Received: 22 February 2022 | Accepted: 29 July 2022

DOI: 10.1002/pmh.1563

RESEARCH ARTICLE

Personality and Mental Health

Relationship of DRD5 and MAO-B VNTR polymorphisms with paranoid and antisocial personality disorders in polydrug users

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Funding information
Centro Superior de Investigación en Salud Pública, Generalitat Valenciana, Grant/Award Number: CS2003-05-05; Fundación de Investigación del Hospital Provincial de Castellón, Grant/Award Numbers: CAF 15-049, 21-042, 21-043; Conselleria de Sanitat, Generalitat Valenciana, Grant/Award Number: T4591000

Abstract

Although multiple studies have shown the role genetics plays in personality disorders and in addictions, few have studied the genetic aspects of their comorbidity. Here, we carried out a cross-sectional study in a sample comprising 303 Caucasian polydrug-consuming patients. The presence of personality disorders was evaluated using the International Personality Disorder Examination, and genes related to dopamine, serotonin and monoamine oxidase (MAO) were genotyped. A significant relationship was observed between the bp 279 *DRD5* variable number of tandem repeat (VNTR) polymorphism and paranoid personality disorder $(\mathrm{OR}(95\%\mathrm{CI}) = 2.186\,(1.074;4.449); p = 0.006)$. The bp 182 $(\mathrm{OR}(95\%\mathrm{CI}) = 0.407\,(0.178;0.931); p = 0.033)$ and bp 184 $(\mathrm{OR}(95\%\mathrm{CI}) = 0.391\,(0.188;0.813); p = 0.012)$ alleles of the *MAOB* VNTR were also associated with antisocial personality disorder. Among patients with addictions, paranoid personality disorder should also be considered in addition to the importance of antisocial and borderline personality disorders. The higher frequency of the bp 279 *DRD5* VNTR allele found in patients with paranoid personality disorder, as well as the associations between alleles of the *MAOB* VNTR and antisocial personality disorder, support the monoaminergic bases of these personality disorders, especially when dealing with patients with addictions.

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INTRODUCTION

A personality disorder (PD) constitutes the expression of personality traits that interfere with the daily activities of life and that often lead to significant suffering and/or functional limitations (Ekselius, 2018). Among the big five personality traits, neuroticism and openness to experiences were shown to be the most heritable (Abdellaoui et al., 2019; Power & Pluess, 2015). Genome-wide association studies (GWAS) have indicated that personality traits have a polygenic character. Studies with increasing sample sizes found a greater association with certain genes, which was also compatible with a polygenic model (Sanchez-Roige et al., 2018). The possibility that maladaptive personality traits may be related to polygenic inheritance could correspond to an increased vulnerability to developing a PD (Lo et al., 2017). Indeed, a recent study of GWAS found a partially shared genetic background for borderline personality disorder (BPD) and neuroticism and openness (Streit et al., 2022).

Epidemiological studies carried out in families, twins and adoptions have proven to be more effective in determining the heritability of certain traits (Mateu et al., 2008). The most studied Group A PD is schizotypal personality disorder (SPD), which has been examined in terms of its association with schizophrenia (Cassady et al., 1998; Kendler et al., 1994; Kendler & Diehl, 1993). Previous studies have suggested an association of lower dopamine receptor density with Cluster A PDs [including paranoid personality disorder (PPD) and schizoid personality disorder (ScPD)] (Farde et al., 1997; Kestler et al., 2000). For example, polymorphisms in exon 6 of the *DRD2* gene have been associated with Cluster A PDs (Rosmond et al., 2001). However, there is little evidence on the role of serotonergic and monoamine oxidase gene polymorphisms associated with Cluster A PDs, as most research involves very few patients presenting these disorders and tends to focus on their association with genes of the dopaminergic pathway (Bukh et al., 2014; Reichborn-Kjennerud, 2010).

