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# *TaqI*-A polymorphism linked to the *DRD2* gene and P300 in alcoholic patients

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ABSTRACT – *Background and Objectives:* Different studies carried out mainly in young non-consuming children of alcoholics show an association of P300 abnormalities with alcoholism and with the *TaqI*-A1 allele. Since the relationship between P300 and the *TaqI*-A1 allele has not been specifically studied in alcoholic patients, our objective was to investigate whether the association exits in this population.

*Methods:* Our sample consisted of 176 recently detoxified male alcohol-dependent patients. These patients had been alcohol dependent from a mean age of 22.6 years and consumed on average 164.63 (± 142.99) $cm^3$ of alcohol daily. P300 was studied using an auditory paradigm. *TaqI*-A polymorphism genotyping was performed. The association between P300 and *TaqI*-A, and correlation with age and alcohol consumption, was studied.

*Results:* The *TaqI*-A1 allele was found in 38.6% of our patients (n = 68). The latency and amplitude of P300 were 361.64 milliseconds and 17.53 microvolts, respectively. P300 wave latency in alcoholic patients was longer than the reference value obtained from a sample of healthy men of the Event-Related Potentials Unit ($p < 0.001$). Alcoholic patients who carried the *TaqI*-A1 allele showed more prolonged P300 latency than non-carriers, and these in turn more than the control subjects. P300 characteristics varied according to age, but an association with amount of alcohol or number of years consuming was not found.

*Conclusions:* There is a relationship between the *TaqI*-A polymorphism and P300 wave characteristics in alcoholic patients. Further investigations need to be carried out in non-consuming alcoholic patients and in healthy control subjects to confirm this association and to clarify the possible influence of the neurotoxic effects of alcohol on P300 physiology.

## Background and Objectives

Several studies have related the presence of a lower amplitude or a longer latency of the *Event-Related Potentials* P300 (P300) with alcoholism (Polich *et al.* 1986, Cohen *et al.* 1995, Nacher 2000, Polich and Ochoa 2004). It has been suggested that these alterations of P300 would have a strong genetic load (Anokhina *et al.* 2000, Enoch *et al.* 2002) and could represent a risk endophenotype for the development of alcohol dependence (Van der Stelt *et al.* 1994, Cohen *et al.* 1997a, Cohen *et al.* 1998, Berman and Noble 1995, Hesselbrock *et al.* 2001). In addition, P300 has been associated to a family history of alcoholism (Benegal *et al.* 1995, Hill *et al.* 1999a), a family history of antisocial behaviour (Hesselbrock *et al.* 1993, Preuss *et al.* 1999, Houston *et al.* 2004) and with different cognitive alterations related to attentional processes (Berman and Noble 1997, Cohen *et al.* 1997b, Ratsma *et al.* 2002).

The discovery of P300 abnormalities in patients suffering Parkinson's disease had suggested that they could be related to a lower dopaminergic activity (Polich *et al.* 1994); this association was confirmed by later studies (Hansenne 2000, Nacher 2000). These findings justified later investigations of the relationship between P300 alterations and genetic markers related to the dopaminergic system. Amongst them, the importance of the Single Nucleotide Polymorphism (SNP) which constitutes the *TaqI*-A polymorphism has been highlighted by different studies (Blum *et al.* 1996, Comings & Blum 2000). The *TaqI*-A1 allele of this polymorphism, located in the 3´ region of the gene which encodes the dopaminergic D2 receptor (DRD2) (Grandy *et al.* 1989, Blum *et al.* 1991) has been associated with severe alcoholism in caucasian populations (Blum *et al.* 1991, Noble, 2003) and with different psychiatric disorders related to addictions and impulsiveness (Blum *et al.* 2000, Comings y Blum 2000, Ponce *et al.* 2003, Rodriguez-Jimenez *et al.* 2005). Although the *TaqI*-A polymorphism was initially described as a non-functional marker of genetic variations pertaining to *DRD2*, it is now known that the *TaqI*-A SNP is a functional polymorphism which belongs to the adjacent gene *ANKK1* (Duan *et al.* 2003, Dubertret *et al.* 2004) and encodes a kynase protein. Since the *TaqI*-A1 allele is in linkage disequilibrium with the *DRD2* gene and could be involved in dopamine synthesis (Laakso 2005) it is still considered an adequate genetic marker for the study of dopaminergic function.

