

DRD2 and ANKK1 genotype in alcohol-dependent patients with psychopathic traits: association and interaction study

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Background

The *TaqI-A* polymorphism of the *ANKK1* gene, adjacent to the *DRD2* gene, has been associated with alcoholism and other psychiatric conditions, although other *DRD2* gene variants, such as the C957T polymorphism, could be related to these phenotypic traits.

Aims

To investigate the contribution of the *TaqI-A* and the C957T polymorphisms to the presence of psychopathic traits in patients with alcoholism.

Method

We performed association and interaction analyses of the polymorphisms in 150 controls and 176 male alcohol-dependent patients assessed for the presence of

dissocial personal disorder, using the Psychopathy Checklist-Revised (PCL-R).

Results

There was a significant association of the *TaqI-A* and C957T polymorphisms when both genotypes were present, with PCL-R scores of $F_{1,171}=0.13$ ($P=0.01$) and a frequency of dissocial personal disorder OR=10.52, $P<0.001$.

Conclusions

The *TaqI-A* of the *ANKK1* gene and the C957T of the *DRD2* gene are epistatically associated with psychopathic traits in alcohol-dependent patients.

Declaration of interest

None

The A1 allele of the *TaqI-A* polymorphism, located 9.4Kb downstream from the coding region of the *DRD2* gene, has been associated with a variety of phenotypes/endophenotypes, among them, severe alcoholism and psychopathic traits in alcohol-dependent patients.^{1,2} However, a functional polymorphism of the *DRD2* gene (C957T) has been proposed as being responsible for some of the phenotypic features which had been previously associated with the A1 allele, such as D₂ dopamine receptor availability in the striatum.³ The C957T *DRD2* single nucleotide polymorphism (SNP) affects messenger RNA stability and protein synthesis *in vitro*.⁴ Additionally, it is now known that the *TaqI-A* polymorphism is located in a nearby novel gene named *Ankyrin Repeat and Kinase Domain Containing (ANKK1)* where it causes a missense substitution.⁵ A question that remains to be answered is which other phenotypes previously associated with the A1 allele are better explained by the proximity to the C957T *DRD2* polymorphism, and which are related to *ANKK1* itself. Interestingly, the *TaqI-A* SNP of the *ANKK1* gene, but not C957T of the *DRD2* SNP, is associated with increased striatal activity of aromatic L-amino acid decarboxylase, the final enzyme in the biosynthesis of dopamine.⁶

From the clinical point of view, a major issue is the relationship of A1+ genotype with antisocial behaviours,^{2,7} given the importance of antisocial personality disorder in patients with alcoholism and other substance misuse disorders.^{8,9} It has been proposed that the concept of psychopathy, as defined by Hare's Psychopathy Checklist-Revised (PCL-R),¹⁰ would be helpful for the identification of a more homogeneous group among alcohol-dependent patients with behavioural disturbances. This concept, based in Cleckley's criteria,¹¹ places more weight upon the psychological nuclear characteristics rather than non-adaptive behaviours.

Taking into account all this information, we have investigated the hypothesis that the risk for psychopathic traits in

alcohol-dependent patients may be related to both *TaqI-A ANKK1* SNP and C957T *DRD2* SNP.

Methods

Participants

The study included 176 alcohol-dependent Spanish males who had consecutively requested detoxification at the Addictive Behaviour Unit of the 'Doce de Octubre' University Hospital. Inclusion criteria were (a) males aged 18–65 years and (b) alcohol dependence according to DSM-IV criteria.¹² Exclusion criteria included the presence at baseline evaluation of another axis I psychiatric disorder diagnosed according to DSM-IV¹³ (except nicotine addiction). In addition, a number of other more general factors were considered such as the absence of family relationships and family history of immigration. Both historical data and immunogenetic studies have previously shown that the Spanish population is ethnically homogeneous and has been stable for at least 500 years.¹⁴ Patients of other ethnic backgrounds were not included in this study. The general characteristics of the sample patients were as follows: mean age, 42.1 years (s.d.=10.7); mean age at misuse onset, 23.2 years (s.d.=7.0); mean age at dependence onset, 30.1 years (s.d.=9.1); mean grams of alcohol per intake, 224.2 g (s.d.=166.2); number of patients with physiological dependence, 145 (82.4%); number of patients with family history of alcoholism, 97 (55.1%); and number of patients with alcohol-related medical problems, 79 (44.8%).

