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ANTICIPATION, IMPRINTING, TRINUCLEOTIDE REPEAT EXPANSIONS AND PSYCHOSES

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Contents

Abstract

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1. Since 1991, approximately 20 trinucleotide repeat expansion type neurodegenerative disorders have been reported. They are clinically characterized by anticipation, i.e., worsening severity or earlier age at onset with each succeeding generation for an inherited disease, and imprinting, i.e., a process whereby specific genes are differentially marked during parental gametogenesis, resulting in the differential expression of these genes in the embryo and adult.
2. The phenomenon of anticipation in psychoses has been pointed out since the 19th century; however, it was ignored because no one knew the genetic mechanism underlying this type of inheritance pattern at the time, and because of several possible biases.
3. The discovery of trinucleotide repeat expansion diseases has reawakened interest in the phenomenon of anticipation in psychiatric diseases. Anticipation has been confirmed in schizophrenia, mood disorders, and anxiety disorders in much more sophisticated manners, although still not perfectly.
4. Molecular approaches as well as clinical ones have been taken to reveal the involvement of trinucleotide repeat expansion mechanism in psychoses by means of direct analyses of candidate genes, RED and DIRECT. Most efforts have been made for CAG type trinucleotide repeats. So far, direct analyses have failed to reveal pathogenic gene(s). There were several positive RED data at first, however, nowadays there seems to be a tendency of much more negative results. The DIRECT results did not support trinucleotide repeat expansions mechanism in psychoses either. One plausable explanation for the 'false positive' result is the presence of

CAG trinucleotide repeats which are highly polymorphic but not associated with an obvious abnormal phenotype. Screening for trinucleotide repeats other than ones of the CAG type remained to be performed.

Keywords: anticipation, anxiety disorder, gene, imprinting, mood disorder, schizophrenia, trinucleotide repeat expansion disease, triplet

Abbreviations: alanine (Ala), amino acid (AA), androgen receptor (ANR), asparatic acid (Asp), autosomal dominant (AD), autosomal recessive (AR), cleidocranial dysplasia (CCD), direct identification of repeat expansion and cloning technique (DIRECT), dentatorubral-pallidoluysian atrophy (DRPLA), Fragile X syndrome (FRAX), flanking region (FKR), Friedreich's ataxia (FA), glutamine (Gln), Huntington's disease (HD), inheritance (IN), multiple epiphyseal dysplasia (MED), Machado-Joseph disease (MJD), myotonic dystrophy (DM), non-Mendelian (NM), oculopharyngeal muscular dystrophy (OPMD), pseudoachondroplasia (PSACH), repeat expansion detection (RED), spinal bulbar muscular atrophy, or Kennedy's disease (SBMA), spinal cerebral ataxia (SCA), synpolydactyly (SYN), trinucleotide repeats (TNR), trinucleotide repeat disease (TRD), untranslated region (UTR), Jacobsen syndrome (JS), X-linked (X), X-linked recessive (XR).

1. Introduction

Psychiatric diseases are thought to be clinically and etiologically heterogeneous disorders. Several studies have suggested the importance of environmental factors. For instance, prenatal exposures such as infection, nutritional deficiency, immunological incompatibility may play an etiological role in schizophrenia (Susser et al., 1999). About 10% excess of persons with schizophrenia is born during winter season.

On the other hand, twin, adoption, and family studies suggested the presence of genetic factors in psychiatric diseases, although little is known about its mechanisms. Recent discovery of a new type of mutation consisting of unstable expansions of trinucleotide repeats in neurological diseases may provide a new key in the search for the genetic studies of psychiatric diseases.

2. Trinucleotide Repeat Diseases

In 1991, genetic diseases of a new type were reported in rapid succession. The fragile site of an expanded CGG repeat in FRAXA was reported by Verkerk et al. (1991) and Kremer et al. (1991), respectively. Almost at the same time, La Spada and colleagues (1991) found an expansion of the CAG repeat in SBMA. These diseases were characterized by the same mechanism for the expansion of trinucleotide repeats, termed "trinucleotide repeat disease" (TRD) mechanism in this paper. To date, approximately 20 TRDs have been reported (Table 1), and the number of TRDs should grow. Such TRDs constitute a major field in their own right for which excellent reviews exist (Caskey et al.,

1992; Paulson and Fischbeck, 1996; La Spada, 1997; Ross et al., 1998; Margolis et al., 1999).

