



## Assessment of parent-of-origin effect in families unilineally affected with panic disorder-agoraphobia

M. Battaglia<sup>a,b,\*</sup>, S. Bertella<sup>b</sup>, S. Bajo<sup>b</sup>, F. Binaghi<sup>b</sup>, A. Ogliari<sup>b</sup>, L. Bellodi<sup>b</sup>

<sup>a</sup>H. San Raffaele Scientific Institute, Department of Neuropsychiatric Sciences, 29 via Prinetti, 20127 Milan, Italy

<sup>b</sup>Department of Psychology, University 'Vita-Salute San Raffaele', Milan, Italy

Received 7 January 1998; revised 18 March 1998; accepted 1 September 1998

While the mode of transmission of psychiatric disorders remains elusive, new paradigms to investigate the genetics of mental illnesses (Petronis & Kennedy, 1995) are suggested by the recent findings reported by some, but not all, studies of bipolar illness and schizophrenia (McMahon et al., 1995; Petronis & Kennedy, 1995) of trinucleotide repeat (TNR) amplifications (i.e., genetic mutations where quantitative changes in phenotype correspond to the size of the expansion of one group of simple trinucleotides repeats), the related phenomena of anticipation (i.e., the decrease of age at onset or the increase in severity in successive generations) and parent-of-origin effect (i.e., differential expression of diseases alleles, depending on whether the genetic material has come from the mother or the father).

Our recent finding of anticipation of age at onset of first panic attack and of panic disorder-agoraphobia (PDA) (Battaglia et al., 1998) led us to assess the possible presence of a parent-of-origin effect in the same set of pedigrees.

This investigation is based on a family study of thirty-eight unilineal multigenerational families with multiple subjects with PDA, taken from a study group of 551 consecutive outpatients. This was an extension of a previous study group with the original recruitment and methods unchanged (Battaglia et al., 1995; Battaglia et al., 1998).

Direct interviews with 65% of all living first- and second-degree relatives ( $n = 323$ ) were obtained, and 72% of all affected relatives were directly interviewed, while family histories from multiple informants were obtained for the remaining subjects ( $n = 174$ ).

In addition to the transmission of disease-related trinucleotide repeats from a parent to his/her offspring (Paulson & Fischbeck, 1996), an observed parent-of-origin effect can derive from mitochondrial inheritance (Hall et al., 1990) and genomic imprinting (Skuse et al., 1997).

Transmitting parents were defined (McMahon et al., 1995) as those with affected offspring who were themselves affected, or had an affected sibling or parent on the basis of direct interview assessment.

The indices were (a) the frequency of affected- and transmitting mothers versus fathers, (b) the morbidity risk (MR) for PD/PDA/SA for the offspring of affected- and transmitting mothers vs fathers, (c) the MR in the maternal vs paternal relatives of probands. The MR rates were age-corrected by a computer program based on Cox's model (Battaglia et al., 1995).

For comparisons based on affected parent's sex, siblings in which an affected parent could not be identified by direct interview were excluded. Pedigrees contained 131 siblings, a transmitting parent was identified for 47 siblings, and an affected parent for 30 siblings.

Since index probands and their siblings cannot be classified as 'maternal' or 'paternal' (McMahon et al., 1995), they were excluded from comparisons of maternal vs paternal relatives.

Since PDA is more common in women, we first controlled for possible excess of female sex among offspring at risk for PDA which might mimic parent-of-origin effect. Sex distributions were similar among offspring of affected mothers vs affected fathers (women 31/58 vs 18/32,  $\chi^2 = 0.65$ ,  $df = 1$ ,  $P = \text{NS}$ , respectively), among offspring of transmitting mothers vs transmitting fathers (women 44/72 vs 19/38,  $\chi^2 = 1.25$ ,  $df = 1$ ,  $\text{NS}$ , respectively), and maternal vs paternal relatives of probands (women 68/116 vs 34/55,  $\chi^2 = 0.16$ ,  $df = 1$ ,  $P = \text{NS}$ , respectively).

The frequency of affected mothers vs fathers was 20 vs 12, reflecting the 2:1 sex ratio usually described for PD; the same proportion was maintained for transmitting mothers to transmitting fathers: 32 and 15.

After dividing offspring in all family-transmitting pairs into two subgroups, one with affected fathers ( $n = 12$ ), the other with affected mothers ( $n = 27$ ), no significant difference in the anticipation of age at onset of PD effect was found (Mann-Whitney  $U = 140.5$ ,  $P = 0.50$ ).

