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**A positive association between a polymorphism
in the *HTR2B* gene and cocaine-crack
in a French Caribbean population**

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Objectives: Cocaine dependence has a strong heritability component. This study was aimed to investigate the putative association between the serotonin 2B receptor gene (*HTR2B*), patients with crack use disorders and impulsivity.

Methods: A French Caribbean male population of patients with crack use disorders (n=80) was compared to healthy male controls (n=60). Comorbid ADHD and impulsivity were assessed. Five Single Nucleotide Polymorphisms (SNPs) in the *HTR2B* gene on chromosome 2 were selected: rs643700, rs6736017, rs1549339, rs17586428 and rs3806545. These five SNPs were chosen to cover most of the linkage disequilibrium (LD) blocks in *HTR2B*. The French translation of the Barratt Impulsivity Scale BIS-11 was used to evaluate impulsivity. Comorbid ADHD was diagnosed using the Wender Utah Rating Scale-25 item for the Attention Deficit-Hyperactivity Disorder.

Results: We have found a positive association between the rs6736017 polymorphism and crack use disorders in a French Afro-Caribbean male population.

Conclusion: The risk effect of *HTR2B* rs6736017 appeared to be specific to individuals who are crack users rather than being driven by impulsivity alone or ADHD alone.

Keywords: cocaine; crack; *HTR2B* gene, impulsivity, ADHD.

Introduction

Cocaine addiction remains a serious public health concern worldwide. The annual prevalence rate of cocaine use (defined as the number of people aged 15–64 years who have consumed the drug at least once during the last 12 months) is 0.35 worldwide with important regional differences between North America (1.77), Oceania (1.54), Western and Central Europe (1.08) and Asia (0.04) (Peacock et al., 2018). When compared to controls with no history of substance abuse, cocaine and/or crack users exhibited higher levels of impulsiveness (for review Czeremainski et al., 2017). In addition, attention deficit-hyperactivity disorders (ADHD) and substance use disorders often coexist in adults, the risk of developing cocaine abuse is two times higher in individuals with (vs. without) ADHD; the prevalence of ADHD is also high among patients with cocaine dependence (20-25%) (for review Miguel et al., 2016). Using the BIS-11 scale, ADHD patients who asked for treatment of cocaine use disorders, compared with those without ADHD, had higher motor impulsivity (Pérez de los Cobos et al., 2011).

Cocaine dependence has a strong heritability component. Siblings of cocaine-dependent subjects had an estimated relative risk of 1.8 of developing cocaine dependence compared with those without cocaine-dependent siblings (Bierut et al. 1998). A higher rate of concordance was also observed among monozygotic twins relative to dizygotic twins (Kendler et al., 2003). A relatively common stop codon (Q20*) was identified in the serotonin 2B receptor gene (*HTR2B*) in a Finnish founder population and it was associated with impulsivity (Bevilacqua et al., 2010). Moreover, Tikkanen et al. (2015) have reported that the presence of the *HTR2B* Q20* predicted impulsive and aggressive behaviors particularly under the influence of alcohol.

Although crack is derived from cocaine, it has distinct patterns of consumption and potential for addiction (Gossop et al., 1994; Gossop et al., 2006). Yet, there is a lack of studies investigating the genetic factors involved in patients with crack use disorders, whose use is gradually increasing.

This study was aimed to investigate the putative association between the serotonin 2B receptor gene (*HTR2B*), crack-cocaine use disorders and impulsivity in a French Caribbean crack-cocaine male population of patients with crack use disorders as compared to healthy male controls.