TRDs can be classfied into several groups based on their trinucleotide repeat type and their derivative molecular as well as clinical characteristics (Paulson and Fischbeck, 1996; Margolis et al., 1999); CAG/polyglutamine type, alanine/asparagine type, and untranslated type (Table 1).

CAG/polyglutamine type TRDs except SCA 6 are caused by about 40 or more CAG repeat expansions in the coding regions of the disease genes that encode polyglutamine tracts. In contrast, SCA6 is caused by less than 30 CAG repeats of the corresponding gene (Zhuchenko et al., 1997). It is believed that the expansion of CAG/polyglutamine tracts leads to a toxic gain of function, because of the following evidence; 1) The inheritance pattern for most of this type of TRDs is dominant, 2) the disease gene is expressed in the disease state, 3) the loss of function of one CAG repeat gene in ANR leads to androgen insensitivity syndrome, which is entirely different from SBMA, and 4) a transgenic mouse model supports the gain of function hypothesis (Paulson and Fischbeck, 1996).

Second, it was found that the expansion of GCN (N = any nucleotide) and GAC trinucleotides, which encode alanine and asparagine, causes TRDs of CCD, OPMD, PSACH, MED, and SYN. The numbers of trinucleotides in normal cases and expansion are relatively small in comparison with in CAG/polyglutamine type TRDs.

The last group is characterized by much greater expansion of trinucleotide repeats localized outside the protein coding region. The expansion of the trinucleotide repeat does not seem to have an effect on the protein function but on expression of the gene. The type of trinucleotide/corresponding TRD combinations are: GAA/FA; CGG/FRAX types A, E and 16A, and Jacobsen syndrome; GCC/FRAX type F; CTG/DM and SCA 8; and CAG/SCA 12. In general, the numbers of trinucleotide repeats in the disease genes are much larger than those in the cases of CAG/polyglutamine type TRDs.

The mechanisms of PSACH and MED should be mentioned. They are both autosomal dominant skeletal dysplasias caused by heterozygosity for mutations of the cartilage oligomeric matrix protein gene. About one -third of PSACH cases result from heterozygosity for deletion of one codon in (GAC)5 [i.e., (GAC)4], which encodes five consecutive aspartic acid residues within the calmodulin-like region of the COMP protein (Hecht et al., 1995). On the other hand, Délot and colleagues (1999) identified two expansion mutations in this repeat: an MED patient carrying a (GAC)6 allele and a PSACH patient carrying a (GAC)7 allele. Thus, expansion as well as shortening of the repeat can cause the same disease.

Another type of dynamic mutation, expansion of a 12-bp polymorphic tandem repeat, was found

in the 5' flanking region of the STFB gene in a case of progressive myoclonus epilepsy Type 1 (Lafrenière et al., 1997).

These new types of nucleotide repeat diseases other than traditional TRDs were found successively.

3. Anticipation and Imprinting

Anticipation refers to worsening severity or earlier age at onset with each succeeding generation for an inherited disease (Harper et al., 1992). It has been observed in DRPLA (Naito and Oyanagi, 1982; Takahashi et al., 1988), HD (Ridley et al., 1988), DM (Höweler et al., 1989; Ashizawa et al., 1992), and SCA (Schut, 1954; Kennedy et al., 1968). Prior to the identification of the genes responsible for these illnesses, several hypotheses were proposed: epigenetic effects, gene conversion, crossingover defects, and artifacts resulting from sampling bias (Höweler et al., 1989). After the discovery of TRDs, it was pointed out that expanded repeats are unstably transmitted and the repeat length tends to increase in successive generations, and that the age at onset and clinical severity are correlated with the length of the trinucleotide repeat (Paulson and Fischbeck, 1996).

Anticipation has also been reported in which the etiological mechanism is unknown, such as autosomal dominant limb-girdle muscular dystrophy (Speer et al., 1998), Chron's disease (Bayless et al., 1998), leukemia (Horwitz et al., 1996), nodal osteoarthritis (Wright et al., 1998), Parkinson's disease (Bonifati et al., 1994), rheumatoid arthritis (McDormott et al., 1996), and truncal heart defects (Bleyl et al., 1995) other than psychiatric diseases which are described below.

