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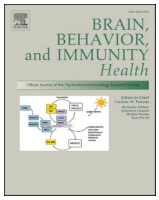

Genetic association of the kynurenine pathway to suicidal behavior

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A B S T R A C T

Suicidal behavior has been associated with dysfunctions in the kynurenine pathway, including alterations in the levels of neuroprotective and neurotoxic metabolites. Changes in the catalytic activity of enzymes within the pathway may contribute significantly. Variations in the genes encoding enzymes within the pathway can significantly affect their catalytic activity, playing a crucial role in the process. To explore this possibility, we hypothesized that these genetic variations would occur more frequently in patients with a history of suicidal behavior compared to non-suicidal individuals. Thus, we investigated the relationship between a history of suicide attempts and five single nucleotide polymorphisms (SNPs) within genes involved in the kynurenine pathway: *IDO1* (rs7820268), *IDO2* (rs10109853), *KMO* (rs1053230), *KAT1* (rs10988134), and *ACSMD* (rs2121337). Our sample comprised 849 subjects: 325 individuals who had attempted suicide in their lifetime (SAs), 99 individuals with a history of major depression disorder but no previous suicide attempts (non-SAs), and 425 non-psychiatric controls (CTRL). We performed SNP association analyses using codominant, dominant, and recessive models. Adjustment for sex and multiple comparisons was applied. After adjustment, the analysis revealed that SAs showed a significantly higher frequency of T alleles and TT genotypes of the rs1053230 SNP compared to CTRL across nearly all models. Furthermore, in the recessive model, non-SAs displayed a higher prevalence of the TT genotype of the rs10109853 SNP compared to CTRL.

The rs1053230 and rs10109853 SNPs could play a role in the previously observed metabolic dysregulation among SAs and non-SAs, respectively. To validate our findings, it is crucial to conduct functional analyses to investigate the impact of rs10109853 and rs1053230 SNPs on the expression and/or catalytic activity of the corresponding enzymes.

1. Introduction

Inflammatory processes are associated to the pathophysiological process of suicidal behavior (SB) (Brundin et al., 2017), a major public health problem. Inflammation induces the kynurenine (KYN) pathway, where 99% of the tryptophan not used in protein synthesis is

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transformed (Bender, 1983). The KYN pathway has received increasing attention as its connection to psychiatric conditions and SB became more apparent.

Pro-inflammatory cytokines associated with SB, such as IFNγ IL-6, IL-1β, TNFα, and TGFβ, can activate the IDO (idoleamine-2,3- dioxygenase), the enzyme catalyzing the first limiting step of the KYN pathway, allowing the transformation of tryptophan into KYN (Baumgartner et al., 2019) (Fig. 1). Downstream of IDO, other enzymes like KAT (kynurenine aminotransferase I to IV), KMO (kynurenine monooxygenase), and ACMSD (amino-carboxy muconate semialdehyde decarboxylase) enable the synthesis of metabolites with activity in neurotransmission, neuroinflammation, energy metabolism and oxidative stress modulation (Mithaiwala et al., 2021). Irreversible transamination of KYN by KAT leads to the formation of kynurenic acid (KYNA), a non-competitive N-methyl D-aspartate receptor (NMDAr) antagonist (Birch et al., 1988) to have neuroprotective and anticonvulsant properties (Foster et al., 1984), and reduces extracellular glutamate concentration (Carpenedo et al., 2001). KYN can also undergo catalytic action by KMO, leading to the production of 3-hydroxykynurenine (3-HK) in the first place and quinolinic acid (QUIN) later. 3-HK is known to exhibit a neurotoxicity/neuroprotection duality in its effects on the central nervous system (CNS). Its neurotoxicity is attributed to its ability to generate reactive oxygen species (ROS), while its neuroprotection is due to its antioxidant properties. QUIN is an NMDAr agonist present in mammalian brains at nanomolar concentrations. This metabolite exerts its neurotoxicity through various mechanisms, including stimulating NMDAr and triggering a cascade of toxic cellular processes. Additionally, QUIN has is able to increase neuronal glutamate release and reduce its reuptake by astrocytes (Guillemin, 2012).

Sublette et *al.* were the first to suggest an impairment of the KYN pathway in subjects with SB. Plasma KYN levels were higher in depressed subjects with a history of suicide attempts than in depressed subjects with no such history (Sublette et al., 2011). Later studies reported that the level of KYNA in the cerebrospinal fluid (CSF) was lower in suicide attempters compared to non-attempters, all of them affected by schizophrenia (Carlborg et al., 2013), while the level of QUIN was higher in suicide attempters than in healthy controls (Erhardt et al., 2013). These results, i.e. decreased KYNA and increased QUIN in the CSF of suicidal patients, seem to be stable in the long term, according to a report in an independent sample comparing suicide attempters to healthy controls repeatedly over 2 years (Bay-Richter et al., 2015). Plasma and CSF levels of picolinic acid (PIC) also appear to be lower in suicide attempters compared to healthy subjects (Brundin et al., 2016). Impairment of the KYN pathway was also observed in Treatment-Resistant Depression (TRD) (Serafini et al., 2017). Compared to treatment responders, subjects with TRD are more likely to exhibit SB

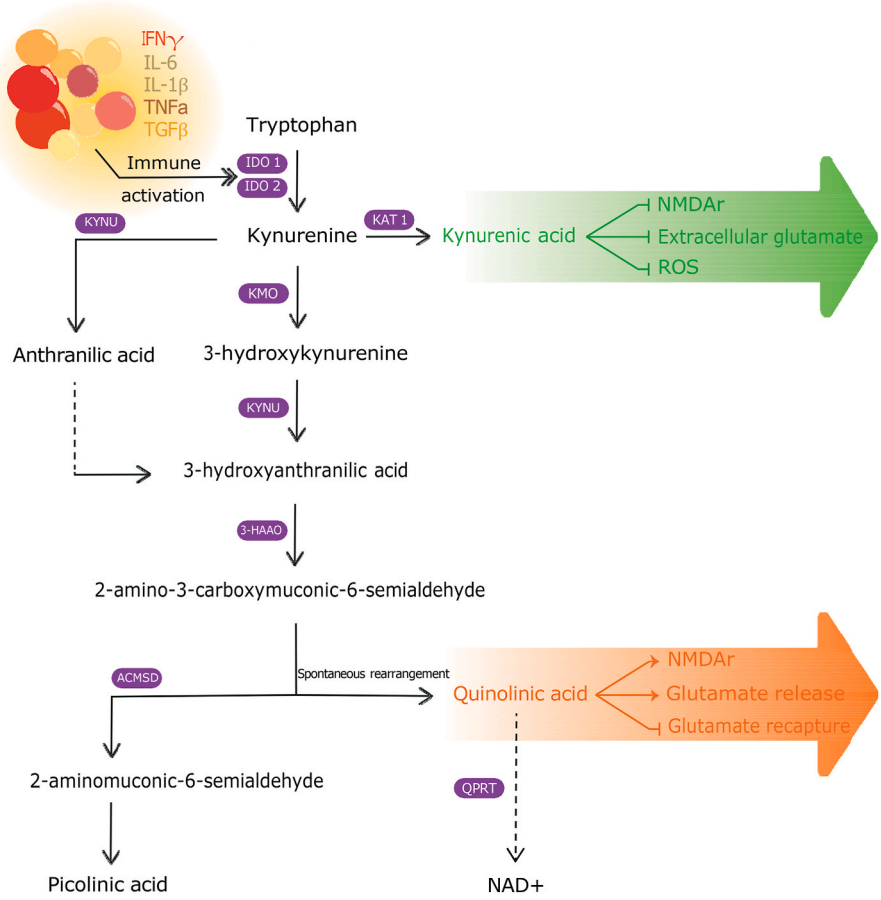

Fig. 1. Simplified diagram of the kynurenine pathway.
The kynurenine pathway consists of two branches with opposite actions. A neuroprotective branch (in green) represented by KYNA and a neurotoxic branch (in red) represented by QUIN. KYNA is a non-competitive NMDA receptor antagonist that reduces extracellular glutamate and acts as a ROS scavenger. QUIN is a potent NMDA receptor agonist that increases glutamate extracellular release by neurons and inhibits its uptake by astrocytes. IDO: idoleamine-2,3- dioxygenase, TDO: tryptophan 2,3-dioxygenase, KATs: kynurenine aminostransferases, KMO: kynurenine 3-monooxygenase, KYNU: kynureninase, 3-HAAO: 3-hydoxyanthranillic acid dioxygenase, ACMSD: 2-Amino-3-carboxymuconic-6-semiladehyde decarboxylase, QPRT: quinolonate phosphoribosyl transferase, NMDAr: N-methyl-D-aspartate receptor, ROS: reactive oxygen species, NAD: Nicotinamide adenine dinucleotide, IFNγ: Interferon gamma, IL-6: interleukin 6, IL-1β: interleukin 1beta, TNFα: tumor necrosis factor alpha, TGFβ: transforming growth factor beta. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(Nelsen and Dunner, 1995).