In terms of Group B PDs, the main fields of investigation are the genetics of BPD and antisocial personality disorder (APD) (Mateu et al., 2008). When evaluating the molecular models that might be involved, dopamine D5 receptor genes were associated with APD (Sunahara et al., 1991; Vanyukov et al., 2000). In twin populations, common genetic ($r = 0.64$) and environmental ($r = 0.40$) aetiological factors have been found between loneliness and the presence of BPD (Schermer et al., 2020).

Indeed, BPD has been associated with a three-allele polymorphism in the 5′promotor region of the serotonin transporter gene (*5-HTTLPR*) as well as polymorphism of the monoamine oxidase A (*MAOA*) gene (Reichborn-Kjennerud, 2010). This *MAOA* polymorphism is associated with antisocial traits (Jacob et al., 2005), and, in fact, *5-HT2C*, *MAOA* and *TPH2* have also been associated with BPD (Ni et al., 2009). A genetic and epigenetic influence on receptors of the serotonergic and dopaminergic pathways has also been found in both BPD and schizotypal, antisocial and avoidant traits (Bulbena-Cabre et al., 2018). Furthermore, other studies have linked anxiety traits with *5-HTTLPR* polymorphism (Lesch et al., 1996).

The association between some PDs and substance use is notable. In a study of Norwegian twins, an association was found between cocaine use and the presence of antisocial (OR = 4.24) and borderline (OR = 2.19) traits (Gillespie, Aggen, Gentry, et al., 2018). In another study, Group B personality traits were associated with cannabis use and the development of cannabis use disorder. Indeed, genetic risks for antisocial and borderline personality traits explained 30%–60% of the total variance in cannabis use and in cannabis use disorder (Gillespie, Aggen, Neale, et al., 2018). Regarding genetic markers associated with polydrug use, a significant association was found between polymorphism in the *MAOB* gene and addiction to cocaine and opioids (Mateu et al., 2021).

The objective of this study was to evaluate the association between certain variable number of tandem repeat (VNTR) polymorphisms in several genes related to dopamine, serotonin and monoamine oxidase (MAO) with the presence of PDs in substance users. Our specific objectives were to (a) evaluate the presence of substance use disorders; (b) evaluate the presence of PDs according to the DSM-IV-TR; (c) genotype VNTR polymorphisms in the dopaminergic pathway (DBH, DRD5 and TH), serotonergic pathway (HTR1B, HTR1D, HTR2C, and TPH) and the MAO enzyme (MAOA and MAOB); and (d) relate these polymorphisms to PPD and APD while also accounting for their relationship with addictions. Our hypothesis was that the PDs we studied would be significantly associated with the genetic polymorphisms we analysed.

MATERIALS AND METHODS

Sampling and phenotyping

The sample was obtained by consecutively recruiting patients who came to receive treatment either in the Hospital Detoxification Unit at the Hospital Clínico Universitario in Valencia (Spain) or as walk-in patients in the Addictive Behaviours Units at the San Marcelino and Padre Porta clinics in Valencia or the Dual Pathology Program at the Hospital de La Ribera (Alzira, Valencia).

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All the patients were aged 18–65 years, presented dependence on opiates, cocaine or alcohol (according to the DSM-IV-TR criteria) and did not have any Axis I pathologies other than addiction. The data were either obtained from their medical histories for hospitalised patients and through the MINI International Neuropsychiatric Interview (Sheehan et al., 1998).

The sample size was calculated using G*Power software (v3.1.9.4) (Faul et al., 2009). With an effect size of 0.25, alpha of 0.05, power of 0.95 and 4 degrees of freedom, we calculated that a sample size of 298 patients would be required. The sample comprised 303 Caucasian polyconsumers, 231 (76.24%) male and 72 (23.76%) female, aged an average of 34.5 ($SD = 8.01$) years.