Genomic imprinting, a parent of origin effect, refers to the process whereby specific genes are differentially marked during parental gametogenesis, resulting in the differential expression of these genes in the embryo and adult (Nicholls, 1994). Genomic imprinting is observed in pronuclear transplantation in mice, triploidsdy in humans, uniparental chromosomal disomies in mice and humans, chromosomal deficiencies in mice and humans in relation to specific syndromes and cancers, transgene expression in mice, and expression of specific genes in mice and humans (Hall, 1990). Genetic imprinting has also been reported in some insects and plants, but not in amphibians, reptiles, birds, or marsupials (Hall, 1990). Although much remains to be studied as to the process of genetic imprinting, it is assumed to be associated with DNA methylation, chromatin compaction, and DNA replication (Nicholls, 1994).

Table 1

Neurodegenerative Diseases Belonging to the Trinucleotide Repeat Expansion Diseases

Disease	IN	TNR	Locus	Region	Gene	Encoded AA	Product of TNRs	Normal no. of TNRs	Expanded no.of TNRs
CAG/Polyglutamine Type									
HD	AD	CAG	4p16.3	Exon	*HD*	Gln	huntingtin	6−35	36−121
DRPLA	AD	CAG	12p13.3	Exon	*DRPLA*	Gln	DRPLA	3−35	49−88
SBMA	X	CAG	Xq11-q12	Exon	*AR*	Gln	ANR	9−36	38−62
SCA1	AD	CAG	6p22-p23	Exon	*SCA1*	Gln	ataxin-1	6−38	39−83
SCA2	AD	CAG	12q24.1	Exon	*SCA2*	Gln	ataxin-2	14−31	32−77
SCA3 (MJD)	AD	CAG	14q32.1	Exon	*SCA3*	Gln	ataxin-3	12−39	56−86
SCA6	AD	CAG	19p13	Exon	*SCA6*	Gln	ataxin-6	4−19	20−30
SCA7	AD	CAG	3p12-21.1	Exon	*SCA7*	Gln	ataxin-7	7−35	38−200
Alanine/Asparagine Type									
CCD	AD	GCN	6p21	Exon	*CBFA1*	Ala	CBFA1	17	27
OPMD	AD/R	GCG	14q11	Exon	*PABP2*	Ala	PABP2	6	7−13
PSACH/ MED	AD	GAC (same as PSACH)	19p12-13.1	Exon	*COMP*	Asp	COMP	5	6−7 (expansion) 4 (contraction)
SYN	AD	GCN	2q31	Exon	*HOXD13*	Ala	HOXD13	15	22−25
Untranslated Type									
DM	AD	CTG	19q13.3	3'- UTR	*DM*	none	DMPK	5−30	50−2000+
FA	AR	GAA	9q13	Intron	*frataxin*	none	frataxin	8−22	120−1700
FRAXA	XR	CGG	Xq27.3	5'- UTR	*FMR1*	none	FMR - 1	6−54	200−2000+
FRAXE	XR	CGG	Xq28	5'- UTR	*FMR2*	none	FMR - 2	4−35	>200
FRAXF	XR	GCC	Xq28	5'- UTR	*FRAXF*	none	FRXF	6−29	>900
FRA16A	A	CGG	16p13.11	5'- UTR	*FRA16A*	none	FRA16A	16−49	>1000
JS	NM	CGG	11q23	5'- UTR	*CBL2*	none	CBL2	8−14	>100
SCA8	AD	CTG	13q21	3'- UTR	*SCA8*	none	SCA8	16−37	107−127
SCA12	AD	CAG	5q31-33	5'- UTR	*PPP2R2B*	none	PR2APR55 β	7−28	66−78

Main references: HD, Huntington's disease collaborative research group, 1993; DRPLA, Koide et al., 1994; SBMA, La Spada et al., 1991; SCA1, Banfi et al., 1994; SCA2, Imbert et al., 1996; SCA3, Ikeda et al., 1996; SCA6, Zhuchenko et al., 1997; SCA7, David et al., 1997; CCD, Mundlos et al., 1997; PSACH/MED, Hecht et al., 1995; Délot et al., 1999; OPMD, Brais et al., 1998; SYN, Muragaki et al., 1996; DM, Brook et al., 1992; FA, Campuzano et al., 1996; FRAXA, Verkerk et al., 1991; FRAXE, Knight et al., 1993; FRAXF, Parrish et al., 1994; FRA16A, Nancarrow et al., 1994; JS, Jones et al., 1995; SCA8, Koob et al., 1999; SCA12, Seltzer et al., 1999.