Subjects and Methods

Sixty healthy male controls and eighty French Afro-Caribbean male patients with crack use disorders were included in this study. Participants were diagnosed patients with crack use disorders using DSM-IV-R criteria. Healthy controls were consecutively recruited at the blood transfusion center of Martinique, without lifetime personal and family history of psychiatric disorder, including substance abuse. The clinical evaluations were performed by a psychiatrist. All subjects (patients and controls) were male, African Caribbean, and had at least three African-Caribbean grandparents. Healthy controls and patients with crack use disorders were matched for age.. All subjects agreed to participate in the study and signed an informed consent. Medical and drug use histories, socio-demographic characteristics were reported using self-report and medical files. Personal and family psychiatric history of patients and controls were evaluated by a psychiatrist or a psychologist, blind to the genotyping results and trained to the Diagnostic Interview of Genetic Studies (DIGS). (Nurnberger et al. 1994). The French translation of the Barratt Impulsivity Scale BIS-11 (Patton et al., 1995; Bayle et al., 2000) was used to evaluate impulsivity. A score above 71 indicates a high level of impulsivity (Stanford et al., 2009). Comorbid ADHD was diagnosed using the Wender Utah Rating Scale-25 item for the Attention Deficit-Hyperactivity Disorder

with a cut off value at 46 (Ward et al., 1993; French translation Baylé et al., 2003). Sensation seeking (using the Zuckerman Sensation-Seeking Scale form V-40 item (Zuckerman et al. 1978; French translation Carton et al., 1990) and comorbid psychiatric disorders (using the MINI (Lecrubier et al., 1997) were also assessed (Table 1). The study was approved by the local Ethics Committee (LEC Sud-Ouest et Outre Mer III; CPP: 2009/96; NCT01025219 (ClinicalTrials.gov).

DNAs were collected from blood or saliva samples. A 4 ml venous blood or 2 ml saliva sample (Oragene DNA OG-500 self-collection kit) was collected from each subject. Genomic DNA was extracted according to standard methods. All SNP in samples were genotyped using the Taqman assays (Thermo Fisher). DNAs were genotyped for *HTR2B* polymorphisms (Tables 2 and 3). The *HTR2B* gene contains 4 exons and 3 introns. As described in Figures 1 and 2 and Tables 2 and 3, five SNPs in the *HTR2B* gene on chromosome 2 were selected based on the 1000 Genomes project (<https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/>) including rs643700, rs6736017, rs1549339, rs17586428 and rs3806545. All five SNPs met the criteria of a call rate of >95%; minor allele frequency of >0.05; and Hardy–Weinberg equilibrium of $p > 0.05$. The allele frequencies in our sample were very similar to those of the same ethnicity in the HapMap dataset. These five SNPs were chosen to cover most of the linkage disequilibrium (LD) blocks in *HTR2B* (Figures 2 and 3). The distribution of the SNPs encompassing *HTR2B* gene were in Hardy-Weinberg equilibrium.

Statistical analyses

Data analyses were conducted using chi square, ANOVA, Fisher's exact tests and a general linear model. Fisher's exact test interactions between ADHD or impulsivity (qualitatively) and the association between crack status and polymorphisms were tested. A general linear model was used to test interactions between ADHD or impulsivity (quantitatively) and the association between crack status and polymorphisms. Significance was set at $p < 0.05$.

Results

No differences were observed between controls and patients with crack use disorders for age, sensation seeking or BIS attentional scores. Using the WURS-25, and a cut off score of 46, the prevalence of ADHD among patients with crack use disorders (71.4%, $n=40$) was significantly higher compared with controls (27.3%, $n=12$) ($p<0.001$). Using the BIS-11, compared to controls, patients with crack use disorders had a higher level of total, motor and nonplanning impulsivity ($p<0.001$) (Table 1). Similarly, using a cut off score of 71 (BIS total > 71), patients with crack use disorders had a significantly higher prevalence of total impulsivity (21.7% $n=13$) as compared to controls (3.4%, $n=2$) ($p<0.004$). Therefore statistical analyses were adjusted for these variables.