\* Corresponding author. Tel.: +39-2-2643-3315; fax: +39-2-2643-3265; e-mail: marco.battaglia@hsr.it.

Table 1

Age-corrected morbidity risks (MR) for Panic Disorder-Agoraphobia of maternal vs paternal relatives in thirty-eight pedigrees multiply affected with Panic Disorder

	Maternal line		Paternal line		z	p
	Number affected/ number affected + number at risk	MR	Number affected/ number affected + number at risk	MR		
Offspring of affected parents	35/53.8	0.649	18/27.04	0.665	0.10	0.92
Offspring of transmitting parents	36/65.09	0.553	21/31.01	0.677	0.93	0.35
Relatives of probands	37/121.89	0.304	19/47.70	0.398	1.1	0.31

Comparisons by test for the difference between two proportions, two tailed.  
Index probands and their siblings were excluded from analyses.

Table 1 shows the results of the other comparisons: all differences are nonsignificant. When analyses were repeated after the exclusion of subjects with SA, or for PD/PDA alone, all differences remained nonsignificant.

No suggestion of parent-of-origin effect (including possible mitochondrial inheritance, since several examples of transmitting fathers were observed) was found through different comparison schemes applied to 38 unilineal pedigrees multiply affected with PD/PDA.

This points to the issue of whether the absence of a clear parent-of-origin effect on familial risks would, or would not, strongly argue against genuine anticipation in PD/PDA, since the presence of parent-of-origin effect is thought to be important to corroborate a finding of anticipation (Ridley et al., 1991).

While the large majority of known unstable DNA diseases consistently show the TNR-anticipation-parent-of-origin effect phenomena (Paulson & Fischbeck, 1996), some noteworthy exceptions are becoming available and suggest greater complexity than previously thought. For instance, spinocerebellar ataxia type 2 is very likely to be a TNR disease (Petronis & Kennedy, 1995) in which anticipation, but no parent-of-origin effect, has been reported (Pulst et al., 1993). In bipolar disorder and schizophrenia evidence both in favour of and against, anticipation and parent-of-origin effect have been reported (Petronis & Kennedy, 1995), with some groups admitting anticipation even without evidence of parent-of-origin effect (Petronis et al., 1995).

It should also be remembered that the specific type of parent-of-origin effect named genomic imprinting is a crucial mechanism only with mendelian anticipating disorders (Hall, 1990; Petronis et al., 1995). With complex polygenic disorders several genes are thought to be involved in the transmission of the liability to a disease: if a proportion of these genes have a maternal imprinting, and another proportion a paternal imprinting, the detection of an imprinting effect becomes exposed to both false-negative and false-positive results, or even be mis-

leading, while the anticipation effect would still operate (Petronis et al., 1995).

With negative results, an important issue is that of the power of analysis, and one may wonder to what extent this sample size may be responsible for these findings.

While the TNR paradigm is interesting and is gaining better definition as more exceptions to its rules come to our knowledge, the neuropsychiatric disorders remain complex domains in which the intrinsic heuristic value of anticipation needs to be evaluated and absence of parent-of-origin effect needs prudent consideration.

#### Acknowledgments

The authors are grateful to Drs Arturas Petronis and Andrew Paterson of the Clarke Institute of Toronto for a useful discussion of some of the ideas in this article.

#### References

- Battaglia M, Bertella S, Bajo S, Binaghi F, Bellodi L. Anticipation of age at onset in panic disorder. *American Journal of Psychiatry* 1998;155:590–5.
- Battaglia M, Bertella S, Politi E, Bernardeschi L, Perna G, Gabriele A, Bellodi L. Age at onset of panic disorder: influence of familial liability to the disease and of childhood separation anxiety disorder. *American Journal of Psychiatry* 1995;152:1362–4.
- Hall JG. Genomic imprinting: review and relevance to human diseases. *American Journal of Human Genetics* 1990;46:857–73.
- McMahon FJ, Stine OC, Meyers DA, Simpson SG, DePaulo JR. Patterns of maternal transmission in bipolar affective disorder. *American Journal of Human Genetics* 1995;56:1277–86.
- Paulson HL, Fischbeck KH. Trinucleotide repeats in neurogenetic disorders. *Annual Review of Neuroscience* 1996;19:79–107.
- Petronis A, Sherrington RP, Paterson AD, Kennedy JL. Genetic anticipation in schizophrenia: pro and con. *Clinical Neuroscience* 1995;3:76–90.
- Petronis A., Kennedy JL. Unstable gene-unstable mind ? *American Journal of Psychiatry* 1995;152:164–72.

متن کامل مقاله

دریافت فوری ←

**ISI**Articles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات