Letters to the Editor

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Monoamine Oxidase A Gene and Bipolar Affective Disorder

To the Editor:

In the June 1993 issue of the *Journal,* Brunner et al. (1993*b*) reported evidence for disturbed monoamine metabolism and an X-linked borderline mental retardation with prominent behavioral disturbance in a Dutch kindred. They subsequently found a point mutation in the eighth exon of the monoamine oxidase A (MAOA) structural gene (Brunner et al. 1993*a*). This finding of an association between abnormal behavior and the mutation in the MAOA gene may be of wider relevance.

All affected males in the pedigree exhibited borderline IQ and such behavioral problems as aggression, attempted rape, arson, exhibitionism, and voyeurism. Although there was no specific mention of the prevailing mental state that accompanied these behavioral changes, the authors reported that "aggressive behavior was usually triggered by anger and was often out of proportion to the provocation" and that the "aggressive behavior tended to cluster in periods of 1–3 d, during which the affected male would sleep very little and would experience frequent night terrors" (Brunner et al. 1993*b,* p. 1035). These descriptions are similar to symptoms exhibited by bipolar patients during the manic phase of their illness. According to DSM-III-R diagnostic criteria (American Psychiatric Association 1987), a manic syndrome must have (1) a distinct period of abnormally and persistently elevated, expansive, or irritable mood; (2) during the period of mood disturbance, at least three of the seven symptoms (grandiosity, decreased need for sleep, more talkative than usual, subjective experience that thoughts are racing, distractibility, psychomotor agitation, and excessive involvement in pleasurable activities that have a high potential for painful consequences, such as sexual indiscretions); and (3) mood disturbances sufficiently severe to cause marked impairment in occupational functioning or social activities or relationships with others or to necessitate hospitalization to prevent harm to self or others.

The concept of an X-linked subgroup of bipolar disorder is not new, although its existence remains controversial (Hebebrand 1992). In bipolar disorder, linkage analysis of such X-linked markers as Xg, color blindness, and factor IX has produced inconsistent results (Risch et al. 1986; Gershon 1991). Association to a pseudoautosomal marker DXYS20 (Yoneda et al. 1992) has also not been replicated (Nöthen et al. 1993).

However, abnormal levels of MAO activity have been reported in affective disorders (Samson et al. 1985; von Knorring et al., 1985). Indeed, the MAOA gene is a strong candidate locus for this neuropsychiatric disorder. We therefore hypothesized that either the point mutation reported by Brunner et al. (1993*a*) or other MAOA mutations might contribute to bipolar affective disorder. To test this hypothesis, we carried out an association study using the same microsatellite repeat polymorphism (Black et al. 1991) as was used in the Brunner et al. (1993*b*) study. Allelic association may be demonstrated when either the polymorphism itself or another mutation in linkage disequilibrium with the

Table 1

Distribution of Alleles at MAOA Locus

Allele	Frequency	
	Cases (N=98)	Controls (N=99)
a_0	3	8
a_1	0	3
a_2	10	21[a]
a_3	0	3
a_4	4	0
a_5	18	9[b]
a_6	57	50
a_7	6	2
a_8	0	3

NOTE.—Overall χ^2 = 24.63; df = 8; P = .0018 (exact P-value < .0019) (nine alleles, critical P value = .0057).

[a] χ^2 = 4.50; df = 1; P = .0339.

[b] χ^2 = 3.58; df = 1; P = .0584.

polymorphism affects gene function and thereby contributes to the bipolar-affective-disorder phenotype.

We genotyped a sample of 57 unrelated bipolar patients and 59 matched normal controls of western European extraction. The patients were diagnosed using the Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS-L) (Endicott and Spitzer 1978) and satisfied the research diagnostic criteria (Spitzer et al. 1978) for bipolar affective disorder. The alleles were undetermined in one male case and one female control; therefore these individuals were excluded from the analysis. The total numbers of alleles in cases and controls were 98 (14 males and 42 females) and 99 (17 males and 41 females), respectively.

