



ORIGINAL RESEARCH ARTICLE

Pathological gambling and DNA polymorphic markers at MAO-A and MAO-B genes

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This study was conducted to detect a possible association of MAOA and/or MAOB genes with pathological gambling (PG). DNA polymorphisms in MAOA and MAOB genes were screened by molecular analysis in 68 individuals (47 males and 21 females) meeting ICD-10 and DSM-IV criteria for pathological gambling and 68 healthy comparison controls matched for age and sex. There were no significant differences between pathological gamblers and healthy volunteers in overall allele distribution at the MAOA gene polymorphism. However there was a significant association between allele distribution and the subgroup of severe male gamblers ($n = 31$) compared to the males in the group of healthy volunteers ($\chi^2 = 5246$; $df = 1$; $P < 0.05$ [Bonferroni corrected]). No association was found between the MAOB polymorphic marker and PG. Allele variants at the MAOA, but not the MAOB gene may be a genetic liability factor in PG, at least in severe male gamblers. *Molecular Psychiatry* (2000) 5, 105–109.

Pathological gambling is an impulse control disorder and it has also been proposed as a model of addiction without substance.¹ As defined by DSM-IV its essential feature is a persistent and recurrent maladaptive gambling behaviour. It is a progressive, chronic and highly disabling disorder that is poorly understood and often underdiagnosed despite affecting 1–3% of the adult population.² At present, little is known about the biological correlates of pathological gambling. A growing literature suggests the involvement of genetic factors in behavioral disorders related to pathological gambling such as alcoholism, substance abuse, attention-deficit-hyperactivity disorder, and smoking.³ An increased incidence of about 20% of pathological gambling in first-degree relatives within clinical samples of pathological gamblers has been reported^{4,5} and it has led to consideration of the possible role of a genetic component in the development of this disorder. Moreover, there is evidence for genetic influence derived from a large twin study performed on 3359 twin pairs in United States. This study revealed that inherited factors explained 62% of the diagnosis of pathological gambling disorder.⁶ Recently, a positive association

has been reported between pathological gambling and DNA polymorphism at the D2 and D4 receptor genes.^{7,8}

Monoamine oxidases A (MAOA) and B (MAOB) play a critical role in the degradation of several neurotransmitters which could be involved in the pathogenesis of pathological gambling. Decreased platelet MAOB activity has been reported in pathological gambling^{9,10} and other impulse control disorders.^{11,12} Although MAOA activity has never been studied in pathological gambling, previous research suggests that abnormal MAOA activity may play a role in the pathophysiology of disorders with impaired impulse control.¹³ Decreased MAOA activity was associated with impulsive behaviors in several affected males from a large Dutch family with a mutation in that locus.¹⁴ Differences in MAOA activity have been associated with specific alleles of the structural gene.¹⁵ Polymorphic variants at MAOA and/or MAOB genes have been reported to be associated with alcoholism, substance abuse and other impulse control disorders.^{16–18} In light of these findings we sought to investigate the possibility of an association between genetic variants at MAOA and/or MAOB genes and pathological gambling.

The patient group consisted of 68 unrelated pathological gamblers (47 men and 21 women) with a mean age of 42.24 years (SD = 13.45). We found psychiatric comorbidity in 62% of patients, personality disorders being the most common psychiatric diagnosis associated (44.1%), followed by alcohol abuse/dependence (33.8%). The mean South Oaks Gambling Screen (SOGS) score was 12.65 (SD = 2.60; range 6–17) and the Global Clinical Impression (GCI) was in the severe range (4 = severe or 5 = very severe disorder) in 63% of patients, all of them with a SOGS score of ≥ 12 . Family history of pathological gambling in first-degree relatives was found in 14 of 68 patients (20.5%) and in 25 of 68 (36.8%) when second-degree relatives were included. Control individuals were 68 unrelated and unaffected blood donors (47 men and 21 women) with a mean age of 42.9 years (SD = 12.8).