There are few studies which relate the *TaqI*-A1 allele and alterations of P300. One of them (Blum *et al.* 1994), carried out on a general psychiatric population, found that subjects with the A1A1 genotype showed significant prolongation of P300 latency compared with A2A2 genotype subjects; no association was found between P300 abnormalities and alcoholism in this population. With respect to alcoholism, there are three studies which analise the relationship between the *TaqI*-A1 allele and alterations of P300. They were not carried out on alcoholic patients but on non-consuming children of alcoholic subjects (Noble *et al.* 1994, Hill *et al.* 1998, Ratsma *et al.* 2001). The first of these studies found prolongation of the P300 wave latency associated to the presence of the *TaqI*-A1 allele (Noble *et al.* 1994); the second found a significantly lower amplitude of P300 in the *TaqI*-A1 allele group, compared with the *TaqI*-A2 allele group (Hill *et al.* 1998). The third study, however, performed on older descendents of alcoholics, could not confirm this association between P300 and *TaqI*-A (Ratsma *et al.* 2001). In fact, the influence of age as a confounding factor has been seen in a previous study car-

ried out on alcoholic patients (Costa *et al.* 2000), since the decrease in P300 amplitude only appeared in those aged 30 or less.

The scarcity of findings associating P300 abnormalities with *TaqI*-A polymorphisms and alcoholism, and the fact that the majority of the data regarding these relationships has been obtained exclusively in young, non-consuming children of alcoholics, could be due to certain factors such as age, gender, or even alcohol intake, which may be masking these associations in actively consuming alcoholic patients.

Due to the absence of previous studies carried out specifically in alcoholic patients, and considering the possible factors which could mask the relationship between the P300 wave and the *TaqI*-A polymorphism, we decided to study this association in a sample of male alcoholic patients, in order to control for the gender factor, and to make an exploratory approach to the possible effect that age and level of alcohol consumption could have on this association.

## Methods

This is a cross-sectional study which compares P300 amplitude and latency in a group of alcoholic patients with the reference values in a sample of healthy control subjects, as well as within the group of patients according to the presence or absence of the *TaqI*-A1 allele.

### Study Population

Our sample consisted of 176 adult alcoholic males consecutively recruited in the Alcoholic Programme of *Hospital Universitario 12 de Octubre*, of Madrid, Spain. Their mean age was 41.39 years and 87% of them drank daily, with an average intake of 164.63 (± 142.99) $cm^3$ of alcohol per day. These patients met alcohol abuse criteria from a mean age of 22.61 years, and alcohol dependence criteria from age 30.13. Their mean SADS score was 31.42. In our sample of alcoholic patients, 38.6% (n = 68) were carriers of the *TaqI*-A1 allele (see Table I).

The following were used as *Inclusion Criteria*: male alcoholic patients with ages ranging from 18 to 65 years, meeting DSM-IV criteria for Alcohol Dependence, having completed their detoxification period, having at least three previous generations born in Spain, and having expressed their written informed consent. The following were used as *Exclusion Criteria*: the existence of any other associated DSM-IV Axis I psychiatric diagnoses, the presence of any current neurological disorder, the detection of any auditory deficit, the presence of any serious or chronic somatic illness not related to alcoholism and requiring treatment, having immigrant ancestors and/or the existence of consanguinity with other subjects included in the study (since this could cause genetic stratification in the test).

*Instruments:*

A semi-structured interview was used to collect sociodemographic data. The Structured Clinical Interview (SCID) (First *et al.* 1999) from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) was used as the diagnostic instrument for substance abuse or dependence. The Severity of Alcohol Dependence Scale (SADS) was also used.

*Genotyping:*

Genotyping was performed using a polymerase chain reaction (PCR) as previously

described (Ponce *et al.* 2002). Twenty microlitres of the PCR product were digested with two units of the TaqI restriction enzyme (Boheringer Mannheim) for 4 hours at 65 °C. The resulting fragments were: 310, 185 and 125 bp for the A2/A1 genotype, 185 and 125 bp for the A1/A1 genotype and 310 bp for the A2/A2 genotype. The patients in our study were grouped according to the presence of the *TaqI*-A1 allele [n = 68, A1(+): genotypes *TaqI*-A1/*TaqI*-A1 and *TaqI*-A1/*TaqI*-A2] or the absence of this allele [n = 108, A1(-): genotype *TaqI*-A2/*TaqI*-A2].

*Electrophysiological Recording and Event-Related Potentials:*

The P300 study was carried out in the Event-Related Potentials (ERP) Unit at the *Hospital Universitario 12 de Octubre*, after verifying the absence of an auditory deficit in our patients with a tonal audiometry. An ERP model *Sapphire* device, brand *MED-ELEC*, type 2nd was employed. The bioelectric cerebral activity of long latency was registered after an unexpected and infrequent stimulation (*odd-ball*). The stimulation was a high-pitched (8000 Hz) aleatory sound with a presence of 10% in a sequence of regular sounds (1000 Hz). During the test the patient had to memorise the number of infrequent (8000 Hz) stimuli. The EEG was recorded at parietal (Pz) scalp locations, and digitised at 200 Hz, amplified with a filter bandpass of 1 Hz to 50 Hz.

