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Letter to the Editor

Smoking cessation improves clinical outcome in severe mental disorders and is modulated by genetic variability at *CHRNA5* gene

Smoking has been traditionally tolerated for patients with mental disorders due to its hypothesized self-medication function (Schroeder and Morris, 2010). Although tobacco use has been associated with greater symptom severity and other health-threatening conditions, persons diagnosed with a mental disorder are 2–4 times more prone to smoking than the general population (Aubin et al., 2012). Both self-medication and shared vulnerability hypotheses have been considered to understand increasing use of tobacco in mental disorders (Sagud et al., 2018). Genetic studies report high heritability rates of nicotine dependence (~60%) (Berrettini and Doyle, 2012). The nicotinic receptor (nAChR), and specifically the nAChR subunit genes *CHRNA5/A3/B4/A7* have been associated with nicotine addiction, smoking cessation and severe mental disorders (Han et al., 2019; Jackson et al., 2013).

In order to examine whether smoking cessation i) affected the illness severity course and ii) was modulated by *CHRNA5/A7* variability, we analysed a sample of 60 patients with schizophrenia ($n = 48$) or bipolar disorder ($n = 12$) under a smoking cessation treatment for 36 weeks. We assessed the self-reported cigarettes per day (CPD), nicotine psychological (Psy-D) and physical (Phys-D) dependence and illness severity. Cessation treatment consisted of the use of transdermal nicotine patches (TNP) or varenicline. At week 36, patients were considered abstinent (ABS) if CPD = 0 the last 7 days and breath carbon monoxide was <9 ppm. SNPs at *CHRNA5* (rs680244, rs16969968) and *CHRNA7* (rs6494223) were genotyped using TaqMan exonuclease assay (Applied Biosystems) (all SNPs were in Hardy-Weinberg equilibrium) (See Supplementary Methodology). All statistical approaches are detailed in Supplementary Material.

Clinical variables were measured at baseline and weeks 12, 24 and 36 after smoking cessation treatment initiation (Table 1). Genotype distributions of SNPs are shown in Supplementary Table 1. The Clinical Research Ethics Committee of Hospital Universitario Central de Asturias in Oviedo approved the study protocol (Ref. 64/2010). Written informed consent was obtained from all subjects before enrolment.

At baseline, CPD was positively correlated with basal nicotine Psy-D ($r = 0.317$; $p = 0.015$), Phys-D ($r = 0.307$; $p = 0.017$), illness severity ($r = 0.313$; $p = 0.015$) and associated with gender [males (mean = 31.66 ± 12.53) vs females (mean = 24.26 ± 7.64); $t_{53.44} = 2.815$; $p = 0.007$]. Moreover, a trend of association was found between baseline CPD and rs680244 genotype distribution ($p = 0.076$) (Supplementary Table 2) with T-carriers consuming more CPD than CC individuals (31.65 ± 12.64 vs 24.65 ± 7.79, respectively; $t_{55.27} = -2.639$; $p = 0.011$).

At week 36, 24 (40%) patients were classified as ABS and 36 (60%) as non-abstinent (nonABS). Both groups were equivalent in terms of gender ($\chi^2_1 = 0.428$; $p = 0.572$), age ($t_{41} = 1.055$; $p = 0.289$) and diagnosis ($\chi^2_1 = 0.147$; $p = 0.193$). When comparing, ABS and nonABS groups did not differ for their scores on CPD or nicotine dependence (Psy-D/Phys-D) at baseline, but at weeks 12, 24 and 36, ABS patients reported lower scores in all three measures ($p < 0.001$ for all measurements) (Table 1). Interestingly, although ABS and nonABS patients reported similar illness severity scores at baseline, ABS showed a significant decrease of their illness severity at week 12 ($p = 0.019$), 24 ($p = 0.012$) and 36 ($p = 0.021$) (Table 1).

Additionally, *CHRNA5*-rs680244-CC had 4 times more risk of being nonABS at week 36 than T-carriers (OR = 4; 95%CI [1.13, 14.08]; $\chi^2_1 = 5.00$; $p = 0.03$). No statistical differences were found for the other SNPs (Supplementary Table 2).

Our results showed higher tobacco consumption in males and – as previously reported but still a subject of controversy – no gender differences in cessation success (Filia et al., 2014). In line with previous literature, we found positive correlations between CPD, nicotine dependence and illness severity at baseline (Dodd et al., 2010; Donny et al., 2008).

Smoking cessation groups did not differ for baseline CPD, Psy-D, Phys-D or illness severity, suggesting that cessation treatment success was independent from these variables. ABS patients reported lower illness severity since the first assessment after treatment initiation. Likewise, previous studies show that smoker patients with schizophrenia or bipolar disorder report worse global psychopathological status (Dodd et al., 2010; Krishnadas et al., 2012).

The relationship between severe mental disorders and smoking is complex and so far remains inconclusive. Nonetheless, it is widely accepted that dysfunction in central nAChRs represents a common substrate for schizophrenia and comorbid nicotine dependence. Our work reflected the effect of *CHRNA5* on initial tobacco use and smoking cessation success. Intriguingly, the rs680244-T allele was associated with both higher baseline CPD and greater treatment success. These results fit with the hypothesis of conceptualizing genes as "plasticity genes" instead of "vulnerability genes", leading susceptible individuals to both adverse and positive environmental influences (Belsky et al., 2009). Previous results showed that replacement therapy response (Sarginson et al., 2011) and nicotine dependence (Greenbaum et al., 2006) were influenced by rs680244. Despite intronic, rs680244 acts as an expression quantitative trait loci (eQTL) with the T allele increasing *CHRNA5* expression in multiple brain regions.