The allele distribution of MAOA polymorphism analyzed is shown in Table 1. Only three (A, B, and C) of the five different alleles described by Hinds *et al*¹⁹ were found in our sample. Genotype frequencies were distributed according to Hardy–Weinberg equilibrium

Table 1 Distribution of MAOA alleles in pathological gamblers and the comparison group

Group	<i>n</i> + 2 <i>n</i> ^a	Allele B (%)	Allele C (%)	χ ²	<i>P</i>
Total group					
Comparison group	87	22 (25.3)	65 (74.7)	2.354	0.085
Pathological gamblers	89	32 (36.0)	57 (64.0)		
By gender					
Males					
Comparison group	47	11 (23.4)	36 (76.6)	2.443	0.090
Gamblers	47	18 (38.3)	29 (61.7)		
Females					
Comparison group	40	11 (27.5)	29 (72.5)	0.329	0.370
Gamblers	42	14 (33.3)	28 (66.7)		
By severity					
Total group					
Comparison group	87	22 (25.3)	65 (74.7)	4.254	0.031
‘Severe and very severe’ gamblers	55	23 (41.8)	32 (58.2)		
Males					
Comparison group	47	11 (23.4)	36 (76.6)	5.246	0.021
‘Severe and very severe’ gamblers	31	15 (48.4)	16 (51.6)		
Females					
Comparison group	40	11 (27.5)	29 (72.5)	0.244	0.413
‘Severe and very severe’ gamblers	24	8 (33.3)	16 (66.7)		

^a*n* refers to the number of total alleles at MAO-A locus ('*n*' in males, '2*n*' in females). Chi-square test was performed; data were tabulated as a 2 × 2 table. χ^2 and *P* values are shown.

both in pathological gamblers ($\chi^2 = 0.43$; *df* = 1; *P* = 0.51) and controls ($\chi^2 = 2.84$; *df* = 2; *P* = 0.41). Allele A was only found in one control female; therefore this subject was excluded from the global analysis in order to preserve statistical power as suggested by other authors.²⁰ We found differences in overall allele distribution, but they did not reach statistical significance ($\chi^2 = 2.354$; *df* = 1; *P* = 0.085). When stratifying by gender, similar differences in overall allele distribution were found in males ($\chi^2 = 2.443$; *df* = 1; *P* = 0.090) but not in females ($\chi^2 = 0.329$; *df* = 1; *P* = 0.370). Interestingly, allele B was more represented in most severe cases ('severe' or 'very severe' in GCI) than in healthy volunteers ($\chi^2 = 4.254$; *df* = 1; *P* = 0.031). However, differences were not significant when Bonferroni correction was applied. Nevertheless, when stratifying by gender, the most severe male pathological gamblers showed significant differences in allele distribution compared with male controls ($\chi^2 = 5.246$; *df* = 1; *P* = 0.021 [*P* < 0.05, Bonferroni corrected]). No differences were found in females.

Of the genotypes, considering male hemizygotes and female homozygotes together, the most frequent genotype was 'C or C/C' (0.687 in controls and 0.573 in patients), followed by 'B or B/B' (0.179 in controls and 0.309 in patients) and 'B/C' only found in females (0.134 in controls and 0.118 in patients). No differences in overall genotype distribution were found between gamblers and controls ($\chi^2 = 3.083$; *df* = 2; *P* = 0.214). Genotype 'B or B/B' was identified in 17 of the 43 most severe patients and in 12 of the 67 controls; differences were significant only in males ($\chi^2 = 5.246$;

df = 1; *P* < 0.05; Bonferroni corrected), but not in females ($\chi^2 = 1.340$; *df* = 2; *P* = 0.512).

Table 2 shows the allele distribution of MAOB polymorphism analyzed.²¹ We found eight different alleles in our sample corresponding to one, two, three, four, five, six, seven and 11 repeats of the (GT)_{*n*} sequence. The seven-repeat allele was only found in one pathological gambler and the 11-repeat allele was only found in one control. Therefore they were grouped with the six-repeat allele into one category as it has been suggested in the analysis of other polymorphic genetic markers with more than five alleles.²² The genotype frequencies were distributed according to Hardy-Weinberg equilibrium both in controls ($\chi^2 = 14.66$; *df* = 15; *P* = 0.47) and in pathological gamblers ($\chi^2 = 12.20$; *df* = 15; *P* = 0.66). Data were grouped in 2 × 6 contingency tables to compare allele distribution and in 2 × 2 contingency tables to compare the frequencies of each allele against the others combined in a single allele class. As described above, male hemizygotes and female homozygotes were considered together for the purpose of genotypic analyses. No statistically significant differences were found either in total samples or in a subgroup of more severe pathological gamblers compared with controls either in allele distribution or in genotypic analyses.