This phenomenon of genetic imprinting is also seen in TRDs. Instability of CAG type trinucleotide repeats occurs more frequently and strongly upon transmission from a male than from a female, with a clear tendency towards an increased size. On the other hand, some untranslated type TRDs including FRAX, FA, and DM are dominant on maternal transmission (Paulson and Fischbeck, 1996).

4. Anticipation and Imprinting in Psychoses

The phenomenon of anticipation in psychoses was first reported by Morel (1857), and subsequently by Mott (1910; 1911) and Lombroso (1911). At that time, as no one knew the genetic mechanism underlying this type of inheritance pattern, the idea was ignored due to several possible biases (Penrose, 1945; 1948; 1971).

The discovery of trinucleotide repeat expansion diseases has reawakened interest in the phenomenon of anticipation in psychiatric diseases; mood disorders (Denica et al., 1991; McInnis et al., 1993; Nylander et al., 1994; Engström et al., 1995; Grigoroiu-Serbanescu et al., 1997; Ohara et al., 1998), schizophrenia (Denica et al., 1991; Bassett and Honer, 1994; Chotai et al., 1995; Thibaut et al., 1995; Stöber et al., 1995; Gorwood et al., 1996; Bassett and Husted, 1997; Johnson et al., 1997; Ohara et al., 1997c; Imamura et al., 1998; Valero et al., 1998; Borrmann-Hassenbach et al., 1999; Heiden et al., 1999; McInnis et al., 1999b; Mérette et al., 2000), and anxiety disorders (Battaglia et al., 1998; Ohara et al., 1999) (Tables 2 and 3).

The mean age of onset in the parental generation is approximately 40 years, while that in the offspring generation is about 25 years, irrespective of the kind of psychiatric disease. Thus, the difference in the age of onset between two generations is about 15 years. The results as to anticipation of severity in schizophrenia have been contradictory: some studies provided evidence of an increase in the severity of psychosis and/or in the rate of hospitalization for the disease (Bassett and Honer, 1994; Bassett and Husted, 1997, Heiden et al., 1999), whereas others did not (Johnson et al., 1997; Ohara et al., 1997c; Mérette et al., 2000). On the other hand, several studies revealed an increase in the episode frequency over successive generations in mood disorders (McInnis et al., 1993; Nylander et al., 1994; Engström et al., 1995). Mérette and colleagues (2000) reported that the evidence of anticipation with the five severity indices in schizophrenia and bipolar disorders vanished after control of the quality and quantity of clinical information.

Another phenomenon of imprinting in psychiatric diseases is less clear in comparison with anticipation, but has also been reported in mood disorders (McMahon et al., 1995; Grigoroiu-Serbanescu et al., 1995, 1997), and schizophrenia (Ohara et al., 1997c; Husted et al., 1998). Maternal imprinting expressed through a higher morbidity risk for bipolar disorders in relatives of bipolar mothers was reported by McMahon and colleagues (1995), while paternal imprinting as to the age at onset of bipolar disorders was reported by Grigoroiu-Serbanescu et al. (1995, 1997). Husted et al. (1998) showed that age at onset anticipation was greater with paternal than with maternal transmission in a sample of 127 parent-offspring pairs with schizophrenia. We found that the negative symptom scores and clinical course scores in the offspring generation for

paternal transmission were significantly higher than those for maternal transmission. In addition, the mean doses of antipsychotic drugs administer to the patients tended to be higher for paternal transmission than those for maternal transmission (Ohara, et al., 1997c). Stöber and associates (1998a) reported in periodic catatonia that paternal transmission was associated with a trend for a younger age at onset in probands compared to that observed in the case of maternal transmission. In addition, paternal affection did lead to a decrease in male offspring and maternal affection caused an increased frequency of non-affected male offspring. On the other hand, Valero et al. (1998) found nonsignificant differences in age at onset between the offspring of affected mothers and the offspring of affected fathers in 25 families with schizophrenia.