The International Personality Disorder Examination (Loranger et al., 1994) and an ad hoc survey about sociodemographic, clinical and substance use variables (Haro et al., 2004) were used. We also employed the Fagerström Nicotine Dependence Test (revised version) (Heatherton et al., 1991) and the European Addiction Severity Index (EuropASI) (Kokkevi & Hartgers, 1995). In the case of hospitalised patients, psychometric tests were performed between the fifth and sixth day after admission to avoid the possibility that withdrawal from psychoactive substances might alter the results of the tests.

Genotyping

The DNA extraction process and sample genotyping was performed by following the protocol described by Freeman et al. (2003) by the Institute of Psychiatry at King's College London. An epithelial cell sample was obtained for DNA extraction from a cotton bud that the participants rubbed on the inside of their cheeks for at least 30 s.

For all the markers, the sense and antisense PCR primer reagents were combined in equal amounts to create a single reagent. All the primers in the PCR reaction were optimised to work in a single reaction. A group of genes with a VNTR polymorphism in the dopaminergic pathway (*DBH*, *DRD5* and *TH*), serotonergic pathway (*HTR1B*, *HTR1D*, *HTR2C* and *TPH*) and related to MAO (*MAOA* and *MAOB*) were chosen. Each multiplex PCR reaction contained 9 μl of true allele PCR mix (PE Biosystems, Foster City, CA, USA), 0.33 μM *DRD5* primers, 13.5 pmol/L of *MAOB* primers, 5.7 pmol/L of *5HT1B* primers, 15.4 pmol/L of *5HT2C* primers and 25 ng of DNA.

A novel marker for *5HT1B* was identified using the Tandem Repeat Finder program (Benson, 1999). Where possible, viable markers were selected and primers designed to amplify the repeating region of the genes; primers for the remaining genes were obtained from Konradi et al. (1992) for *MAOB* and Yuan et al. (2000) for *5HT2C* (Konradi et al., 1992; Yuan et al., 2000). The gene markers consisted of a (TG)n repeat 25,498 bp downstream of *5HT1B*, a (GT)n repeat in intron 2 of *MAOB* and a (GT)n repeat in the bp 1027 promoter upstream of *5HT2C*, as described in Nash et al. (2005).

Statistical analysis

The statistical analysis was performed using SPSS software (Version 21.0; IBM Corp., Armonk, NY). After the exploratory and descriptive study, Student's *t*-tests and chi-squared tests were used. Logistic regression models were developed to evaluate how independent variables (genetic, using the base pair with the lowest number as the reference category) can predict the different diagnoses of PDs (using the absence of the disorder as the reference category) while also considering age and sex (using women as the reference category) and substance dependence (using non-dependence as the reference category).

Non-Caucasian patients were excluded from the genetic analysis ($n = 6$). Polymorphisms with a frequency of less than 10% were grouped into a 'dummy' allele (allele 1000) whose results were not considered. A binary logistic regression model was created for each of the PDs whose prevalence had exceeded 5%. Thus, avoidant, narcissistic, schizoid, schizotypal, obsessive–compulsive, dependent and histrionic PDs were excluded.

Furthermore, given that there are common genetic and environmental underlying characteristics for all PDs (Newton-Howes et al., 2015), patients with unspecified PDs were excluded in order to detect the differential characteristics of the most frequent PDs in our sample. Because most of the probable PDs would be classified as personality disorder-not otherwise specified (PD-NOS), they were also excluded. Thus, only APD, BPD and PPD were considered for the logistic regressions. The reference category was the absence of the disorder.

RESULTS

Sociodemographic characteristics, addictions and polymorphisms

The sociodemographic characteristics of polydrug users included in this sample are summarised in Table 1. Opioids (70.9%), followed by cocaine (47.9%), were the substances with the highest consumption prevalences. The results for the frequency of polymorphisms are shown in Table 2.

