

# A functional polymorphism in the promoter of monoamine oxidase A gene and bipolar affective disorder

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## Abstract

The genes encoding for the enzymes monoamine oxidase (MAO) A and B are good candidates to investigate bipolar affective disorder. A 30 bp repeat in the MAOA promoter was recently demonstrated to be polymorphic and to affect transcriptional activity. In a family-based association design we found that none of the different repeat copies was preferentially transmitted from mothers ( $n = 131$ ) to their children affected with bipolar disorder ( $\chi^2 = 2.75$ , 4 d.f.,  $p = 0.6$ ). Following on our previous finding of an excess of low-activity genotypes of catechol-*O*-methyltransferase in patients with a rapid cycling form of illness, we examined for a similar trend with MAOA alleles. In an extended sample we found a non-significant trend for patients with an ultra-rapid cycling form of illness ( $n = 29$ ) to have a higher frequency of low-activity alleles compared with 92 bipolar patients with a non-rapid cycling course of illness ( $\chi^2 = 2.37$ , 1 d.f.,  $p = 0.13$ ).

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## Introduction

Monoamine oxidase (MAO) is an outer membrane mitochondrial enzyme that catalyses the degradation of several amines, including the neurotransmitters serotonin, noradrenaline and dopamine. Two isozymes of MAO have been described (A and B). They are encoded by two tightly linked genes that are arranged in a tail-to-tail configuration on chromosome Xp11.23–11.4 (Chen et al., 1992; Grimsby et al., 1991). They span approx. 60 kb each, share 73% homology, consist of 15 exons, and have identical intron–exon organization suggesting that they are derived from a duplication of the same ancestral gene (Grimsby et al., 1991) (Figure 1). MAOA preferentially deaminates serotonin and norepinephrine, and MAOB acts on phenylethylamines and benzylamine. Dopamine is a substrate for both forms of MAO. The different promoter organization of the two genes provides the basis for their different tissue- and cell-specific expression (Zhu et al., 1992).

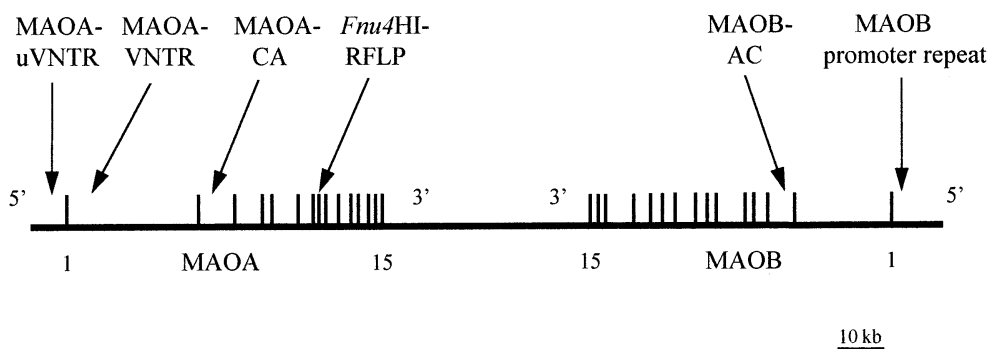
The MAO genes are strong candidates for affective disorders. Monoamines are widely implicated in the pathogenesis of affective disorders (Diehl and Gershon, 1992; Goodwin and Jamison, 1990). MAOA inhibitors are effective drugs in the treatment of depressive disorders (Himmelhoch et al., 1991; Quitkin et al., 1988). A nonsense mutation in the MAOA gene has been shown to be associated with a syndrome of mild mental retardation and impulsive aggressive behaviour in a single large family (Brunner et al., 1993). Finally, transgenic mice with a deletion of the MAOA gene exhibit difficulty in righting, fearfulness as pups and enhanced aggression as adult males (Cases et al., 1995).