A group of 150 healthy individuals were recruited as controls on whom a genetic study was also performed following a clinical interview to ensure non-dependence on alcohol or other drugs. All alcohol-dependent patients and controls were unrelated to individuals within their group.

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The study was approved by an ethics committee and informed written consent was obtained from all participants.

Assessment of psychopathy and antisocial behaviour

In order to evaluate psychopathic traits in the patients, the PCL-R¹⁰ was used as described in Hoenicka *et al.*¹⁵ We applied the version that had previously been standardised by Moltó *et al.*¹⁶ for its use in male prison inmates in Spain. Given that cut-off values have not been established for the PCL-R scale in populations of alcohol-dependent patients, this scale was not employed to make a diagnosis of psychopathy. The PCL-R was, therefore, used in a dimensional manner in order to evaluate the degree of association of genetic markers with the total score across the whole scale. The PCL-R scale sub-factors were also evaluated dimensionally.¹⁷

We used criteria from ICD-10¹⁸ for the diagnosis of dissocial personality disorder as a categorical approach, since it has been proposed that the attributes measured by the PCL-R are similar in many respects to this disorder.¹⁹ The diagnosis of dissocial personality disorder was made by applying the International Personality Disorder Examination (IPDE; ICD-10 module).²⁰

Genotyping

High molecular weight genomic DNA was purified from peripheral blood leukocytes using standard methods. This DNA served as a template for subsequent analysis by polymerase chain reaction-based methods. Genotyping was performed by *Taqman* assays, designed to run on an ABI 7900HT machine with sequence detection system software. The sequence-specific primers for *TaqI*-A *ANKK1* SNP, 5'-CTGCCTCGACCAGC-3' and 5'-CTGCCTTGACCAGC-3', were designed and used for the C (A2) and T (A1) allele respectively, in addition to a common reverse primer 5'-GCAACACAGCCATCCTCAAAG-3'. Ten samples for each genotype were confirmed by direct sequencing analysis. The resulting genotypes for the *TaqI*-A *ANKK1* SNP were clustered according to the presence of at least one A1 allele (A1+ genotype: A1 allele homozygous and heterozygous; A1- genotype: homozygous for the A2 allele) as described by Blum *et al.*²¹ European population estimates for A1+ genotype frequencies range from 20.8 to 43.4% (National Center of Biotechnology Information (NCBI), www.ncbi.nlm.nih.gov; identification number rs1800497).

The C957T *DRD2* SNP was analysed as previously described by Hoenicka *et al.*¹⁵ Briefly, the sequence-specific primers for *Taqman* assays 5'-CTGTCCGGGAGTGCTG-3' and 5'-CTGTCCAGGAGTGCTG-3 were used for the C and T alleles respectively, and the common reverse primer 5'-GCCCATTTCTCTGGTTTGG-3'. The genotypes obtained were grouped assuming a recessive model for the C957 allele: homozygous individuals for the C allele *v.* heterozygous and homozygous individuals for the T allele. European population estimates for CC genotype frequency range from 12.5 to 17.2% (NCBI, identification number rs6277).

The Hardy-Weinberg equilibrium test with the Genetic Data Analysis software version 1.1 for Windows found no deviation from either controls (*TaqI ANKK1* SNP, $P=0.44$; C957T *DRD2* SNP, $P=0.78$) or patients (*TaqI ANKK1* SNP, $P=0.37$; C957T *DRD2* SNP, $P=0.98$).

Taking into account the size of our sample of patients and an α -value of 0.05, we calculated the power of the genotype study for the two SNPs using Power Sample Size version 2.1.31 software for Windows. Our study varies with OR=2.4 and a power of 86.6% for *TaqI*-A *ANKK1* SNP, and OR=2.0 and a power of 80.6% for C957T *DRD2* SNP.

Statistical analysis

To evaluate the non-random association of the two SNPs, pairwise linkage disequilibrium statistics D' and correlation coefficient r^2 were calculated using Haploview software version 3.2 for Windows (Whitehead Institute for Biomedical Research, www.broad.mit.edu/mpg/haploview/index.php). D' explains the difference in frequency between the observed and expected number of SNP pairs. Being scaled to D_{\max} , it spans the range -1 to 1, and r^2 is the squared correlation coefficient between the markers. We found a low degree of *TaqI*-A to C957T linkage disequilibrium (patients $D'=0.576$, $r^2=0.13$; controls $D'=0.58$, $r^2=0.14$).

Case-control association genetic study with alcoholism

To compare differences between alcohol-dependent patients and healthy controls with respect to the genotype for each SNP, a chi-squared test was employed.