Table 2

Anticipation and Imprinting in Families with Mood Disorders and Anxiety Disorders

Authors	Family Number	Age of Onset [Mean (SD) Years] Parental Generation	Offspring Generation	Anticipation of Severity	Imprinting
Mood disorders					
Bipolar disorder					
Denica et al. (1991)	12	37.2 (15.5)	20.2 (8.5)		
McInnis et al. (1993)	34	30	18	+	
Nylander et al. (1994)	14	35.1 (10.3)	25.0 (8.4)	+	−
Grigoroiu-Serbanescu et al. (1995)	115	28.5−29.3	21.3−23.2		+
Mérette et al. (2000)@	4−48	26.6−34.1	25.3−26.6	−	
Unipolar disorder					
Engstöm et al. (1995)	31	48.9 (15.6)	33.3 (9.81)	+	−
Both					
Ohara et al. (1998)	26	48.8 (11.0)	29.5 (11.8)		−
Anxiety disorders					
Ohara et al. (1999)	17	44.3 (12.2)	23.8 (12.2)		
Panic disorder					
Battaglia et al. (1998)	38	37.4 (11.9)	23.3 (7.9)		

@, three generations were analyzed.

Table 3

Anticipation and Imprinting in Families with Schizophrenia

Authors	Family Number	Age of Onset (Mean [SD] Years) Parental Generation	Offspring Generation	Anticipation of Severity	Imprinting
Denica et al. (1991)	7	30.9 (10.8)	18.4 (19.7)		
Bassett and Honer (1994)	8	34.0 (17.3)	26.2 (8.28)	+	
Chotai et al. (1995)	19	37.3 (6.0)	20.8 (4.4)		
Thibaut et al. (1995)	26	37.5	21.5		−
Stöber et al. (1995)	29	43.6 (15.1)	25.1 (10.6)		−
Gorwood et al. (1996) Yaw et al. (1996)	24	32.3 (9.13)	21.8 (4.66)		−
Bassett and Husted (1997)	248	35 - 40	25	+	
Johnson et al. (1997)	33	*	*	−	
Ohara et al. (1997c)	24	35.3 (11.5)	21.4 (6.14)	−	+
Husted et al. (1998)	127	39−41	23−25		+
Imamura et al. (1998)	44	33.4	20.8		−
Valero et al. (1998)	24	31.6 (6.01)	19.8 (2.79)		−
Borrmann-Hassenbach et al. (1999)#	122	25−34	19−21.5		
Heiden et al. (1999)	15	40.2 (9.2)	21.6 (6.6)	+	
McInnis et al. (1999b)	101	18−30	16−20		
Mérette et al. (2000)@	11−39	24.1−32.7	18.8−24.1	−	

*, three indices of age of onset were used, and anticipation was demonstrated.
#, the positive anticipation findings were compensated for after controlling for age at investigation bias.
@, three generations were analyzed.

5. Ascertainment Biases for Anticipation

While several studies have suggested the occurrence of anticipation in psychiatric diseases, there still remains the question of whether the evidence of anticipation is due to the trinucleotide repeat mechanism or biases. Several probable biases for 'false anticipation' have been proposed, and attempts have been made to overcome them by several investigators, as follows.

It is preferrable to select parents with late age of onset, since an earlier onset would result in reduced fertility, and thus would cause false anticipation. Yaw and co-workers (1996) studied anticipation in multiplex schizophrenia pedigrees, analyzing two subgroups of parent-child pairs subdivided on the basis of early-onset parents and late-onset parents. Analysis of the late-onset parent group showed significant age at onset differences between the two generations, whereas analysis of the early-onset parent group did not reveal significant intergenerational differences in age at onset. Johnson et al. (1997) analyzed anticipation in schizophrenia in random pairs, one randomly

affected member of the older generation being paired with one randomly selected member of the younger generation. This scheme included childless members of the older generation, addressing the bias that arises when severely ill members of the older generation do not produce children. The results support age of onset anticipation in random pairs.

Preferential selection of offspring with earlier onset or greater severity of the disease should be preferred, since symptoms in the offspring of affected parents are more likely to be detected earlier; and they are younger at the time of observation. This was addressed in the study of Johnson and colleagues (1997) through separate analysis of intergenerational differences in disease onset in older- and younger-ascertained pedigrees, and through an expanded Cox proportional hazards model that took into account the generation of ascertainment as a predictor variable.