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TABLE 1 Sociodemographic and clinical characteristics of the study sample

VARIABLE		MEAN/%	*SD/n*
AGE		34.40	8.09
SEX	MEN	76	238
	WOMEN	24	75
ADICCTION	OPIOIDS	70.9	222
	ALCOHOL	28.8	90
	COCAINE	47.9	150
	CANNABIS	29.4	92
	BENZODIAZEPINES	28.1	88
	ANPHETAMINES	1	3
PERSONALITY DISORDER (PD)	PARANOID	8.9	28
	SCHIZOID	1.9	6
	SCHIZOTYPIC	0.3	1
	BORDERLINE	16.9	53
	HISTRIONIC	0.3	1
	NARCISSISTIC	1.6	5
	AVOIDANCE	4.9	15
	DEPENDENT	1	3
	OBSESSIVE–COMPULSIVE	1	3
	ANTISOCIAL	13.4	42
	NOT SPECIFIED	15.3	48
PRESENCE OF PDs		49.5	155
NUMBER OF PDs	0	50.5	158
	1	38.7	121
	2	7.3	23
	3	1.6	5
	4	1.9	6

Relationships between addictions, sociodemographic characteristics and polymorphisms

A significant association between sex and cocaine addictions was found ($\chi^2 = 5.96$; $p = 0.015$; ASR, males = 2.4). No significant sex associations were found for any of the *HTR1B* ($\chi^2 = 0.43$; $p = 0.805$), *HTR1D* ($\chi^2 = 0.88$; $p = 0.644$), *HTR2C* ($\chi^2 = 1.14$; $p = 0.284$), *TPH* ($\chi^2 = 1.57$; $p = 0.456$), *DBH* ($\chi^2 = 1.59$; $p = 0.661$), *DRD5* ($\chi^2 = 2.01$; $p = 0.156$), *TH* ($\chi^2 = 3.30$; $p = 0.508$), *MAOB* ($\chi^2 = 0.84$; $p = .839$) or *MAOA* ($\chi^2 = 0.67$; $p = 0.410$) genetic polymorphisms. Age was related to opiate [$t = 4.70$; $p < 0.001$; $\overline{X}$ no addiction = 37.95 ($SD = 10.75$) > $\overline{X}$ addiction = 33.05 ($SD = 6.68$)], alcohol [$t = 7.19$; $p < 0.001$; $\overline{X}$ addiction = 39.16 ($SD = 8.72$) > $\overline{X}$ no addiction = 31.70 ($SD = 6.98$)], cocaine [$t = 6.61$; $p < 0.001$; $\overline{X}$ no addiction = 41.84 ($SD = 10.11$) > $\overline{X}$ addiction = 31.86 ($SD = 6.37$)], cannabis [$t = 3.54$; $p = 0.001$; $\overline{X}$ no addiction = 37.04 ($SD = 10.79$) > $\overline{X}$ addiction = 32.35 ($SD = 6.62$)] and benzodiazepine [$t = 2.25$; $p = 0.025$; $\overline{X}$ no addiction = 35.19 ($SD = 8.88$) > $\overline{X}$ addiction = 32.97 ($SD = 6.61$)] addiction.

We found a significant association between opiate addiction and the presence of the *MAOB* polymorphism ($\chi^2 = 8.10$; $p = 0.044$; ASR bp 184: 22.6). Alcohol addiction was significantly related to the presence of *DBH* polymorphism ($\chi^2 = 8.23$; $p = 0.041$; ASR bp 299: −2.1; ASR bp 321: 2.1). Cannabis addiction was related to *MAOB* polymorphism ($\chi^2 = 24.54$; $p < 0.001$; ASR bp 182: −4; ASR bp 184: 3.8). Finally, benzodiazepine addiction was related to *HTR1B* polymorphism ($\chi^2 = 6.03$; $p = 0.049$; ASR bp 302: 2.2; ASR bp 304: −2.2).