Analysis of the data showed a statistically significant overall association between the disorder and alleles of the MAOA locus. The contingency table is so sparse that the usual χ^2 distribution with 8 df may not yield accurate P values. Therefore, we used StatXact Version 3 (1993) and carried out an exact analysis. The exact P value is <.0019.

We then tested for association with individual alleles by counting the total number of each allele in the two comparison groups and presented the numbers in a 2 × 2 table. When examining for association between the disease and all alleles separately, it is necessary to allow for multiple testing. For a conventional value of .05, the critical P value is derived from $1 - (1\text{-}P)^N = .05$, or $P = 1 - (.95)^{1/N}$, where N is the number of alleles tested (Walsh et al. 1992). The frequencies of the a_2 allele were lower in the patients than in the controls (cases = 10/98; controls = 21/99; P = .0339). An opposite trend was observed for the a_5 allele (cases = 18/98; controls = 9/99; P = .0584). However, these P values were greater than the critical P value of .0057 for this locus (table 1).

The strength of the association is weak but significant, which suggests that alleles at the MAOA locus contribute to susceptibility to bipolar disorder rather than being a major determinant (Greenberg 1993). Although our sample number is small, the tentative association we report here suggests that this candidate region warrants further investigation.

LIONEL C. C. LIM,*,‡ JOHN F. POWELL,† ROBIN MURRAY,* AND MIKE GILL*

*Departments of *Psychological Medicine and †Neuroscience, Institute of Psychiatry, London; and ‡Department of Psychological Medicine, National University of Singapore, Singapore*

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Additive Influence of Maternal and Offspring DM-Kinase Gene CTG Repeat Lengths in the Genesis of Congenital Myotonic Dystrophy

To the Editor:

Myotonic dystrophy (DM) is an autosomal dominant multisystemic genetic disorder affecting ~1 in 8,000 individuals. The mutation consists of an unstable trinucleotide CTG repeat sequence in the 3′ UTR of a gene encoding a putative member of the serine-threonine protein kinase family (Brook at al. 1992; Fu et al. 1992; Mahadevan et al. 1992). The trinucleotide repeat sequence is amplified in DM individuals, the severity of the disease being positively correlated with the number of repeats. The congenital form of the disease (CDM) is more severe, with different phenotypic features, and is maternally inherited. The number of repeats seen in CDM is generally higher than that seen in non-CDM cases (Tsilfidis et al. 1992).

The intergenerational amplification of this repeat is influenced by the sex of the parent transmitting the mutant allele (Harley et al. 1993; Lavedan et al. 1993; Redman et al. 1993), in that, overall, a greater average intergenerational amplification (addition of CTG repeats) is seen on maternal transmission. Moreover, paternal transmission of DM demonstrates a higher frequency of reductions (loss of repeats) than does maternal transmission. As a result of these observations it has been proposed (Lavedan et al. 1993; Mulley et al. 1993) that the exclusive maternal origin of CDM derives from the parent-of-origin differences in behavior of the mutant allele when transmitted to the next generation.

Our analysis of the dynamics of the mutation in >300 transmissions (174 maternal and 127 paternal) indicates that this explanation is incomplete. We have found that, while a high number of repeats seems to be a necessary condition for CDM, this alone cannot explain its exclusive maternal inheritance. This is most clearly reflected in the fact that, in our study group, approximately one-quarter of DM cases inherited from affected fathers have repeat numbers equal to or greater than those found in the CDM cases with the lowest number of repeats (~700 repeats).

Furthermore, the following two significant correlations need to be considered: First, although only very few CDM cases had DM mothers with a very low number of CTG repeats, these CDM cases generally presented with a number of repeats in the upper end of the CDM range (fig. 1). Second, although mothers with a higher number of repeats tended to have a higher percentage of CDM offspring, the number of repeats in these offspring was, in general, at the lower end of the CDM cases (fig. 1).

These two observations, together with previous studies on maternal phenotypes of CDM offspring (Koch et al. 1991), suggest that CDM arises from an "additive" pathology comprising both maternal and offspring components; it may be that CDM is the result of metabolic disturbances of a DM mother on a developing DM fetus with a sufficiently high number of CTG repeats. The DM mother must make some contribution to the phenotype of the CDM fetus, in addition to having