A number of different polymorphisms in MAOA and MAOB genes has been identified and several of them have been tested for association with bipolar disorder. The results have been mixed. Lim et al. (1995) in a case-control design (57 patients, 59 controls) found evidence for association with alleles at three MAOA markers: a dinucleotide repeat in intron 2 (MAOA-CA), a VNTR in intron 1 (MAOA-VNTR) and an *Fnu4HI* RFLP in exon 8 [though not with a dinucleotide repeat at intron 2 of the MAOB gene (MAOB-AC)]. Kawada et al. (1995) reported a significant association between Japanese bipolar cases ( $n = 58$ ) and controls ( $n = 68$ ) and MAOA-CA. Craddock et al. (1995) in a case-control design (84 patients, 84

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**Figure 1.** Schematic representation of the MAOA and MAOB genes and the location of the polymorphisms referred to in the study. The relative positions of exons are based on the data from Grimsby et al. (1991) and Chen et al. (1991).

controls) found no evidence for association with MAOA-CA, MAOA-VNTR and *Fnu4HI* RFLP. Rubinsztein et al. (1996) also in a case-control design (39 patients, 39 controls) found significant association with alleles at the MAOA-CA but not with *Fnu4HI* RFLP. There have been two published studies which used family-based internal controls and both have been negative. Nöthen et al. (1995) tested the MAOA-CA in 82 parent-offspring trios and Parsian and Todd (1997) tested the MAOA-CA and MAOB-AC in 56 parent-offspring trios. None of these polymorphisms has been shown to affect enzyme activity or expression levels.

The published sequence of the MAOA promoter (GenBank no. M89636) contains four exact repeats of a 30 bp sequence located at positions  $-1262$  to  $-1143$  (the A of the ATG initiation codon is defined as  $+1$ ). They are followed by a half repeat consisting of the first 15 bp of the repeated motif. Recently Sabol et al. (1998) demonstrated that this repeat (MAOA-uVNTR) is polymorphic and affects transcriptional activity of the promoter. Alleles with 4 and 3.5 copies of the sequence were transcribed 2–10 times more efficiently than alleles of 3 and 5 copies, suggesting an optimal length for the regulatory region. Deckert et al. (1999) replicated these results but found that allele 5 also had high transcriptional activity. We wanted to examine whether different alleles at this polymorphic repeat alter susceptibility to bipolar affective disorder.

Association studies using the case-control design have the potential to produce false-positive or false-negative results due to population stratification, even when careful matching has been performed. We employed a method which overcomes this problem by using the parents of probands and examining whether one allele is preferentially transmitted over the other from heterozygous parents to affected offspring [the transmission/disequilibrium test (TDT), Spielman et al., 1993].

The published sequence of the MAOB promoter (GenBank no. M89637) also contains a repeat region. It

consists of two 29 bp direct repeats with 100% homology (Zhu et al., 1992). The two repeats are located from  $-807$  to  $-750$  (the A of the ATG initiation codon is defined as  $+1$ ). The promoters of MAOA and MAOB share 61% sequence identity (Zhu et al., 1992). It is feasible to hypothesize that, in analogy with the 30 bp repeat at the MAOA promoter, this repeat sequence in MAOB might also be involved in regulation of transcription. We examined this repeat for length polymorphism.

Finally, we wanted to examine whether alleles conferring low transcriptional activity were more frequent among patients with a rapid cycling form of illness. This hypothesis originated from our previous report that low activity genotypes of catechol-*O*-methyltransferase (COMT) are more common among such patients (Kirov et al., 1998).

## Materials and methods

### Parent-offspring trios

The sample consisted of 128 probands of British Caucasian origin and their parents. In addition, for this study, we included three mother-son pairs because such families are fully informative for the TDT when markers on the X chromosome are examined. Diagnoses were made according to DSM-IV by two raters on the basis of all available information, including personal interviews with the SCAN instrument (Wing et al., 1990) and hospital notes. There were 124 probands with a bipolar I disorder (BP I) and 7 probands with bipolar 2 disorder (BP II). Fifty-eight probands were male and 73 were female. The mean ages for probands, fathers and mothers were 34.8 yr (s.d. = 8.7), 64.4 yr (s.d. = 9.7) and 61.8 yr (s.d. = 9.4), respectively. The mean age at onset of illness in patients was 22.4 yr (s.d. = 6.3). The rate of bipolar disorders in fathers and mothers was 8 and 10%, respectively. All patients gave informed consent for participation in genetic

linkage and association studies. Ethics Committee approval was obtained in all local health authorities where patients were recruited.