Parent-offspring pairs consisting of a parent with early age at onset and a child with late age at onset would be unlikely to be ascertained, since most studies can only obtain reliable information for a limited period of time. Subjects in the families who showed age of onset anticipation, the mean age at the time of the investigation for the offspring generation was higher than the mean age of onset for the parental generation, which may provide some support for the presence of 'real' anticipation in the families studied. Several studies showed evidence of this in their papers of figures of 'parental age of onset and differential age of onset' (Thibaut et al., 1995; Stöber et al., 1995; Ohara et al., 1997c; Ohara et al., 1999). Battaglia et al. (1998) showed in panic disorder families that 70% of the offspring of the early-onset parents had an earlier onset than that of their affected parent.

Petronis and Kennedy (1995) assumed that indirect transmission in the two generations, i.e., the generation of the probands and their siblings, and that of their parents, and their uncles and aunts, might be considered as controls that are independent of the above three ascertainment biases. They suggested that if there are no real intrageneration similarities or intergeneration differences in affected families, there may be great variability in the age at onset and severity in the group of probands plus their affected siblings and in that of parents plus their affected siblings. Bassett and Husted (1997) reanalyzed the familial mental illness sample which Penrose analyzed in 1944, finding that aunt/uncle-niece/nephew schizophrenia pairs showed age at onset anticipation ($n = 111$; $p = 0.0001$) with a median intergenerational difference (MID) of 8 years, as well as significant anticipation in parent-offspring pairs ($n = 137$, $p = 0.0001$, MID = 15 years). Grigoroiu-Serbanescu et al. (1997) studied 115 bipolar I patients and their first- to third-degree relatives, and showed that the mean age of onset was very similar in probands and their siblings (22.8 yr. vs. 22.1 yr.), and in the probands' parents, and uncles and aunts (28.5 yr. vs. 29.1 yr.). We studied age of onset

anticipation in families with anxiety disorders, and found that there was no difference in the age of onset between direct families (n = 10) and indirect families (n = 7) [mean (S.D.) of 21.0 (19.1) vs. 19.7 (10.0)] (Ohara et al., 1999).

The different ages at interview of parents and children may be a possible bias in studies of anticipation. Heiman and associates (1996) investigated this age-at-interview bias because parents have passed through more of the risk period than their offspring. They found that the timing of diagnostic assessment can strongly affect the ascertainment of parent-child pairs, a severely biased sample exhibiting apparent anticipation being possible. Borrmann-Hassenbach et al. (1999) studied the age at onset in 96 schizophrenic parent-offspring pairs and 26 aunt/uncle-niece/nephew pairs. They showed that age at onset differences in the parent-offspring sample were in favor of anticipation (12.5 years, $p < 0.0001$), whereas these positive anticipation findings were compensated for (1.32 years, $p = 0.129$) by controlling age-at-interview. Additional selection procedures such as the exclusion of late-onset schizophrenia, the analysis of pairs where both members were beyond the age of risk, or the selection of aunt/uncle-niece/nephew pairs could not overcome the age-at-interview effect. They concluded that the age-at-interview effect is an essential bias in investigating anticipation. leading to false-positive age at onset anticipation results. However, Gorwood and colleagues (1996) used a method involving calculaton of the expected age at onset according to the age at interview, comparing the younger generation subjects' expected ages at interview with the observed ages at interview, as the average of all the ages at onset in the older generation that are below the subjects' age at interviews. They showed that the observed age at onset in the younger generation of patients was earlier than the expected age at onset, demonstrating anticipation.

The bias of the so-called regression to the mean was proposed by Asherson et al. (1994). They found a simple linear relationship between anticipation and age at onset in the parental generation, with a line of best fit very close to the one expected under the assumption that age at onset in offspring was normally distributed around the mean. However, several researchers showed it is a distinct phenomenon from anticipation (Petronis et al., 1994; Hodge and Wickramarante, 1995).

The age cohort effect could also affect the age of onset of the disease. There is a tendency for an illness to show a progressively earlier age at onset in successive birth cohorts, and this has been consistently shown for mood disorders in people born after 1945, but not for panic disorders (Klerman and Weissman, 1989; Burke et al., 1991). Engström and associates (1995) tested the birth cohort effect in unipolar affective disorder by calculating the correlation between the birth-year

difference and the onset-age difference within pairs, finding the correlation to be nonsignificant. They also used the Cox proportional hazards model to analyze the relationship between generation membership and onset age while controlling the birth cohort effect. They divided individuals into two birth cohorts, i.e. those born before 1925, and those born in 1925 and after. They found nonsignificant regression coefficients for generation membership and birth cohort (Engström et al. 1995).