Case-case association genetic study with psychopathic traits and dissocial personality disorder

In the sample of patients, in order to evaluate the effect of each genotype on the average score on the PCL-R scale, we performed analyses of covariance using age as a covariate, since it has been reported that PCL-R scores may vary with age.¹⁷

Chi-squared tests were employed to compare genotype frequencies between alcohol-dependent patients with and without a diagnosis of dissocial personality disorder. A stepwise logistic regression model was used to calculate the independent association of each gene with the presence of dissocial personality disorder. Odds ratios, 95% confidence intervals and Wald values were estimated.

Case-case interaction study

A *post hoc* regression analysis of the interaction between genotypes and the effect upon the presence of dissocial personality disorder was also carried out.

The total sample of alcohol-dependent patients was subdivided according to the number of risk genotypes in order to study the global effect on dissocial personality disorder and PCL-R scores. Again, the chi-squared test was used to compare the presence of dissocial personality disorder between these subgroups, and *post hoc* analyses of covariance to compare PCL-R scores.

In order to correct for multiple comparisons, a Bonferroni-corrected α -level of $P < 0.025$ ($0.05/2$) was used for the two independent variables examined in Table 1. Otherwise, an α -level of 0.05 was used throughout. These statistical calculations were performed using the SPSS Statistical Package, version 11.1D for Windows.

Results

Case-control association genetic study with alcoholism

Population estimates for CC and A1+ genotypes in our controls are comparable to those previously reported (see Methods). We then analysed the C957T *DRD2* SNP and found a higher prevalence of the CC genotype in alcohol-dependent patients than in healthy controls. This difference did not reach statistical significance when multiple-comparison correction was applied. In the case of the *TaqI*-A *ANKK1* SNP, we did not observe significant differences in the frequencies of the genotypes between alcohol-dependent patients and healthy controls (Table 2).

Table 1 Distribution of *TaqI*-A *ANKK1* SNP and C957T *DRD2* SNP genotypes in controls and alcohol-dependent patients

Group	<i>TaqI</i> -A, n (%)		C957T, n (%)	
	A1+	A1-	CC	CT/TT
Controls (n=150)	49 (32.67)	101 (67.33)	18 (12.00)	132 (88.00)
Alcohol-dependent (n=176)	68 (38.64)	108 (61.38)	37 (21.02)	139 (78.98)
	$\chi^2=1.00, P=0.30$		$\chi^2=4.07, P=0.04$	
Alcohol-dependent with dissociative personality disorder	20 (58.82)	14 (41.18)	14 (41.18)	20 (58.82)
Alcohol-dependent without dissociative personality disorder	48 (33.80)	94 (66.20)	23 (16.20)	119 (83.80)
	$\chi^2=6.227, P=0.013$		$\chi^2=8.86, P=0.003$	
Alcohol-dependent without dissociative personality disorder v. controls	$\chi^2=0.007, P=0.935$		$\chi^2=0.745, P=0.388$	
Alcohol-dependent with dissociative personality disorder v. controls	$\chi^2=7.01, P=8.09 \times 10^{-3}$		$\chi^2=14.46, P=1.44 \times 10^{-4}$	

SNP, single nucleotide polymorphism.

Case-case association genetic study with dissociative personality disorder

When patients were separated according to whether they had comorbid dissociative personality disorder, the CC genotype for the C957T SNP was found to be overrepresented in the group of patients with dissociative personality disorder (OR=5.13), as well as the A1+ genotype for the *TaqI*-A SNP (OR=2.95). These differences were statistically significant (Table 1). Furthermore, no statistically significant differences were observed between healthy controls and alcohol-dependent patients without dissociative personality disorder.

A logistic regression analysis was then performed using the presence of dissociative personality disorder as a dependent variable, which confirmed that the A1+ genotype has a significant effect that cannot be explained by the presence of C957T (CC: OR=3.26, 95% CI 1.4–7.5, Wald=7.71, P=0.005; A1+: OR=2.51, 95% CI 1.1–5.5, Wald=5.27, P=0.022), and *vice versa*. The *post hoc* logistic regression analysis showed a significant pattern of interaction (OR=10.52, 95% CI 3.74–29.62, P<0.0001).

To gain more insight into the possible interaction between the *DRD2* and *ANKK1* genes, we studied the effect of carrying none, only one, or both risk genotypes identified in this study. The

expression of dissociative personality disorder in individuals that were carriers of both risk genotypes (CC and A1+) was higher than that of patients who were carriers of none or only one risk genotype, either A1+ or CC ($\chi^2=26.56, d.f.=3, P<0.001$) (Fig. 1).