A statistically significant association ($p=0.029$) was observed between the rs6736017 polymorphism allele T and patients with crack use disorders (Table 2). The level of significance was even higher when 12 patients with crack use disorders with a comorbidity of schizophrenia or bipolar disorder were excluded from the sample, $p=0.015$, Odds Ratio 2.99, confident interval of 95% [1.19-7.49] (Table 3). A corrected p value of 0.075 was carried out for multiple tests, showing a trend for association between the rs6736017*T and crack use disorders. A tendency was observed for rs1549339 polymorphism with patients with crack use disorders (Table 2) but it disappeared when psychiatric comorbidity (schizophrenia or bipolar disorder) was taken into account (Table 3). There was neither interaction between ADHD, crack status and any polymorphism studied (Supplementary Table 1), nor between a high score of impulsiveness, crack status and any polymorphism studied (Supplementary Table 2). Using a general linear model to study the interactions between the scores obtained using the

BIS-11 and the WURS-25, clinical status $\times$ *HTR2B* genotype interactions were not significant suggesting that the relationship between impulsivity or ADHD and *HTR2B* genotype in patients with crack use disorders was not different from that observed in controls (Supplementary Tables 3 & 4). There was no clinical status $\times$ *HTR2B* genotype interaction for novelty seeking.

Discussion

We have observed a positive association between the rs6736017 polymorphism (a missense variant located in exon 4 of the *HTR2B* gene) and crack use disorders in a French Afro-Caribbean male population. The risk effect of *HTR2B* rs6736017 appeared to be specific to patients with crack use disorders rather than being driven by impulsivity or ADHD alone; however these results need replication in larger sample of patients as well as in populations of different genetic backgrounds. The level of impulsiveness and the prevalence of ADHD were actually significantly higher in our population of patients with crack use disorders as compared to controls, but a lack of power may have contributed to the lack of interaction observed. One unsolved question is the putative functional consequence of the rs6736017 polymorphism introducing a Met421/Val substitution at the C-terminal cytoplasmic tail of the 5-HT_{2B} receptor (Supplementary Figure 3), which was not found in any sequenced *HTR2B* in primates.

Bevilacqua et al. (2010) observed that a stop codon in exon 2 (*HTR2B* Q20*) led to an interruption in the expression of the 5-HT_{2B} receptor and found that this mutation was associated to impulsive behavior. Among these *HTR2B* Q20* carriers, temperamental traits resembled a passive-dependent personality profile, and the presence of the *HTR2B* Q20* predicted impulsive and aggressive behaviors particularly under the influence of alcohol (Tikkanen et al., 2015). These impulsive/aggressive traits have also been found in mice lacking 5-HT_{2B} receptor gene (*Htr2b*^{-/-}) (Bevilacqua et al., 2010). The *HTR2B* gene may function by modulating levels of both serotonin and dopamine in brain regions involved in impulsivity (Doly et al., 2008). In agreement with the fact that, to date, the *HTR2B* Q20* was exclusively reported in a Finnish founder population (0.012% of the population) (Bevilacqua et al., 2010), we have not found this stop codon in our population. Furthermore, a recent genome-wide association study (GWAS) of physical aggression occurring under the influence of cannabis in African Americans implicated the *HTR2B*-rs17440378 TT genotype, which was not previously considered a key cannabis target (Montalvo-Ortiz et al., 2018). Interestingly, treating the 5-HT_{2B} receptor knockout mice with THC resulted in increased aggressive behavior in the resident-intruder paradigm, while the opposite effect was observed in wild type mice. Thus, *HTR2B* variation in expression moderates the effects of cannabis on aggression and social interactions (Montalvo-Ortiz et al., 2018). Interestingly, null expression or blockade of 5-HT_{2B} receptors diminishes the reinforcing effects of psychoactive drugs by modulating serotonin and dopamine signaling. The direct effects of *HTR2B*-rs17440378 (an intronic polymorphism) on protein function, including regulation is unknown. In general, crack users have a higher level of impulsivity as compared to cannabis users, which means that it may be more difficult to disentangle the respective roles of impulsivity and crack use disorders effects in the association with SNPs, especially in a small sample.