Vieland and Huang (1998) proposed taking into account the right truncation of the age at onset distribution of each generation when studying anticipation. This right truncation of the age at onset distribution would be more pronounced in children than in their parents, and would produce a tendency for the mean observed age at onset in the children to be lower than the mean in their parents. They thought the power of any age of onset anticipation test may be low when the underlying biological mechanism is an expanding trinucleotide repeat.

Potential subjects in the late-onset parental generation would be more likely to die young and thus less likely to be investigated. Late-onset parents may be differentially lost from a sample when the contact between parents and offspring is lost due to illegitimacy or family breakdown. Battaglia and colleagues (1998) showed anticipation in panic disorder, after including dead members of the older generation who were likely to have had the disease with a mean age at onset corresponding to that of the proband generation, on the basis of family histories derived from multiple information.

While these biases may not be surmountable, they would best be minimized by studies of large, multigenerational and systematically ascertained pedigrees (Thibaut et al., 1995; Gorwood et al., 1996). Therefore, evidence of 'true anticipation' will remain equivocal until the molecular mechanism is revealed clearly.

6. Screening of ExpandedTrinucleotide Repeats in Psychoses

Parallel with clinical studies on the phenomena of anticipation and imprinting in psychiatric diseases, molecular research on trinucleotide repeats has been performed. So far, most efforts have been focused on CAG/polyglutamine type trinucleotide repeats.

In 1993, Schalling and colleagues developed a technique, RED, that can detect trinucleotide repeat expansion without prior knowledge of the chromosomal location. Several studies, showed by means of RED, that the median length of CAG repeats was longer in probands with psychoses than

in healthy control subjects in schizophrenia (Morris et al., 1995; O'Donovan et al., 1995; 1996; Burgess et al., 1998) and mood disorders (Lindblad et al., 1995, 1998; O'Donovan et al., 1995; 1996; Mendlewicz et al., 1997; Oruc et al., 1997). However, it should be mentioned that most subjects studied were sporadic and not from families showing anticipation, and a correlation between age of onset anticipation and the CAG repeat size was not shown. Besides, the RED method does not detect the alleles of CAG repeats at specific loci but indicates the allele size distributions at various loci in the genome. In addition, several subsequent studies failed to replicate their findings in familial and/or sporadic cases, which suggests that the occurrence of unstable DNA in psychoses may be less prevalent than previously reported in schizophrenia (Petronis et al., 1996; Vincent et al., 1996, 1998, 1999b; Laurent et al., 1998; Li et al., 1998b; Martorell et al., 1999) and mood disorders (Vincent et al., 1996, 1999b; Craddock et al., 1997; Li et al., 1998b; Zander et al., 1998).

Direct analyses of the specific candidate trinucleotide gene loci for psychoses have not been successful and/or the results are contradictory for mood disorders (Guy et al., 1997; Speight et al., 1997; Chandy et al., 1998; Hawi et al., 1999a, 1999b; McInnis et al., 1999a) and schizophrenia (e. g., Lesch et al., 1994; Rubinsztein et al., 1994; St. Clair, 1994; Bowen et al., 1996; Sasaki et al., 1996; Ohara et al., 1997a, 1997b; Speight et al., 1997; Bengel et al., 1998; Bowen et al., 1998; Chandy et al., 1998; Li et al., 1998a; Stöber et al., 1998b; Bonnet-Brilhault et al., 1999; Breen et al., 1999; Hawi et al., 1999a, 1999b; Joo et al., 1999).

Several groups searched for expanded glutamine repeats by means of antibodies in psychoses, although the results are inconsistent. Jones and co-workers (1997) examined Western blots prepared from lymphoblastoid cell lines and left frontal cortex tissue samples from patients with schizophrenia and bipolar disorder using a monoclonal antibody (mab1c2) against expanded polyglutamine sequences. They failed to detect any proteins containing expanded polyglutamine sequences. Schürhoff et al. (1997) also failed to detect a specific protein exhibiting polyglutamine expansion in 3 schizophrenics and 4 bipolar disorder probands using the same antibody. On the other hand, Joober et al. (1999) studied total protein extracts derived from lymphoblastoid cell lines of schizophrenic patients with the same antibody, and found three abnormal proteins with molecular weights of approximately 50 kDa in two unrelated schizophrenics and in a sibling. Moriniere et al. (1999) identified an approximately 52-57 kDa protein in lymphoblasted cell lines from some child onset schizophrenics with the mab1c2 antibody.