*Statistical analysis:*

The chi-squared test was used to study sociodemographic and clinical differences between our patients and the reference values obtained from a sample of healthy men of the ERP Unit, and between the A1(+) and A1(-) subgroups. Quantitative variables were compared using ANOVA. In addition, a MANCOVA analysis was carried out, with amplitude and latency of the P300 wave as the dependent variables, and the presence of the *TaqI*-A1 allele as the independent variable. The other independent variables which had been previously identified as possible confounding factors (age, duration and amount of alcohol consumed) were included as covariates when a significant correlation was found with latency or amplitude of P300. The SPSS statistical package version 11.5 was used for analyses. Hardy–Weinberg equilibrium was fulfilled in our sample ($c2 = 0.24$, df = 1, $p = 0.62$).

## Results

Table I shows the clinical characteristics of the total sample and of the A1(+) and A1(-) subgroups. As can be seen the A1(+) patients exhibited a significantly lower age of onset of abuse ($p = 0.004$). No differences were found between the two subgroups of alcoholic patients with respect to other variables.

In this sample of male alcoholic patients, the mean amplitude of the P300 wave was 17.53 microvolts (SD = 2.00) and the mean latency was 361.65 milliseconds (SD = 23.42). This P300 wave latency is significantly greater than the reference value obtained from the sample of healthy men of the ERP unit, matched by age (350 ms, SD = 23.75; $t = 4.69$, $p < 0.001$). No significant differences were found with respect to the reference values for P300 amplitude (17.85 mV; SD = 2.23; $p = 0.15$).

A bivariate correlation between amplitude and latency of P300 was performed. In addition, a partial correlation correcting by

age was performed to analyse the effect of the variable *years of consumption*. Since when comparing the A1(+) and A1(-) subgroups significant differences were found with respect to the *age after which abuse criteria were met* ($p = 0.004$), this variable was also included in the analysis. Only the current *age* of the subjects correlated with both amplitude ($r = -0.198$; $p = 0.008$) and latency ($r = 0.448$; $p < 0.001$) (see Table II).

Table I

| | Total sample (n = 176) | A1(-) (n = 108) | A1(+) (n = 68) | F | p |
|---|---|---|---|---|---|
| Mean age (years) | 41.39 (SD: 9.85) | 41.64 (SD: 9.31) | 40.99 (SD: 10.72) | 0.183 | 0.67 |
| Age at first contact with alcohol | 13.10 (SD: 3.71) | 13.37 (SD: 3.63) | 12.66 (SD: 3.82) | 1.53 | 0.22 |
| Age of onset of regular alcohol use | 16.81 (SD: 4.84) | 16.08 (SD: 5.22) | 16.38 (SD: 4.17) | 0.88 | 0.35 |
| Age of onset of abuse | 22.61 (SD: 6.65) | 23.73 (SD: 7.42) | 20.82 (SD: 4.71) | 8.32 | 0.004 |
| Age of onset of dependence | 30.13 (SD: 8.75) | 30.80 (SD: 8.99) | 29.07 (SD: 8.31) | 1.62 | 0.204 |
| Daily alcohol consumption ($cm^3$) | 164.63 (SD: 142.99) | 221.41 (SD: 128.54) | 237.78 (SD: 164.63) | 0.44 | 0.510 |
| Weekly alcohol consumption ($cm^3$) | 1324.03 (SD: 993.83) | 1325.74 (SD: 923.29) | 1321.33 (SD: 1103.45) | 0.001 | 0.979 |
| SADS | 31.42 (SD: 19.33) | 32.74 (SD: 20.12) | 29.15 (SD: 17.84) | 1.132 | 0.289 |

Table II

| | Amplitude | Latency |
|---|---|---|
| Age | r = -0.198<br>p = 0.008 | r = 0.448<br>p = 0.000 |
| Alcohol consumption (grams/day) | r = -0.082<br>p = 0.315 | r = 0.017<br>p = 0.833 |
| Duration of alcohol consumption (corrected according to current age) | r = -0.12<br>p = 0.14 | r = 0.05<br>p = 0.50 |
| Age at which abuse criteria were met | r = -0.022<br>p = 0.77 | r = 0.021<br>p = 0.784 |

A MANCOVA analysis carried out using *age* as a covariate (see Table III) showed that the P300 latency was increased in alcoholic patients [both A1(+), $p < 0.001$, and A1(-), $p < 0.001$] with respect to control subjects. It can also be seen that the increase in P300 wave latency exhibited by patients in the A1(+) subgroup was significantly greater ($p = 0.017$) than the increase in the A1(-) subgroup. No differences were found in P300 wave amplitude between the A1(+) and A1(-) subgroups or with respect to the reference values of the control group.