Our findings of no association between specific alleles at MAOB intron 2 polymorphism and pathological gambling seem to indicate that decreased platelet MAOB activity reported in pathological gambling^{9,10} may not be related to structural variants of the MAOB gene. This finding does not exclude a genetic influence

Table 2 Distribution of MAOB alleles in pathological gamblers and the comparison group

Group	<i>n</i> + 2 <i>n</i> ^a	Allele 1 (%)	Allele 2 (%)	Allele 3 (%)	Allele 4 (%)	Allele 5 (%)	Allele 6 and others (%)	χ^2 (<i>df</i> = 5)	<i>P</i>
Comparison group									
Male	47	1 (2.1)	16 (34.0)	10 (21.3)	10 (21.3)	7 (14.9)	3 (6.4)		
Female	42	3 (7.1)	12 (28.6)	9 (21.4)	11 (26.2)	5 (11.9)	2 (4.8)		
Total pathological gamblers								2.505 ^b	0.776
Male (<i>n</i>)	47	2 (4.3)	11 (23.4)	16 (34.0)	12 (25.5)	5 (10.6)	1 (2.1)		
Female (2 <i>n</i>)	42	2 (4.8)	12 (28.6)	7 (16.7)	13 (31.0)	7 (16.7)	1 (2.4)		
'Severe and very severe' gamblers								2.286 ^c	0.808
Male	31	1 (3.2)	8 (25.8)	10 (32.3)	8 (25.8)	4 (12.9)	0 (0.0)		
Female	24	1 (4.2)	6 (25.0)	4 (16.7)	7 (29.2)	5 (20.8)	1 (4.2)		

^a'*n*' refers to number of total alleles at MAO-B locus ('*n*' in males, '2*n*' in females).

^bChi square and *P* values of comparison between total gamblers and total comparison group (males + females samples).

^cChi square and *P* values of comparison between the subgroup of 'severe and very severe' gamblers vs comparison subjects (males + females samples).

No statistical significance was found either in overall comparisons or when considering comparisons by gender (χ^2 and *P* values not shown).

in the low MAOB activity observed in pathological gamblers, since decreases in enzymatic activity may be due to alterations in regulatory DNA sequences.²³ Moreover, previous research has failed to identify an association between the number of GT(*n*) repeat units at polymorphic sequence in MAOB intron 2 and the level of platelet MAOB activity, suggesting that structural alterations at the gene for MAOB are not the primary determinant of activity levels in platelets.²⁴

Although MAOA activity appears to be more important than MAOB in metabolism of neurotransmitters in the brain, little research has been directed towards investigating the behavioral correlates of MAOA activity, probably due to the limited accessibility to MAOA in peripheral tissues (only in cultured skin fibroblasts) compared to MAOB.²⁵ A mutation in the MAOA gene that leads to lack of MAOA activity has been described in several affected males of a single large Dutch kindred, that exhibited borderline mental retardation and increased impulsive behaviours.¹⁴ In this study, we did not find an association between MAOA intron 1 polymorphic marker and the total group of pathological gamblers, although near significant differences in allele distribution were found when only males were considered. However, allele 'B' was found more frequently in the most severe pathological gamblers, and differences reached statistical significance in male severe gamblers compared to male comparison subjects. Nevertheless, it should be pointed out the risk of achieving a false-positive result with the traditional significance level of 0.05, given the low prior probability of selecting the 'right' candidate gene for association studies in behavioral traits.²⁶ However, interestingly we found the most positive findings in the most severe cases; these results could be in agreement with the polygenic model of genetic susceptibility to psychiatric disorders.

Recently, Sabol *et al* have reported a new MAOA

polymorphism located in the gene promoter.²⁷ This polymorphism has been shown to affect the transcriptional activity of the MAOA gene promoter. The high activity promoter alleles have been associated with panic disorder in females.²⁸ It is worth noting that this functional polymorphism is in linkage disequilibrium with other MAOA and MAOB markers.²⁷ Moreover, we have found the same linkage disequilibrium with the MAOA polymorphism analyzed in this study, and this evidence could suggest a positive association between the low activity MAOA gene promoter alleles and pathological gambling (manuscript in preparation).