Hence, specific metabolites within the KYN pathway exhibit dysregulation in individuals who have attempted suicide, notably those that are biologically active in the CNS, including KYNA, QUIN, and PIC. These dysregulations suggest the existence of underlying factors that change the expression and/or activity of enzymes within the KYN pathway and orchestrate metabolic changes. Genetic variations such as single nucleotide polymorphisms (SNPs) might play a role (Bryleva and Brundin, 2017; Claes et al., 2011). Indeed, epidemiological data from genetic studies estimate the heritability of the broad phenotype of SB around 17–55%, and a substantial proportion of the SNP-heritability of SB seems to be independent of psychiatric diagnoses (Ruderfer et al., 2020).

Given the potential role of the KYN pathway in the pathophysiology of SB, we have undertaken a genetic association study to examine the link between five SNPs located in genes encoding four major enzymes in the KYN pathway (IDO 1–2, KMO, KAT, and ACMSD) in a large sample including lifetime suicide attempters with a history of major depressive disorder (SAs), individuals with a history of major depressive disorder but no SB (non-SAs) and non-psychiatric controls (CTRL) (unaffected by SB or mental disorders). We hypothesized that genetic variants linked to the deregulation of neurotoxic and neuroprotective metabolite levels in the KYN pathway would be associated with SAs.

2. Methods

2.1. Study cohorts

We analyzed 851 samples from four cohorts. The first cohort consists of 70 subjects aged 60 or older previously included in the SPAD study (N° ID RCB: 2016-A01375-46) performed at CHU Nimes, France. The second and third cohort consist of 35 and 15 subjects from SUI-PREDICT (N° ID-RCB: 2016-A00845-46) and SMART CRISIS (N° ID-RCB: 2017-A02634-49) studies performed at the same institution. Most of the samples belong to the fourth independent cohort, consisting of 731 subjects included in the "Genética, ambiente y trastornos mentales" study, Madrid, Spain. All four studies aimed at comparing the features of suicide attempters with other populations and used similar assessment methods. The two last cohorts have been described elsewhere (Berrouiguet et al., 2019; Vaquero-Lorenzo et al., 2009). According to the psychiatric assessment and the history of SB, the whole sample was divided into three groups: 325 SAs with a lifetime history of at least one suicide attempt, 99 non-SAs with a diagnosis of current or past major depressive disorder and no personal history of SB, and 425 CTRL without any history of psychiatric disorders or SB. Participants with a diagnosis of psychotic disorder or bipolar disorder were excluded.

2.2. Psychiatric assessment of patients

All participating subjects were assessed by psychiatrists or clinical psychologists. The assessment of depression, SB, and other psychiatric disorders was done using the Mini International Neuropsychiatric Interview (M.I.N.I) (Sheehan et al., 1998), as well as the Columbia Suicide Severity Rating Scale (C-SSRS) in France, and the Columbia Suicide History Form (CSHF) (Posner et al., 2011) in Madrid. HC were recruited using posters and advertisements. For all participants, the following demographic characteristics were collected: age, sex, marital status, educational level, and working status. The clinical and demographic characteristics of the participants are displayed in Table 1. Suicide attempts were defined as potentially self-injurious behavior with a nonfatal outcome, for which there is evidence (either explicit or implicit) that the person intended at some (nonzero) level to kill himself (O'Carroll et al., 1996). A suicide attempt may or may not have resulted in injuries.

Table 1
Clinical and demographic characteristics of the participants.

