		20–52	33·3 (12·5)		
Son		15–37	21·7 (7·4)	11·6 (7·1)	<0·02
Mother–daughter	7				
Mother		30–50	37·7 (8·5)		
Daughter		14–44	26·4 (10·6)	11·3 (5·5)	<0·02

age at onset in offspring) was distributed as shown in fig 2. The plot of anticipation against parental age at onset is shown in fig 3, with the regression line showing a positive intercept.

There was a highly significant correlation ($r=0·71$, $p<0·001$) for age at onset between generations I and II, which can be seen in fig 4. There was also a significant correlation for age at onset between father and offspring ($r=0·94$, $p<0·001$). No such significant correlation was found between mother and offspring and between mother and daughter, respectively. When studying the inheritance from father to son there was a highly significant correlation ($r=0·97$, $p<0·001$, $n=7$) for age at onset between generations I and II.

Maternal and paternal inheritance can be seen in tables 3 and 4. There were significant differences in total episodes per year and age at onset between father and offspring ($p<0·05$, $p<0·008$), mother and offspring ($p<0·005$, $p<0·005$), and mother and daughter ($p<0·03$, $p<0·02$). There was also a significant difference in age at onset between father and son ($p<0·02$).

To search for a possible cohort effect contributing to the difference in age at onset within parent-offspring pairs, we calculated the correlation between the year of birth difference and the onset age difference within the pairs. We found the correlation to be non-significant ($r=0·01$, $p=0·97$, $n=20$), indicating an absence of cohort effect.

Discussion

Our results support the occurrence of anticipation in families with BPAD. We found evidence for both a decrease in age at onset and an increase in severity of the disease in successive generations.

In this study we have exclusively selected families with unilinear inheritance of BPAD in order to avoid the possibility of transmission of genetic material responsible for the disease from both parents. At present it is not possible to exclude the possibility that the BPAD could be a heterogeneous group containing more than one disorder and more than one mode of inheritance. We have also excluded pedigrees containing diagnoses such as schizophrenia, schizoaffective disorder, unipolar depression, and mania for the same reasons. This gives us a fair opportunity to study anticipation as a mode of inheritance in BPAD.

In a recent study of BPAD, the disease had 8·9–13·5 years earlier age at onset and was 1·8–3·4 times more severe in generation II compared with generation I.[9] In our study the disease had about 10 years earlier age at onset and was about twice as severe in the second generation, which is in good agreement with previous results.

Generation II showed a significantly higher ($p<0·03$) frequency of episodes per year during the period without lithium treatment. A significantly higher frequency ($p<0·006$) of episodes per year was also found during treatment with lithium. Therefore, we suggest that lithium is less protective in successive generations,

Table 4 Paternal and maternal inheritance of bipolar affective disorder: episodes per year

Generation pair	*No*	*Episodes per year*			
		Range	*Mean (SD)*	*Diff*	*p*
Father–offspring	9				
Father		0·2–0·7	0·38 (0·15)		
Offspring		0·2–2·5	0·77 (0·70)	0·39 (0·71)	<0·05
Mother–offspring	11				
Mother		0·1–0·6	0·25 (0·19)		
Offspring		0·2–2·0	0·80 (0·51)	0·55 (0·41)	<0·005
Father–son	7				
Father		0·2–0·7	0·40 (0·15)		
Son		0·2–2·5	0·86 (0·78)	0·46 (0·80)	<0·08
Mother–daughter	7				
Mother		0·1–0·6	0·29 (0·19)		
Daughter		0·2–2·0	0·79 (0·59)	0·50 (0·48)	<0·03

which is also an indication that the disease is more severe in the next generation.

Interestingly, we found a highly significant correlation ($p<0·001$) between age at onset in generation I compared to II, which further supports a genetic mode of transmission in BPAD. We also found evidence of only positive anticipation (fig 3). These results suggest the occurrence of anticipation rather than ascertainment bias or some other artefact.[26]

The phenomenon of imprinting, with preferential expression of the maternally or paternally inherited allele, is known to affect gene expression and development. In this study we found that paternal or maternal transmission of genetic material influenced the age at onset and severity of the disease in the second generation equally. However, the correlation coefficients for age at onset between father and offspring was higher than that between mother and offspring.

Sporadic cases are often found in many psychiatric diseases such as schizophrenia, schizoaffective disorder, bipolar affective disorder, unipolar depression, and mania. These cases are usually called non-familial with no obvious hereditary background in the family. If the same phenomenon with the decreasing of trinucleotide repeats between generations (as recently shown for myotonic dystrophy[27]) is occurring in BPAD, followed by an expansion, this could be an explanation for the occurrence of some of the sporadic cases.

Many pedigrees show a heterogeneous pattern with different diagnoses within the same pedigree. Lately, the question has again been raised whether schizophrenia and affective disorder are genetically associated.[28] An inheritance model with a differential expansion of trinucleotide repeats in the same locus for different persons may turn out to be an important candidate to explain the observed heterogeneity.