Another new method, DIRECT, which allows the identification and cloning of gene fragments with expanded CAG repeats, was recently developed (Sanpei et al., 1996). With the DIRECT

method, strong signals for CAG repeats consisting of 43 or more repeat units could be detected, while only a faint signal was obtained for a CAG repeat consisting of 23 repeat units (Sanpei et al., 1996). We screened for a possible expanded CAG repeat by means of DIRECT in subjects with 23 subjects (affected, 14; unaffected, 9) from four two-generation families and two three-generation families with schizophrenia which showed age of onset anticipation (Ohara et al., 2000). However, no unusual expanded CAG/CTG trinucleotide repeat was detected in the subjects with familial schizophrenia.

Several CAG/CTG trinucleotide repeat clones have been isolated, which are highly polymorphic but not associated with an obvious abnormal phenotype. Breschel et al. (1997) reported a heritable expanding CTG repeat in SEF2-1, a gene encoding a transcriptional factor protein on chromosome 18q21.1, and termed it CTG18.1. The association of CTG18.1 with various neurodegenerative diseases has not been reported. On the other hand, another novel long and unstable CAG/CTG trinucleotide repeat (Dir1) mapped to chromosomal region 17q 21.3 was cloned by means of the DIRECT technique (Ikeuchi et al., 1998). The CAG/CTG repeat of Dir1 is highly polymorphic and ranges in size from 10 to 92 trinucleotide repeats in normal individuals. The nt 901 to 1410 of Dir1 are essentially identical to the 720-bp sequence of ERDA1 containing a CAG/CTG repeat, which was reported by Nakamoto et al. (1997), except for the sequence from nt 1085 to 1088 of Dir1, in which Ikeuchi et al. (1998) detected four consecutive adenines, whereas Nakamoto et al. (1997) found only three adenines. Sidransky and colleagues (1998) reported that up to 94% of the trinucleotide repeat expansion detected with RED can be accounted for by PCR analysis of two loci, Dir 1 and CTG18.1. Dir1 has also been studied in subjects with familial schizophrenia, but no significant difference between the affected and unaffected subjects in the allele frequency of Dir1 was found (Ohara et al., 2000). Lindblad and colleagues (1998) suggested that the expanded alleles at the CTG18.1 locus may act as a vulnerability factor for affective disorders, while the ERDA1 locus seems unrelated to a disease. Verheyen and co-workers (1999) demonstrated that 86% of the RED expansions in bipolar disorder could be accounted for by the ERDA1 and CTG18.1 CAG/CTG repeats. Burgess et al. (1998) found that there was a significant association of CAG/CTG expansions although their sample size was small (male patients = 16, male controls = 24). Vincent et al. (1999a) reported significant expansion of CAG/CTG repeats of ERDA1 from one generation to the next in a family demonstrating evidence of anticipation for psychiatric disorders. In this family, a proband was diagnosed as having multiple psychiatric diagnoses, the mother as having schizoaffective disorder, and father as having depression. The meaning of ERDA1 and CTG18.1 in psychiatric diseases should be studied further and more precisely.

7. Conclusions

Since the discovery of TRDs in 1991, many efforts have been made to reveal the association between trinucleotide repeat expansion and psychiatric diseases. The evidence of anticipation in psychoses has been supported by many studies, and the evidence of imprinting by some studies even after removal of possible biases. Molecular studies on CAG type trinucleotide repeats in psychoses involving RED, direct analyses of candidate genes, and DIRECT seem to have negative results. However, as psychoses are very heterogeneous, it is still possible that some families with psychoses are caused by the trinucleotide repeat expansion mechanism. It should also be noted that since very little expansion of CAG repeats (20-30 repeats) in SCA6 could be the pathogenesis, we cannot rule out the possibility that small expansions of CAG repeats are involved in psychiatric diseases. Alternatively, a repeat may act through translation in a form other than CAG/CTG type. Even after taking everything into consideration, I cannot reach a clear conclusion as to the association between psychoses and trinucleotide repeats.

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