Case-case association genetic study with psychopathic traits

When the sample of patients was evaluated for genetic association with psychopathic traits, analyses of covariance revealed that the CC genotype of the C957T *DRD2* SNP was associated with significantly higher scores on the PCL-R total and on both factor 1 and factor 2 of the scale. In contrast, the A1+ genotype of the *TaqI*-A *ANKK1* SNP was associated with significantly higher scores only on factor 1. Moreover, the statistical analysis revealed a significant interaction effect between these two polymorphisms, and *post hoc* analyses (Scheffe) revealed that scores on the PCL-R and its factors were significantly higher only in the group of patients who were carriers of both CC and A1+ genotypes (Table 3), whereas there were not significant differences between the other three groups.

Table 2 Relationship between *TaqI*-A *ANKK1* and C957T *DRD2* SNP genotypes and PCL-R scores

PCL-R score	Mean (s.d.)	$F_{1,171}$	P	Interaction	
				$F_{1,171}$	P
<i>Total</i>					
C957T					
CC	15 838 (12 059)	17 055	<0.001	6810	0.010
CT/TT	8590 (7662)				
<i>TaqI</i> -A					
A1+	11 220 (10 574)	4227	0.041		
A1-	9417 (8228)				
<i>Factor 1</i>					
C957T					
CC	6081 (6148)	13 701	<0.001	6333	0.013
CT/TT	2906 (4364)				
<i>TaqI</i> -A					
A1+	4324 (5653)	5709	0.018		
A1-	3102 (4409)				
<i>Factor 2</i>					
C957T					
CC	8108 (4864)	10 733	0.001	4209	0.042
CT/TT	4818 (5043)				
<i>TaqI</i> -A					
A1+	5853 (4804)	1000	0.319		
A1-	5583 (4190)				

PCL-R, Psychopathy Checklist-Revised; SNP, single nucleotide polymorphism.

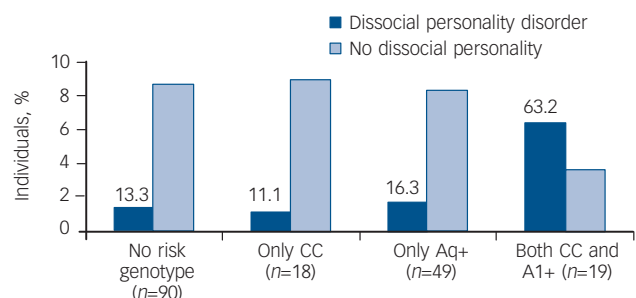


Fig. 1 Percentage of individuals who met criteria for dissociative personality disorder when none, only one or both risk genotypes were present.

The frequency of dissociative personality disorder is the highest in the group of carriers of both risk genotypes, reaching statistical significance. There are no significant differences between the other three groups.

Table 3 *Post hoc* analyses between patients carrying only CC, only A1+, and CT/TT and A1- genotypes

<i>Post hoc</i> analysis ^a	Total PCL-R score	PCL-R factor 1	PCL-R factor 2
CC and A1+ v. CC	P=0.018	P=0.016	P=0.139
CC and A1+ v. A1+	P<0.001	P<0.001	P<0.001
CC and A1+ v. CT/TT and A1-	P<0.001	P<0.001	P=0.001

PCL-R, Psychopathy Checklist-Revised
 a. Differences in comparisons between groups CC, only A1, and CT/TT and A1- were not statistically significant (P>0.1) for total PCL-R and for both factors.

Discussion

Main findings

We found CC and A1+ genotypes to be overrepresented only in alcohol-dependent patients with comorbid dissocial personality disorder. We also identified an association of both risk genotypes with high scores on PCL–R. Moreover, our results suggest that these genes epistatically influence the expression of dissocial personality disorder and psychopathic traits in our sample of alcohol-dependent patients.

This genetic interaction may reflect a functional relationship between the dopaminergic receptor D₂ and the putative kinase *ANKK1*, given that it has been proposed that this protein could exert an effect on dopaminergic neurotransmission itself.⁶ Our results also illustrate the potential benefit of studying interactions between functional polymorphisms known to be involved in the same biological pathway, especially when studying multigenic disorders/traits. In a previous study, we have reported an additive relationship of the A1+ genotype, together with genetic variants for the *CNR1* and *FAAH* genes, with psychopathic traits, using the PCL–R.¹⁵ The new data presented here reveal that the effect of the A1+ genotype on the psychopathic phenotype depends on the interaction with the CC genotype for the *DRD2* C957T SNP.