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TABLE 2 Polymorphism frequencies

GENE	BASE PAIR	%	*N*
HTR1B	302	69.8	399
	304	12.8	73
	308	11.5	66
	1,000	5.9	34
HTR1D	348	45.4	277
	362	17.5	107
	366	12.6	77
	1,000	24.4	149
HTR2C	259	32.7	196
	265	62.2	373
	1,000	5.2	31
TPH	188	37.8	229
	192	15.3	93
	198	25.2	153
	1,000	21.6	131
DBH	299	16.6	94
	301	22.1	125
	319	41.5	235
	321	11.3	64
	1,000	8.5	48
DRD5	279	13.9	82
	281	78	460
	1,000	8.1	48
TH	246	20.9	120
	250	14.8	85
	254	12.7	73
	258	22.8	131
	261	28.7	165
MAOA	319	34.1	197
	348	62.4	360
	1,000	3.5	20
MAOB	180	13.5	82
	182	20.5	124
	184	24.6	149
	y186	30.9	1,187
	1,000	10.6	64

Relationship of PDs to sociodemographic characteristics, addictions and polymorphisms

The presence of PDs and their association with the other variables is summarised in Table 3. Significant associations were found between PPD and the use of benzodiazepines ($\chi^2/F/t = 5.47$; $p = 0.019$) and with the *DRD5* bp 279 polymorphism ($\chi^2/F/t = 4.84$; $p = 0.028$). We also found associations between BPD and age ($\chi^2/F/t = 1.99$; $p = 0.047$; No > Yes), cannabis consumption ($\chi^2/F/t = 5.10$; $p = 0.024$; Yes: 2.3) and the use of benzodiazepines ($\chi^2/F/t = 5.17$; $p = 0.023$; Yes: 2.3). APD was associated with age ($\chi^2/F/t = 3.49$; $p = 0.001$; No > Yes), sex ($\chi^2/F/t = 6.24$; $p = 0.012$; Men: 2.5), opioid consumption ($\chi^2/F/t = 11.08$; $p = 0.001$; Yes: 3.3), alcohol consumption ($\chi^2/F/t = 4.26$; $p = -0.039$; Yes: 2.1), cocaine use ($\chi^2/F/t = 9.59$; $p = 0.002$; Yes: 3.1), cannabis consumption ($\chi^2/F/t = 8.03$; $p = 0.005$; Yes: 2.8), the use of benzodiazepines ($\chi^2/F/t = 21.29$; $p < 0.001$; Yes: 4.6) and the bp 186 *MAOB* polymorphism ($\chi^2/F/t = 9.11$; $p = 0.028$; bp 186: 2.6).

PD regression analysis

When performing regression analysis between the PDs and the predictor variables, the different substance addictions had a greater predictive power than the other variables. These analyses are shown in Table 4. Although PPD was associated with the bp 279 *DRD5* polymorphism and APD was associated with the bp 182 and bp 184 *MAOB* VNTR in unadjusted models, these associations became insignificant when adjusting for substances. When observing the adjusted logistic regression models, the consumption of benzodiazepines had a significant predictive value for PPD [adjusted odds ratio (AOR) 95% = 0.404; $p = 0.006$] and cannabis (AOR 95% = 0.444; $p = 0.017$), benzodiazepine consumption was associated with BPD (AOR 95% = 0.458; $p = 0.019$), and cannabis use was associated with APD (AOR 95% = 0.046; $p = 0.046$).

DISCUSSION

As we had previously hypothesised, we found a significant relationship between the polymorphisms we studied and the predominant PDs. Specifically, the bp 279 *DRD5* VNTR polymorphism was more frequent in patients with PPD. Previous studies have associated different alleles of the *DRD5* polymorphism with some psychiatric conditions including schizophrenia (Zhao et al., 2014), but little information regarding its association with PPD is available.