This study was supported by the Swedish Medical Research Council (B93-21X-10412, B94-21X-03921), Joint Committee North Health Region (Sweden), Stiftelsen Bror Gardelius Minnesfond, Stiftelsen Söderström-Königska, Swedish Doctors Society Research Fund, Swedish Society of Medical Research, and Marcus Borgström's Fund.

1 Winokur G, Tsuang M, Crowe RR. The Iowa 500: affective disorder in relatives of manic and depressed patients. *Am J Psychiatry* 1982;**139**:209–12.
2 Rice J, Reich T, Andreason NC, *et al.* The familial transmission of bipolar illness. *Arch Gen Psychiatry* 1987;**44**: 441–7.
3 Bertelsen A, Harvald B, Hauge M. A Danish twin study of manic depressive disorders. *Br J Psychiatry* 1977;**130**: 330–51.
4 Mendlewicz J, Rainer JD. Adoption study supporting genetic transmission in manic-depressive illness. *Nature* 1977;**268**: 327–9.
5 Egeland JA, Gerhard DS, Pauls DL, *et al.* Bipolar affective disorders linked to DNA-markers on chromosome 11. *Nature* 1987;**325**:783–7.
6 Baron M, Risch N, Hamburger R, *et al.* Genetic linkage between X-chromosome markers and bipolar affective illness. *Nature* 1987;**326**:289–92.
7 Kelsoe JR, Ginns EI, Egeland JA, *et al.* Reevaluation of the linkage relationship between chromosome 11p loci and the gene for bipolar affective disorder in the Old Order Amish. *Nature* 1989;**342**:238–43.
8 Mellon C. Genetic linkage studies in bipolar disorder: a review. *Psychiatr Dev* 1989;**2**:143–58.
9 McInnis MG, McMahon FJ, Chase GA, *et al.* Anticipation in bipolar affective disorder. *Am J Hum Genet* 1993;**53**: 385–90.
10 Howeler CJ, Busch HFM, Gereadts JPM, *et al.* Anticipation in myotonic dystrophy: fact or fiction? *Brain* 1989;**112**: 779–97.
11 Harper PS, Harley HG, Reardon W, Shaw DJ. Anticipation in myotonic dystrophy: new light on an old problem. *Am J Hum Genet* 1992;**51**:10–16.
12 Morel BA. *Traite des dégénérescences.* Paris: J B Baillière, 1857.
13 Mott FW. Hereditary aspects of nervous and mental diseases. *BMJ* 1910;**2**:1013–20.
14 Mott FW. A lecture on heredity and insanity. *Lancet* 1911; **1**:1251–9.
15 Fleischer B. Uber myotonische Dystrophie mit Katarakt: eine hereditäre, familiäre Degeneration. *Arch Ophthalmol* 1918;**96**:91–133.
16 Sherman SL, Jacobs PA, Morton NE, *et al.* Further segregation analysis of the fragile X syndrome with special reference to transmitting males. *Hum Genet* 1985;**69**:3289–99.
17 Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 1993;**72**:971–83.
18 Snell RG, MacMillan JC, Cheadle JP, *et al.* Relationship between trinucleotide repeat expansion and phenotypic variation in Huntington's disease. *Nature Genet* 1993;**4**: 393–7.
19 Andrew SE, Goldberg YP, Kremer B, *et al.* The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. *Nature Genet* 1993;**4**: 389–403.
20 Duyao M, Ambrose C, Myers R, *et al.* Trinucleotide repeat length instability and age of onset in Huntington's disease. *Nature Genet* 1993;**4**:387–92.
21 Drugge U, Andersson R, Chizari F, *et al.* Familial amyloidotic polyneuropathy in Sweden: a pedigree analysis. *J Med Genet* 1992;**30**:388–92.
22 Fu YH, Kuhl DP, Pizzuti A, *et al.* Variation of the CGG repeat at the fragile X site results in genetic instability: resolution of the Sherman paradox. *Cell* 1991;**67**:1047–58.
23 Fu YH, Pizzuti A, Fenwick RG, *et al.* An unstable triplet repeat in a gene related to myotonic muscular dystrophy. *Science* 1992;**255**:1256–8.
24 Mahadevan M, Tsilfidis C, Sabourin L, *et al.* Myotonic dystrophy mutation: an unstable CTG repeat in the 3′ untranslated region of the gene. *Science* 1992;**255**:1253–5.
25 Farmer AE, Wessely S, Castle D, McGuffin P. Methodological issues in using a polydiagnostic approach to define psychotic illness. *Br J Psychiatry* 1992;**161**:824–30.
26 Ridely RM, Frith CD, Crow TJ, Conneally PM. Anticipation in Huntington's disease is inherited through the male line but may originate in the female. *J Med Genet* 1988;**25**:589–95.
27 Abeliovich D, Lerer I, Pashut-Lavon I, *et al.* Negative expansion of the myotonic dystrophy unstable sequence. *Am J Hum Genet* 1993;**52**:1175–81.
28 Baron M, Gruen RS. Schizophrenia and affective disorder: are they genetically linked? *Br J Psychiatry* 1991;**159**: 267–70.