Finally, a major haplotype A–A–G–A (with a frequency of 48%) for rs6437000–rs10194776–rs16827801–rs1549339 (four SNPs located in introns 2 and 3) showed a significant positive association with behavioral-approach-system (BAS) fun seeking in a Han Chinese population (Zhu et al., 2012). BAS fun seeking was also correlated with impulsive behaviors such as drug abuse. Among these four significant SNPs, rs6437000 and rs1549339 were reported to have high linkage disequilibrium with the rare *HTR2B* stop codon Q20*. According to Bevilacqua et al. (2010), *HTR2B* Q20* was found on a single haplotype background A–G–A–

(G/A)–A–A for rs6437000–rs4973377–rs1549339–(stop codon)–rs17586428–rs3806545. In contrast, Tsuchimine et al. (2013) have reported that the *HTR2B* rs10194776 polymorphism was not associated with personality traits, including novelty seeking and impulsivity in healthy Japanese subjects.

The 5-HT_{2B} receptors are expressed in the adult human brain, especially in the frontal cortex, although at a low level. The recent work by Doly et al. (2017) has shown a stronger locomotor response to cocaine, with a doubling the distance traveled by 5-HT_{2B} receptor mutant mice. The 5-HT_{2B} receptors involved have been located on dopaminergic neurons, who innervate the nucleus accumbens (NA), a brain area involved in the reward circuit. Their absence decreases the activity of these latter neurons. Paradoxically, the lack of 5-HT_{2B} receptors induces a decrease of dopamine secretion in the NA (Doly et al., 2017). These results indicate that, by binding on 5-HT_{2B} receptors, serotonin can control the amount of dopamine released by dopaminergic neurons that express the receptor. When these receptors are lacking, this secretion is abnormally low in the NA. Several imaging studies in humans have shown that individuals addicted to cocaine present paradoxically a weaker activation of the NA and a decreased secretion of dopamine in this region (Volkow et al., 2014). Thus, the absence of the 5-HT_{2B} receptor induces a neuronal situation similar to that observed in drug addicts. This similarity between these mutant mice and cocaine addicts suggests that individuals bearing a genetic mutation that invalidates the 5-HT_{2B} receptor or associated to a dysfunction of this receptor could have a greater propensity to become addicted to this drug. Similarly, the chronic 5-HT_{2B}-receptor inhibition makes mice behaving as animals already exposed to cocaine with higher cocaine-induced locomotion. Associated changes in dopaminergic neuron reactivity that includes a local hypodopaminergy, paradoxically and ultimately results in increased cocaine psychostimulant responses without significant change in motivation to the drug whatever the level of impulsivity or hyperactivity observed.

Strengths and limitations of our study

Our results need replication in larger populations, especially, to conclude that there is an association between genetic variants of *HTR2B* gene and crack use disorders, independently to ADHD and impulsivity. We calculated a power analysis using sample size calculator and a risk alpha of 0.05. Considering our sample (80 cases and 60 controls), the percentages of rs6736017*T (0.94 and 0.86 respectively), the estimated power was of 36%. To detect an effect of this magnitude with a power of 80%, one would need to recruit 250 cases and 188 controls. Furthermore, for the interaction studies (with ADHD and impulsivity), the estimated power was of 22% and 32% respectively. Nevertheless, we observed a positive association between crack use disorders and a polymorphism located on the *HTR2B* gene in our sample of 80 male French Afro-Caribbean patients. It should be noted, however, that the SNPs used in this study have different minor allele frequency (MAF) in different ethnic populations based on HapMap Data (<http://www.hapmap.org>) and that replication studies on populations of different genetic backgrounds are needed. The selection of SNPs was based on a high frequency of the heterozygosity and of the minor allele in Caucasian populations since no African Caribbean population was available at the time of our study

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Statement of Interest

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Table 1. Characteristics of patients and controls.