Table III

| | *TaqI*-A Genotype | Mean | SD | F | p |
|---|---|---|---|---|---|
| P300 wave amplitude | A1(-) (n = 108) | 17.49 | 2.00 | 0.092 | 0.762 |
| | A1(+) (n = 68) | 17.61 | 2.02 | | |
| | Total (n = 176) | 17.54 | 2.00 | | |
| P300 wave latency | A1(-) (n = 108) | 358.93 | 23.60 | 5.792 | 0.017 |
| | A1(+) (n = 68) | 365.97 | 22.63 | | |
| | Total (n = 176) | 361.65 | 23.42 | | |

control subjects vs. A1(+) $F = 46.47$ $p < 0.001$.
control subjects vs. A1(-) $F = 14.59$ $p < 0.001$.

## Discussion

As far as we know, this is the first study specifically designed to analise the relationship between P300 abnormalities and the presence of the *TaqI*-A1 allele in alcoholic patients. It provides the first evidence of an association between the *TaqI*-A1 allele and a prolonged P300 wave latency in this population. Even the latency of the A1(-) subgroup, though shorter than that of A1(+) subgroup, was longer than the reference value obtained from a sample of healthy men of the ERP Unit ($p < 0.01$).

Although previous studies have found a prolongation of P300 wave latency in alcoholic patients (Maes *et al.* 2001, Keenan *et al.* 1997), none of them considered *TaqI*-A as a genetic marker. On the other hand, a study carried out on neuropsychiatrically-ill patients (Blum *et al.* 1994) suggesting a relationship between presence of the *TaqI*-A1 allele and increase in P300 wave latency did not find an association with alcoholism. This means that the data avaliable up to date regarding the relationship between the *TaqI*-A1 allele and P300 wave abnormalities come exclusively from studies carried out in non-consuming descendents of alcoholic patients (Noble *et al.* 1994, Hill *et al.* 1998).

Our findings also highlight the importance of the possible influence on this association of factors such as age. Thus, when the relationship between P300 and the *TaqI*-A1 SNP genotype was analysed using MANOVA with age as a covariate, we found a significant difference between subgroups, with A1(+) patients showing a more prolonged P300 wave latency. With respect to the possible influence of age, it is important to note that data regarding the association between increased P300 wave latency and the *TaqI*-A1 allele obtained in a non-alcoholic population consisting of young non-consuming children of alcoholics (Noble *et al.* 1994), could not be confirmed in similar populations of an older age (Ratsma *et al.* 2001). Our findings could also explain why a significant decrease in P300 wave amplitude in alcoholic patients is only observed in those aged 30 or less (Costa *et al.* 2000), and even why an association between P300 and alcoholism is not found in some studies (Blum *et al.* 1994).

The fact that we could not find a relationship between P300 wave characteristics and amount of alcohol consumed could be interpreted as a lack of effect of *quantity of alcohol* on this electrophysiological variable. Thus, P300 wave alterations would be related to the presence of idiosyncratic vulnerability factors, as has been shown in studies

with non-alcoholic offspring of alcoholic subjects (Rodriguez-Holguin *et al.* 1998). An alternative explanation could be the existence of a significant effect even at low levels of alcohol consumption. The presence of important differences in ethanol metabolism between alcoholic individuals must also be considered. In fact, subjects with greater alcohol consumption exhibit a greater tolerance to ethanol.

Our study highlights the presence of a longer P300 wave latency in those alcoholic patients who are carriers of the *TaqI*-A1 allele, controlling for the statistical effect of age. The *TaqI*-A1 allele has been associated to a phenotype of severe alcoholism and with antisocial personality traits (Blum *et al.* 1991, Hill *et al.* 1999b, Lu *et al.* 2001, Bau *et al.* 2000, Ponce *et al.* 2003) and our study supports the idea that this polymorphism could represent a marker of greater vulnerability for developing a more severe alcohol dependence, as shown by a more prolonged P300 wave latency.

In summary, different tests associate P300 wave characteristics and the *TaqI*-A1 allele with the development of alcoholism and suggest some relationship between P300 and the *TaqI*-A1 allele. The available data does not allow for the establishment, at a molecular level, of a causal relationship between the *TaqI*-A1 allele and P300 alterations. Our study suggests that different expressions of P300 in alcoholic patients and their relatives could be due to hereditary neurobiological conditions (such as those potentially related to the presence of *TaqI*-A1 allele), and to the fact that dopaminergic circuits implied in P300 wave generation are modified by the age of the subject and/or by the neurotoxic effects of alcohol. Age, consumption and abstinence must be taken into account in future experimental studies of the relationship between alcoholism, P300 and the *TaqI*-A1 allele. Our study has limitations deriving from its cross-sectional and exploratory design. Moreover, since it included males exclusively, it cannot consider the possible influence of another factor, gender. These limitations justify the need for further independent, prospective studies, aiming to investigate the effects of maintained abstinence on these patients.

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