### **Sample of rapid cycling and non-rapid cycling patients**

This sample is nearly identical to that described in our previous paper (Kirov et al., 1998). We genotyped 65 unrelated patients with rapid cycling form of illness and 92 patients with a strictly defined non-rapid cycling course of illness. Fifty-six of the patients are probands in the trios sample. The rest were selected from a larger database of bipolar patients that we collected for genetic association studies. Rapid cycling was defined according to DSM-IV criteria (four or more distinct episodes of illness in a 12-month interval, demarcated either by partial or full remission for at least 2 months, or a switch to an opposite polarity). The exact criteria for non-rapid cycling are defined in our previous paper (Kirov et al., 1998) but briefly, they imply a frequency of no more than two episodes per year and an observation period of at least 7 yr. Among the group of 65 rapid cyclers we identified a group of 29 ultra-rapid cyclers (having eight or more episodes of illness per year for at least 2 yr). The age at onset of illness among the non-rapid cycling and the rapid cycling patients was nearly identical [26.2 yr (s.d. = 9.9) vs. 26.6 yr (s.d. = 11.4)], as was the age at observation [44.5 yr (s.d. = 12.6) vs. 43.8 yr (s.d. = 13.0)].

Genotyping of MAOA-uVNTR was performed with primer sets suggested by Deckert et al. (1998): forward 5'-CCCAGGCTGCTCCAGAAAC and reverse 5'-GGA-CCTGGGCAGTTGTGC. They amplify a 239 bp sequence in the presence of four repeats. Polymerase chain reaction (PCR) was performed on an MJ Research DNA Engine Tetrad in 12  $\mu$ l volume with 30 ng genomic DNA, 200  $\mu$ M dNTPs, 5 pmol primers, 0.5 U AmpliTaq Gold<sup>TM</sup> (Perkin-Elmer) in the manufacturer's buffer, and 2.5 mM MgCl<sub>2</sub>. Cycling conditions were 10 min at 95 °C, followed by 45 s at 95 °C and 45 s at 62 °C for 35 cycles and a final extension step of 10 min at 62 °C. The PCR products were separated on 1% Metaphor (Flowgen)/1% agarose gels and visualized by ethidium bromide staining.

Primers flanking the two 29 bp repeats in the MAOB promoter were designed based on the published sequence: forward 5'-ATCCACCACCTCTCCCTG and reverse 5'-ATTTCTTGGCATTCCCAGC. The amplified product is 238 bp. We used the same PCR conditions as above with annealing temperature of 56 °C.

For linkage disequilibrium calculation, alleles were grouped into low and high activity and compared with the bi-allelic *Fnu4HI* RFLP in exon 8 of the MAOA gene.

(We already had genotyping results on this marker from a previous study.) For analysing the magnitude of linkage disequilibrium we used the methods employed in the paper of Sabol et al. (1998): the squared correlation coefficient,  $R^2$  (Sham, 1998) and the proportion of maximum possible linkage disequilibrium given the allele frequencies,  $D^*$  (Lewontin, 1964).

For statistical analysis of transmission/disequilibrium we used the likelihood-based Extended TDT (ETDT) which is designed for multi-allele markers (Sham and Curtis, 1995). Differences between rapid cyclers and non-rapid cyclers were assessed using  $\chi^2$  tests and, where appropriate, odds ratios and confidence intervals.