Implications

Our results regarding the association between the risk genotypes identified in this study and psychopathic traits in alcohol-dependent patients provides further support to previous family studies that have suggested that substance misuse disorders and antisocial behaviour could share, at least in part, common genetic vulnerability factors.²² The psychopathy construct has demonstrated its validity since it correlates with variations in neurobiological function,^{23,24} and a recent heritability study has described that callous-unemotional traits are under strong genetic influence.²⁵ Psychopathy has been considered a condition based on differences in learning mechanisms^{26,27} suggesting the concurrence of the meso-limbic dopaminergic system, which in turn has been repeatedly linked to addictive behaviours.²⁸ Given the central role of dopamine in the reward system, the gene that encodes for the D₂ dopamine receptor has been widely studied in relation to these disorders.

The change in the views regarding the implication of locus 11q23-24 with respect to phenotypic characteristics related to dopaminergic function has received support with the discovery of the *ANKK1* gene,⁵ where the *TaqI*-A SNP is actually located. Recently, more extensive genotyping across *DRD2* and *ANKK1* confirms that the association with substance dependence and antisocial traits might be due to genetic variants in the *ANKK1* gene.^{29,30}

The protein encoded by *ANKK1* is one of a family of proteins involved in signal transduction pathways. Since *TaqI*-A, but not C957T, has been associated with differences in striatal activity of aromatic L-amino acid decarboxylase,⁶ *ANKK1* could be related to dopamine pathways. The *TaqI*-A SNP causes an amino acid substitution within the 11th ankyrin repeat of the putative protein, which may affect substrate-binding specificity.

Combining these results with ours suggests that the fact that the *ANKK1* and *DRD2* genes are so close is not due to chance, instead that they could somehow interact in neurotransmitter pathways, affecting a person's vulnerability to both addiction and antisocial traits.

Study limitations

A limitation of our study derives from the way in which we applied the PCL–R. It must be noted that the PCL–R was not used

for diagnosing psychopathy, but for evaluating specific traits related to antisocial behaviour. The PCL–R's reliability and specificity have been demonstrated in prison inmates in Spain.¹⁶ Although few studies have been performed in substance-dependent patients, the PCL–R is generalisable across prison and substance-dependent samples,³¹ and recent studies have proposed that the psychopathy construct must be separated from criminality.³² On the other hand, the factorial structure of the PCL–R in different populations is still an open issue.^{32,33}

Given the relatively small size of our samples, our results should be considered as preliminary. To validate our results, a study of independent samples of alcohol-dependent patients, as well as populations of individuals free of addictive disorders, would be desirable, although there are obvious difficulties in recruiting samples of individuals with psychopathic personality disorders without confounding comorbidity. The analysis of families in which both alcoholism and antisocial disorders are present would also help to clarify the role of *ANKK1* and *DRD2* variants. In addition, we cannot rule out the existence of phenotypical differences in the A1A1 and the A1A2 genotype carriers. The size of our A1A1 patient sample is small, and hence could be deemed insufficient to detect a real contribution.

Despite these limitations, our study suggests that the expression of antisocial traits in alcohol-dependent patients relies, at least in part, on the existence of a potential interaction between *ANKK1* and *DRD2*.

Finally, one cannot automatically infer biological interaction from statistical interaction, but if our findings are replicated, future research should also examine additional markers covering the two genes, as well as their intergenic linkage disequilibrium and haplotypes. Undoubtedly, functional studies of the *ANKK1* gene, its putative peptide, and its relation with the D₂ receptor, could open new avenues into the investigation of the mechanisms underlying the high comorbidity of antisocial personality disorder with alcoholism and other substance misuse disorders.

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words

Mentalisation: a key skill for psychiatrists and their patients

Jeremy Holmes

Mentalisation: 'mind-mindedness', the ability to see ourselves as others see us, and others as they see themselves; to appreciate that all human experience is filtered through the mind and therefore that all perceptions, desires and theories are necessarily provisional. Psychotherapy, whether cognitive or psychoanalytic, aims to enhance mentalisation skills and to identify situations in which mentalisation is impaired. Mentalisation and arousal are inimical – stress interferes with the ability to mentalise effectively. Stressed non-mentalising psychiatrists and their patients, especially those with borderline personality disorder, are less likely to make good decisions than their mentalising counterparts. Training helps overcome this.

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