Clinical characteristics	Controls (n=60) Mean $\pm$ /S.D.	Patients (n=80) Mean $\pm$ /S.D.	d.f.	F	P value
Age	45.6 $\pm$ 9.2	43.2 $\pm$ 7.5	1/117	2.31	0.13
WURS 25	40.0 $\pm$ 17.7	60.6 $\pm$ 26.6	1/98	19.49	<0.001*
WURS total	52.2 $\pm$ 23	83.0 $\pm$ 32.9	1/98	27.87	<0.001*
BIS 11 motor	6.5 $\pm$ 4.5	22.2 $\pm$ 5.8	1/117	266.34	<0.001*
BIS 11 attentional	17.2 $\pm$ 7.3	17.3 $\pm$ 3.5	1/117	0.004	0.95
BIS 11 nonplanning	13.2 $\pm$ 7.6	24.4 $\pm$ 5.5	1/117	84.48	<0.001*
BIS 11 total	37 $\pm$ 16.9	63.9 $\pm$ 11.9	1/117	101.09	<0.001*
SSS total	15.5 $\pm$ 5.5	16.6 $\pm$ 5.6	1/119	1.09	0.30

An ANOVA was performed to compare patients and controls clinical characteristics.

d.f.: degree of freedom; N: number; S.D.: Standard Deviation

* Significant

Table 2. Allele frequencies and associations of five candidate SNPs in the *HTR2B* gene and clinical status (all patients with crack use disorders (n=80) or controls (n=60)).

Polymorphism	Allele	Case/Control counts	Case/Control, frequencies	Chi square	P value
rs6736017	T	148:10/ 103:17	0.94/ 0.86	4.78	0.029*
rs6437000	C	48:11/31:89	0.30/0.26	0.59	0.44
rs1549339	G	64:90/36:80	0.42/0.31	3.14	0.07
rs17586428	A	111:47/77:41	0.70/0.65	0.78	0.38
rs3806545	A	107:49/75:43	0.69/0.64	0.76	0.38

*Significant

rs6736017: genetic association OR=2.44 CI95%[1.06-5.55]

rs1549339: trends of association

Table 3. Allele frequencies and associations of five candidate SNPs in the *HTR2B* gene and clinical status (patients with crack use disorders (n=68) or controls (n=60)).

Polymorphism	Allele	Case/Control counts	Case/Controls, frequencies	Chi square	P value
rs6736017	T	127:7/ 103:17	0.95/ 0.86	5.92	0.015*
rs6437000	C	37:99/31:89	0.27/0.26	0.06	0.80
rs1549339	G	51:81/36:80	0.39/0.31	1.57	0.21
rs17586428	A	91:43/77:41	0.68/0.65	0.2	0.65
rs3806545	A	87:45/75:43	0.66/0.64	0.15	0.70

*Significant

rs6736017: genetic association OR=2.99 CI95%[1.20-7.50]

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Legends

Suppl Figure 1: *HTR2B* gene organization with SNPs position. This is a schematic representation of *HTR2B* gene with the positions of SNPs, including these genotyped in this study, and SNPs previously associated with disorders
 THC: cannabis; Q20*: stop codon in exon 2 (*HTR2B*); ALS: amyotrophic lateral sclerosis

Suppl Figure 2: Haploview image showing the LD colors of D' observed in our study for the genotyped SNPs. We can observe the presence of an haplotype block in 5' part of the *HTR2B* gene
 Kb:kilobases; rs: polymorphisms

Suppl Figure 3: Clustal W alignment of the C-terminal cytoplasmic tail of primate 5-HT_{2B} receptors showing the unique presence of a hydrophobic residue (Val) of rs 6736017 polymorphism in place of a Met or Thr in other primates.

SNP	Allele	Controls N=60 %	Crack+ADHD* N=40 %	P value	Crack+ADHD** N=36 %	P value
rs643700	A	89	56	0.313	50	0.507
		74.2%	70,00%		69.4%	
	C	31	24		22	
		25.8%	30,00%		30.6%	
rs6736017	C	17	6	0.121	4	0.094
		14.2%	7.7%		5.7%	
	T	103	72		66	
		85.8%	92.3%		94.3%	
rs1549339	A	80	47	0.194	43	0.337
		69,00%	61.8%		61.4%	
	G	36	29		27	
		31,00%	38.2%		38.6%	
rs17586428	A	77	56	0.211	49	0.526
		65.3%	71.8%		70.0%	
	G	41	22		21	
		34.7%	28.2%		30.0%	
rs3806545	A	75	56	0.148	49	0.427
		63.6%	71.8%		70.0%	
	C	43	22		21	
		36.4%	28.2%		30.0%	

Supplementary Table 1.