Although up until now no standardised treatment guidelines for PPD have been published, most therapeutic approaches focus on psychotherapeutic treatments (Cheli et al., 2021). Thus, the possibility that some genes such as *DRD5* may be involved in the dopaminergic

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TABLE 3 Relationship between personality disorders and the variables studied

	PARANOID PDs			BORDERLINE PDs			ANTISOCIAL PDs		
VARIABLE	$\chi^2/F/t$	*p*	ASR/post hoc	$\chi^2/F/t$	*p*	ASR/post hoc	$\chi^2/F/t$	*p*	ASR/post hoc
AGE	1.08	.277		1.99	.047		3.49	.001	
SEX	.008	.928		.69	.405		6.24	.012	Men: 2.5
OPIOIDS	1.05	.304		3.66	.075		11.08	.001	Yes: 3.3
ALCOHOL	1.73	.188		.01	.920		4.26	.039	Yes: 2.1
COCAINE	.29	.588		3.79	.051		9.59	.002	Yes: 3.1
CANNABIS	3.00	.083		5.10	.024	Yes: 2.3	8.03	.005	Yes: 2.8
BENZODIAZEPINES	5.47	.019	Yes: 2.3	5.17	.023	Yes: 2.3	21.29	< .001	Yes: 4.6
DBH	3.12	.372		2.56	.464		2.03	.564	
DRD5	4.84	.028	Bp 279: 2.2; bp 281: −2.2	.01	.921		.35	.550	
HTR1B	.21	.899		5.79	.055		1.44	.487	
HTR1D	.01	.993		3.00	.222		1.78	.410	
HTR2C	.06	.794		.95	.328		1.50	.220	
MAOA	.01	.892		2.74	.098		.08	.769	
MAOB	4.11	.250		3.10	.376		9.11	.028	Bp 186: 2.6
TH	6.51	.164		2.49	.645		2.59	.628	
TPH	.64	.723		.12	.937		1.64	.440	

PD = personality disorder.

pathway opens the door to the potential use of pharmacological approaches to the treatment of PPD, as already proposed in a previously published case series on antipsychotic drug treatments (Birkeland, 2013).

In addition, and also in line with our hypothesis, we found that some monoaminergic genes, specifically the bp 182 and bp 184 alleles of the *MAOB* VNTR, were associated with APD. This association is not novel given that the role of *MAOA* promoter hypermethylation in the presence of antisocial traits has previously been described (Checknita et al., 2015; Ziegler & Domschke, 2018). The association between monoaminergic pathway genes and APD opens up possibilities for new therapeutic approaches, although most antisocial behaviour treatments aim for early therapeutic interventions (Fisher & Hany, 2021) in order to improve the prognosis.

The relationships between the genes and the PDs were replicated in the unadjusted regression models. However, when we adjusted these regressions to consider substance use, the association of these polymorphisms with PDs was lost. Perhaps this could be explained by that fact that a significant unadjusted relationship between PDs and polymorphisms will easily turn insignificant when the different types of addiction are introduced in competition with PDs in an adjusted regression. This is because there is a relationship between addictions and PDs and an even stronger relationship between addictions and polymorphisms. Thus, the results for adjusted odds ratios could be an example of statistical 'over-control'.

In addition, previous studies had indicated a positive correlation between the number of PDs and the number of substance use disorders presented (González et al., 2019). Thirdly, a Norwegian study of adult twins identified a strong individual correlation between meeting all the criteria for both BPD and APD with general substance use; it also showed aetiological continuity that could imply a broad latent factor for both disorders and substance use in the absence of confounding genetic or environmental factors (Rosenström et al., 2021).

Finally, there have been different attempts to determine if there are any common genetic factors between heterogeneous patients who share the same pattern of substance use. In this sense, personality, determined in part by genetics, could be included as a common factor (Oreland et al., 2018). However, a study that looked for common personality and genetic factors among patients with alcohol use disorder reported contradictory results in terms of correlations between functional polymorphisms in serotonin transporter genes (Wang et al., 2013),

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TABLE 4 Odds ratios from unadjusted and adjusted logistic regression models predicting personality disorders