## **Results**

### **MAOA-uVNTR in affected parent-offspring trios**

For MAOA promoter repeat polymorphism we identified six alleles corresponding to 5, 4, 3.5, 3, 2.5 and 2 repeats of the 30 bp sequence. The frequency of these alleles in parents and probands and the results of TDT analysis are presented in Table 1. For TDT analysis only heterozygous mothers are informative because the marker is X-linked and fathers will either not transmit at all (to sons) or will transmit their only allele (to daughters), making them uninformative in either case. It is clear from Table 1 that there was no evidence whatsoever that any one allele was preferentially transmitted, or that there was a preferential transmission of alleles conferring high transcription (4 and 3.5 repeats) or low transcription (3 repeats).

### **Linkage disequilibrium**

Linkage disequilibrium was assessed by examining X-chromosome haplotypes in 199 male subjects and grouping them into a bi-allelic system (high vs. low transcriptional activity, while discarding two rare alleles with unknown activity (2.5 and 5 repeats). Alleles conferring low transcriptional activity were much more likely to be present on chromosomes carrying the restriction site for *Fnu4HI* at exon 8. The calculated squared correlation coefficient was  $R^2 = 0.58$  and the proportion of the maximum linkage disequilibrium was  $D^* = 0.82$ .

### **MAOB promoter repeat**

The MAOB repeat sequence was amplified on a panel of 55 female and 37 male unrelated subjects (147 chromosomes) suffering with BP I ( $n = 53$ ), BP II ( $n = 13$ ) or unipolar depression ( $n = 28$ ). Each individual produced a

**Table 1.** Allele frequencies in parents and their offspring and results from the TDT

	5 repeats	4 repeats	3.5 repeats	3 repeats	2.5 repeats	2 repeats
Fathers (128)	–	82 (64.1%)	3 (2.3%)	42 (32.8%)	1 (0.8%)	–
Mothers (131)	4 (1.5%)	145 (55.3%)	3 (1.1%)	109 (41.6%)	–	1 (0.4%)
Male probands (58)	–	32 (55.2%)	1 (2.7%)	25 (43.1%)	–	–
Female probands (73)	1 (0.7%)	87 (59.6%)	3 (2.1%)	55 (37.7%)	–	–
Total probands (131)	1 (0.5%)	119 (58.3%)	4 (2%)	80 (39.2%)	–	–
Transmitted	1	32	2	32		0
Not transmitted	3	31	1	31		1
$\chi^2$		0.02		0.02		
<i>p</i> value		0.9		0.9		

$\chi^2$  for overall allele-wise TDT is 2.75, 4 d.f.,  $p = 0.6$ . There are 3 fewer fathers because 3 mother–son pairs were included in the analysis.

**Table 2.** Genotype and allele frequencies of the MAOA-uVNTR in non-rapid cyclers, rapid cyclers and ultra-rapid cyclers

	Non-rapid cycling ( <i>n</i> = 92)	Rapid cycling ( <i>n</i> = 36)	Ultra-rapid cycling ( <i>n</i> = 29)
Genotypes			
Male ( <i>n</i> = 67)			
High	28 (68.3%)	6 (54.5%)	9 (60%)
Low	13 (31.7%)	5 (45.5%)	6 (40%)
Female ( <i>n</i> = 90)			
High/high	21 (41.2%)	17 (68%)	3 (21.4%)
High/low	28 (54.9%)	6 (24%)	9 (64.3%)
Low/low	2 (3.9%)	2 (8%)	2 (14.3%)
Allele frequency			
Male + female			
High	98 (68.5%)	46 (75.4%)	24 (55.8%)
Low	45 (31.5%)	15 (24.6%)	19 (44.2%)

Alleles are divided into low and high activity.

Statistical significance of the differences are presented in the text.

uniform band of 238 bp indicating that this is not a tandem repeat polymorphism.

#### **MAOA promoter polymorphism in rapid cycling bipolar patients**

The genotyping results on the rapid cyclers and non-rapid cyclers are presented in Table 2 with alleles recoded as high and low activity. The frequency of low-activity alleles in ultra-rapid cyclers (44.2%) was higher than among non-rapid cyclers (31.5%), as hypothesized, but the difference was not statistically significant ( $\chi^2 = 2.37$ , 1 d.f.,  $p = 0.13$  in a two-tail test). The overall OR for the low-activity allele was 1.72 (95% CI = 0.86–3.46). This trend was not present in rapid cyclers.