No association was observed between SNPs and ADHD in patients with crack use disorders compared to controls

N: Number ; SNP: single nucleotide polymorphism ; %: percentage

* All cases of patients with crack use disorders (Total sample: N=80)

** Patients with crack use disorders without comorbid schizophrenia or bipolar disorder (Total sample: N=68)

SNP	Allele	Controls N=60 %	Crack+BIS11≥50* N=54 %	P value	Crack+BIS11≥50** N=46 %	P value
rs643700	A	89	77	0.368	70	0.873
		74.2%	71.3%		76.1%	
	C	31	31		22	
		25.8%	28.7%		23.9%	
rs6736017	C	17	7	0.084	5	0.067
		14.2%	6.6%		5.6%	
	T	103	99		85	
		85.8%	93.4%		94.4%	
rs1549339	A	80	63	0.123	57	0.457
		69,00%	60.6%		63.3%	
	G	36	41		33	
		31,00%	39.4%		36.7%	
rs17586428	A	77	75	0.231	62	0.656
		65.3%	70.8%		68.9%	
	G	41	31		28	
		34.7%	29.2%		31.1%	
rs3806545	A	75	74	0.198	61	0.559
		63.6%	69.8%		67.8%	
	C	43	32		29	
		36.4%	30.2%		32.2%	

Supplementary Table 2.

No association was observed between SNPs and impulsivity in patients with crack use disorders compared to controls

Crack use disorders with a BIS > 50 (medium + high level of impulsivity)

N: Number ; SNP: single nucleotide polymorphism ; %: percentage

* All cases of patients with crack use disorders (Total sample: N=80)

** Patients with crack use disorders without comorbid schizophrenia or bipolar disorder (Total sample: N=68)

SNP	corrected model		WURS & SNP			WURS & CRACK STATUS			adjusted R ²
	F	P	F	P		P	F	P	
s643700	13.700	<0.001	1.126	0.290	34.795	<0.001	0.417	0.519	0.161
rs6736017	12.279	<0.001	0.045	0.832	12.749	<0.001	0.056	0.814	0.147
rs1549339	12.369	<0.001	0.464	0.497	28.002	<0.001	2.295	0.131	0.150
rs17586428	11.897	<0.001	0.297	0.586	30.319	<0.001	0.01	0.976	0.144
rs3806545	12.050	<0.001	0.685	0.409	30.905	<0.001	0.00	0.998	0.145

Supplementary Table 3.

No interaction was observed between WURS-25 score, crack use disorders and any SNP using the general linear model with WURS-25 score as dependent variable.

N=60 controls and N=80 patients with crack use disorders

P: P value

SNP	corrected model		SNP		CRACK STATUS		SNP x BIS11		adjusted R ²
	F	P	F	P	F	P	F	P	
s643700	68.431	<0.001	1.360	0.245	159.617	<0.001	0.250	0.617	0.460
rs6736017	65.873	<0.001	0.231	0.631	58.870	<0.001	0.037	0.847	0.453
rs1549339	66.022	<0.001	1.111	0.293	180.879	<0.001	0.019	0.890	0.460
rs17586428	64.746	<0.001	0.007	0.935	179.716	<0.001	1.435	0.232	0.451
rs3806545	65.373	<0.001	0.155	0.695	185.259	<0.001	2.286	0.132	0.453

Supplementary Table 4.

No interaction was observed between BIS-11 scores, crack use disorders and any SNP using the general linear model with

BIS-11 score as dependent variable.

N=60 controls and N=80 patients with crack use disorders

P: P value