PD	PREDICTORS	UOR 95% CI	*p*-value	AOR 95% IC	*p*-value
PARANOID	Benzodiazepines	**.371**	.001	**.404**	.006
		.203, .679		**.211, .773**	
	DRD5 (279)	**2.186**	.031	2.096	.063
		1.074, 4.449		.959, 4.579	
BORDERLINE	Age	**.962**	.005	.985	.447
		.935, .988		.948, 1.024	
	Cannabis	**.400**	.002	**.444**	.017
		.226, .709		**.227, .866**	
	Benzodiazepines	**.444**	.002	**.458**	.019
		.269, .734		**.239, .880**	
ANTISOCIAL	Age	**.923**	<.001	.904	.265
		.893, .954		.758, 1.079	
	Sex	**3.636**	.001	6.011	.150
		1.705, 7.754		.523, 69.100	
	Opioids	**.160**	<.001	0	.996
		.068, .376			
	Alcohol	**.417**	.004	.121	.055
		.229, .759		.014, 1.046	
	Cocaine	**.078**	<.001	0	.997
		.019, .328			
	Cannabis	**.252**	<.001	**.046**	.046
		.124, .511		**.003, .757**	
	Benzodiazepines	**.181**	<.001	.251	.200
		.104, .313		.030, 2.075	
	MAOB (182)	**.407**	.033	.251	.285
		.178, .931		.020, 3.174	
	MAOB (184)	**.391**	.012	.839	.902
		.188, .813		.052, 13.498	
	MAOB (186)	.701	.245	6.999	.070
		.386, 1.275		.851, 57.533	

UOR = unadjusted odds ratio; AOR = adjusted odds ratio. The reference categories were the absence of the disorder, base pair with the lowest number, and absence of the addiction. For sex, women were used as the reference category.

with very few polymorphisms found in monoaminergic genes (Wang et al., 2012).

The main limitation of this work was a lack of gender-related associations, probably because our sample predominantly comprised men. Other limitations were the differences in environmental exposure of patients (epigenetics), among other possible biases derived from intentional sampling or the temporal nature of diagnosis. Furthermore, excluding patients with an axis I diagnosis should be considered a limitation in extrapolating the results to clinical practice. Finally, our results indicate that there is a relationship between polymorphisms and PPD and APD, possibly because each of these two disorders shows a specific pattern of addiction. This could be addressed in future studies by including cases with the same PDs but without addiction. However, there is limited access to patients with PPD, APD or BPD with no addictions.

CONCLUSIONS

Among patients with addiction, those with PPD should also be considered in addition to the importance of APD

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and BPD. The higher frequency of the bp 279 *DRD5* VNTR polymorphism found in patients with paranoid personality disorder, as well as the associations between the *MAOB* polymorphism and APD support the monoaminergic bases of these personality disorders when dealing with patients with addictions.

ACKNOWLEDGEMENTS

This research was funded by the Centro Superior de Investigación en Salud Pública, Generalitat Valenciana (grant number CS2003-05-05); the Conselleria de Sanitat, Generalitat Valenciana (grant number T4591000); and the Fundación de Investigación del Hospital Provincial de Castellón (grants numbers CAF 15-049, 21-042 and 21-043).

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

The study was conducted according to the guidelines set out in the Declaration of Helsinki and was approved by the Ethics Committee at the Hospital Clínico Universitario of Valencia (Spain; protocol code 02/089 on 12/13/02). Informed consent was obtained from all patients involved in the study.

AUTHOR CONTRIBUTIONS

Conceptualisation: H.G. and B.A.; methodology: B.A.; software: O.E.; validation: O.M., H.G., and A.B.; formal analysis: A.B.; investigation: G.I. and R.M.; resources: H.G.; data curation: A.B.; writing—original draft preparation: R.M.; writing—review and editing: O.M.; visualisation: O.E.; supervision: H.G.; project administration: G.I.; funding acquisition: H.G. All the authors have read and agreed to the published version of the manuscript.

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How to cite this article: O'Higgins, M., Benito, A., Real-López, M., Gil-Miravet, I., Ochoa, E., & Haro, G. (2023). Relationship of DRD5 and MAO-B VNTR polymorphisms with paranoid and antisocial personality disorders in polydrug users. *Personality and Mental Health*, *17*(1), 77–86. https://doi.org/10.1002/pmh.1563

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