No significant results were found for *CHRNA5*-rs16969968, although it is considered a well-established risk factor for nicotine dependence (Hong et al., 2011) or *CHRNA7*-rs6494223 that – as far as we know – no previous studies have explored its association with illness severity or smoking cessation.

The results of this work should be interpreted in the context of several limitations: i) the open-labelled and non-randomized nature of the study, ii) the lack of an untreated control group may impair the robustness of our results, iii) our sample could be considered small for a genetic approach although a 36-week longitudinal design with extensive and exhaustive psychopathological assessments was considered and a very low dropout rate was detected, iv) multiple testing corrections were not applied since we considered they were likely to be excessive

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Table 1
Assessment of CPD, Psy-D, Phys-D and illness severity along the follow-up in ABS and nonABS patients (defined at week 36) after initiation of the smoking cessation program.

Assessment	Week	All patients mean(SD)	ABS patients mean(SD)	nonABS patients mean(SD)	*t*	df	*p*-Value
CPD	0	29.32(11.67)	29.00(12.22)	29.53(11.45)	−0.170	58.00	0.865
	12	5.98(8.90)	0.17(0.82)	9.86(9.72)	−5.951	35.74	<**0.001**
	24	9.23(10.64)	0.00(0.00)	15.39(9.66)	35.000	35.00	<**0.001**
	36	8.75(9.54)	0.00(0.00)	14.58(8.12)	35.000	35.00	<**0.001**
Psy-D	0[a]	17.41(6.74)[a]	15.87(4.78)	18.45(7.67)	−1.427	55.89	0.123
	12	7.35(7.84)	3.13(3.44)	10.17(8.68)	−4.380	49.23	<**0.001**
	24	8.26(8.58)	2.29(2.49)	12.28(8.89)	−6.373	42.84	<**0.001**
	36	8.98(8.84)	2.83(3.38)	13.08(9.00)	−6.204	48.11	<**0.001**
Phys-D	0	6.18(2.58)	5.92(2.98)	6.36(3.31)	0.650	58.00	0.581
	12	2.18(2.97)	0.21(0.83)	3.50(3.16)	−5.952	41.99	<**0.001**
	24	2.63(3.16)	0.04(0.20)	4.36(3.03)	−8.538	35.48	<**0.001**
	36	3.02(3.08)	0.25(0.85)	4.86(2.59)	−9.889	45.29	<**0.001**
Illness severity	0[a]	3.50(0.99)[a]	3.26(1.09)	3.66(0.91)	−1.499	56.00	0.139
	12[a]	3.34(1.07)[a]	2.96(1.04)	3.62(1.02)	−2.410	56.00	**0.019**
	24	3.37(1.15)	2.92(1.18)	3.67(1.04)	−2.549	58.00	**0.012**
	36	3.40(1.11)	3.00(1.06)	3.67(1.07)	−2.372	58.00	**0.021**

ABS: abstinent; nonABS: non-abstinent; CPD: cigarettes per day; Psy-D: nicotine psychological dependence; Phys-D: nicotine physical dependence. Significant results are marked in bold.
[a] $n = 58$.

in this context in which the selection of the variables of interest and the analyses were performed under a directional hypothesis based on previous findings, v) only three genetic variants were analysed to explain complex and multifactorial phenotypes such as tobacco use and smoking cessation success.

Current trends aim to challenge the disregard of health-threatening effects of tobacco in patients with mental disorders and encourage clinicians to implement the available tools for smoking cessation in mental healthcare facilities (García-Portilla and Bobes, 2016). Further genetic studies could better explain nicotine addiction and ultimately provide tools for personalized therapies.

Declaration of competing interest

MP Garcia-Portilla has been a consultant to and/or has received honoraria/grants from Angelini, Alianza Otsuka-Lundbeck, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, and SAGE Therapeutics.

PA Saiz has been a consultant to and/or has received honoraria or grants from Adamed, CIBERSAM, European Comission, GlaxoSmithKline, Government of the Principality of Asturias, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Plan Nacional Sobre Drogas and Servier.

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All other authors declare they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2020.05.024.

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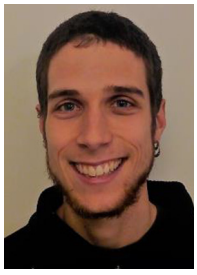

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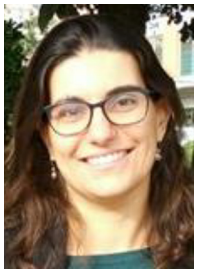

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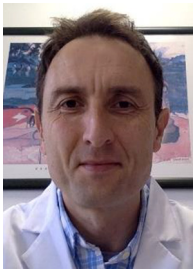

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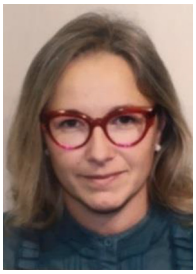

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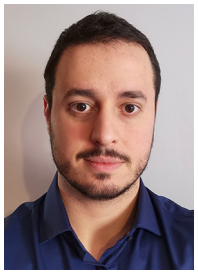

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