#### **Discussion**

Our sample size had 80% power to detect association at the 0.05 level between disease and one of the common alleles at the MAOA promoter VNTR if the presence of that allele increased susceptibility to illness by a genotypic risk ratio of 2 in a multiplicative model of inheritance. There was, however, virtually no difference in the transmission of any alleles from mothers to affected offspring. This absence of a trend reduces the likelihood that we have missed even a smaller genetic effect.

Our estimates of a strong linkage disequilibrium between the MAOA-uVNTR and exon 8 *Fnu4HI* RFLP, which are ~ 50 kb apart ( $R^2 = 0.58$ ;  $D^* = 0.82$ ) are consistent with the work of Sabol et al. (1998). This team

reported a similarly strong linkage disequilibrium of  $R^2 = 0.47$ ;  $D^* = 0.98$  with the MAOA-CA repeat (in intron 2, nearer the MAOA-uVNTR,  $\sim 24$  kb apart), but a much weaker disequilibrium of  $R^2 = 0.05$ ;  $D^* = 0.14$  with the more distant MAOB-AC in the second intron of MAOB ( $\sim 110$  kb apart). This finding was not expected in view of previous work by Hotamisligil and Breakfield (1991) which suggested that alleles, with the presence of the restriction site at *Fnu4HI* RFLP, were associated with high MAOA enzyme activity. It should be pointed out, however, that the association reported in their study was weak and the samples showed over a 100-fold variation in enzyme activity. Another explanation for this discrepancy could be attributed to differences in tissue-specific expression of the gene as Hotamisligil and Breakfield (1991) used fibroblast cell lines, while Sabol et al. (1998) and Deckert et al. (1999) used neuroblastoma and placental choriocarcinoma cell lines.

Our negative results on the MAOA-uVNTR are consistent with our previous negative results on MAOA-CA and *Fnu4HI* RFLP (Craddock et al., 1995), as all three polymorphisms have now been shown to be in strong linkage disequilibrium. As reviewed in the Introduction, only case-control studies have produced evidence for association with polymorphisms at the MAO genes. This is now the third study which used family-based controls and, as the previous two studies (Nöthen et al., 1995; Parsian and Todd, 1997), and the largest one of the case-control studies (Craddock et al., 1995), is negative. Although the previous studies examined different (non-functional) polymorphisms, it is likely that they would not provide evidence for the MAOA-uVNTR either, as these polymorphisms are in strong disequilibrium with each other.

Therefore it appears more likely that different alleles at the MAO genes do not increase susceptibility to bipolar disorders. It is, however, possible that they may play a role in other common psychiatric disorders. Thus Deckert et al. (1999) reported a strong association between high activity MAOA alleles and panic disorder in female patients.

Low-activity genotypes were more common in patients with an ultra-rapid cycling form of illness; however, this difference was non-significant ( $\chi^2 = 2.37$ ,  $p = 0.13$ ) and the association was not present among patients with the rapid cycling form of illness. We have, however, previously reported that alleles determining low activity of the COMT enzyme are associated with a rapid cycling form of illness, particularly the ultra-rapid cycling form, using an identical design (Kirov et al., 1998). Thus we were examining a prior hypothesis. In addition, Papolos et al. (1998) reported that low-activity COMT was more common in patients whose illness occurred in 24–48 h

cycles (ultra-ultra-rapid cyclers) but not in those with only four or more episodes per year (rapid cyclers).

It is acknowledged that tricyclic antidepressants (which block the reuptake of monoamines) can induce a rapid cycling course of illness (reviewed by Goodwin and Jamison, 1990, pp. 647–651). It is possible that a decreased rate of degradation of monoamines (or only catecholamines) by MAOA and COMT, or their increased availability caused by tricyclics are two similar mechanisms leading to acceleration of cycle frequency. However our results are not significant and require independent replication. We found no evidence of interaction between the two polymorphisms but larger samples are needed to test this possibility.

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