As mentioned above the association between allele B of MAOA polymorphism and more severe pathological gamblers was observed in males, but not in females. Other genetic gender differences in pathological gambling have been reported, such as the association between DRD4-7 repeat allele and female gamblers⁸ and between the short variant of 5-HTTLPR and male gamblers.²⁹ Interestingly in both cases the allele variants associated with pathological gambling lead to a poorer functioning of the expressed gene product.^{30,31} Further research is needed to investigate the possible contribution of genetic factors in the pathogenesis of pathological gambling and to elucidate if this contribution could be gender related. Interestingly, there are significant clinical differences between male and female pathological gamblers. Male pathological gamblers have on average an earlier age of onset, higher prevalence of alcohol-related disorders, and more psychopathic traits than female gamblers. In contrast, female pathological gamblers tend to obtain higher scores on depression scales at admission, meet criteria for depressive disorders and have more dependency traits than male pathological gamblers.³² It is unclear to what extent those clinical differences may be related to genetic factors.

In summary, the results of this study suggest a poss-

ible association between the MAOA VNTR intron 1 polymorphism and liability to pathological gambling in males, at least in the most severe cases. However, the sample size is a limitation of the study and further research in larger and different samples is needed to confirm this positive association and to elucidate the functional meaning of this finding.

Methods

Subjects

Sixty-eight patients (47 males and 21 females) admitted to the Pathological Gambling Outpatient Program of 'Ramon y Cajal' Hospital (Madrid, Spain) were included in this study. All subjects met ICD-10³³ and DSM-IV² diagnostic criteria for pathological gambling. The clinical assessment of the patients was performed by a senior psychiatrist (AI) who was blind to their genotypes. Five items-Global Clinical Impression (GCI) and South Oaks Gambling Screen (SOGS)³⁴ were used to assess the severity of pathological gambling. Psychiatric comorbidity in axis I was assessed by clinical interview based on DSM-IV diagnostic criteria. Structured Clinical Interview for Personality Disorders³⁵ was used to assess axis II comorbidity. Family history was assessed according to FH-RDC.³⁶

An equal number of comparison subjects, matched for age and sex, were selected from the Blood Donation Unit of 'Ramon y Cajal' Hospital. People attending this Unit, as well as pathological gamblers, were non-paid voluntary subjects. A senior psychiatrist (AI) in the team interviewed all subjects in the comparison group to exclude subjects with personal or family history of psychiatric disorders, including problem gambling (score of zero in SOGS was required), alcohol and/or substance abuse, and other impulse-control disorders.

All patients and comparison subjects were Caucasian and living in Central Spain. All patients and healthy volunteers signed written informed consent before their inclusion in the study.

DNA amplification and genotyping

All patients and comparison subjects were screened by molecular analysis of specific DNA polymorphisms at the MAOA and MAOB genes. DNA was isolated from 10 ml of peripheral blood samples according to standard methods. DNA was amplified using polymerase chain reaction (PCR). For the MAOA gene we studied a VNTR marker located in the first intron of the gene; PCR amplification was made using the primers and conditions described by Hinds *et al.*¹⁹ For the MAOB gene we analyzed a dinucleotide sequence (GT)_n in the second intron of the gene.²¹ Amplified products obtained by PCR were resolved by electrophoresis in denaturing polyacrylamide gels and detected by silver staining.

Statistical analyses

Before analyzing the data, chi-square goodness-of-fit test was used to verify Hardy-Weinberg equilibrium of genotype frequencies in the patients as well as in the

comparison group. Data were analyzed in two different ways for each marker as suggested by Craddock *et al.*³⁷ First, we used a chi-square omnibus test to determine whether there was an overall association between pathological gambling and allele distribution at the marker locus. Data were tabulated as an $a \times 2$ table where a is the number of alleles at the marker locus. The second analysis was aimed at uncovering possible associations between pathological gambling and each marker separately. For this analysis data were tabulated as a series of 2×2 tables in which all alleles except the one being studied were collapsed into a single allele class in the table. Chi-square tests were used to investigate the association between gambling status and individual alleles. A correction for multiple testing was applied, following the technique described by Walsh *et al.*³⁸ For a conventional significance value of 0.05, the critical P value was calculated from the formula: $[1 - (1 - P)^a] = 0.05$, and consequently $P = [1 - (0.95)^{1/a}]$, where a is the number of alleles at the marker locus. Of the genotypes, since the MAOA and MAOB genes are located in the X chromosome and males have only one allele for this gene, we considered male hemizygotes and female homozygotes together for the purpose of genotypic analyses. Then chi-square tests were used to analyze the association between gambling status and genotypes. Bonferroni correction for multiple testing was applied when analyzing subgroups of gamblers.

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