Characteristic	SAs (n = 325)	Non-SAs (n = 99)	CTRL (n = 425)	*P*-value
Age, mean (SD)	40.8 (16.0)	51.23 (17.0)	36.82 (12.6)	<0.0001
Females, n (%)	211 (64.9)	180 (71.7)	71 (42.4)	<0.0001
Marital status, n (%)				<0.0001
Single	131 (46.3)	33 (47.1)	181 (44.8)	
Married	86 (30.4)	26 (37.1)	206 (51.0)	
Separated	56 (19.8)	7 (10.0)	15 (3.7)	
Widowed	10 (3.5)	4 (5.7)	2 (0.5)	
Education level, n (%)				<0.0001
Low	84 (30.9)	20 (29.40)	92 (22.80)	
Intermediate	128 (47.1)	25 (36.8)	152 (37.7)	
High	60 (22.1)	23 (33.8)	159 (39.5)	
Diagnosis n, (%)				
MDE n (%)	305 (99)	99 (100)	(0) 0.00	<0.0001
General Anxiety disorder n (%)	164 (54.5)	47 (47.5)	1 (0.2)	<0.0001
OCD n (%)	15 (5.2)	12 (12.8)	0 (0.0)	<0.0001
Eating disorder n (%)	31 (10.4)	1 (1)	0 (0.0)	<0.0001
Alcohol use disorder n (%)	65 (22.9)	9 (11.5)	40 (9.4)	<0.0001
Substance use disorder n (%)	51 (18)	7 (9.10)	12 (2.8)	<0.0001
Age of first suicide attempt, mean (SD)	30.6 (14.6)	–	–	–
Number of suicide attempts, mean (SD)	2.7 (3.4)	–	–	–

SAs: suicide attempters, Non-SAs: depressed non-attempters, CTRL: non-psychiatric controls, MDE: major depressive episode, OCD: obsessive compulsive disorder, SD: standard deviation. Missing data are indicated in Supplementary Table 4.

2.3. Ethical considerations

Our study was carried out in agreement with the 'Declaration of Helsinki' of the World Medical Association for medical research involving human subjects (World Medical Association, 2013). The Institutional Review Board of Nimes University Hospital approved the study (IRB/20.03.08). All participants enrolled in the research protocols had given their written consent to participate before inclusion, including for genetic analyses and for their biological samples to be used in additional studies. The study was registered on ClinicalTrials.gov under number: NCT04565834.

2.4. Selection of studied polymorphisms

We identified and selected the studied SNPs from the Single Nucleotide Polymorphism database (dbSNP) of the National Institutes of Health (NIH). All selected SNPs are located in genes encoding KYN pathway enzymes. SNPs were retained if they had a Minor Allele Frequency (MAF) of 5% or more in the general European population (dbSNP). Among the five selected SNPs, rs10109853 located in gene encoding IDO2 is a functional polymorphism. *In vitro* experiments showed that *IDO2* rs10109853 SNP, a nonsynonymous substitution (R248W), reduces the catalytic activity of IDO2 enzyme by 90 % (Metz et al., 2007). The rs10988134 consists of a C/T base change in the three prime untranslated region (3′-UTR) of the *KAT1* gene that may affect the stability of the *KAT1* transcript (Moore et al., 2010). The rs1053230 is a C/T base change in the KMO gene inducing an arginine to cysteine change at the 452nd position. The rs7820268 is a C/T change in intron 5 of the IDO1 gene. The rs2121337 is in the *ACMSD* gene and consists of a C/T base change. Detailed information on the selected SNPs is shown in Supplementary Table 1.

2.5. Selection of predesigned TaqMan® SNP Genotyping Assays

The predesigned TaqMan® SNP Genotyping Assays were selected from the Thermo Fisher Scientific database (https://www.thermofisher.com). Their sequences are protected and have not been communicated by the manufacturer. The assay ID of each TaqMan® SNP Genotyping Assays is shown in Supplementary Table 2.

2.6. Human DNA genomic extraction

Peripheral blood obtained from donors was stored at −80 °C after collection. Human DNA genome was extracted from blood samples using the QIAsymphony® DSP DNA Mini Kit (Qiagen, Hilden, Germany) and QIAsymphony^{SP} instrument (Qiagen, Hilden, Germany). For all samples, DNA purity and concentration were measured using a NanoDrop spectrophotometer (Thermo Scientific, Wilmington, Delaware, USA). Serial dilutions of DNA samples were performed to obtain a final working concentration of 5 ng/µl. All DNA samples were kept at −20 °C until the genotyping process.

2.7. SNP genotyping

SNP genotyping was performed using the Applied Biosystems™ TaqMan® SNP Genotyping Assays (Thermo Fisher Scientific, Vilnius, Lithuania) according to the manufacturer's recommendations. Amplification was performed in 10 µl of reaction mix comprising 5 µl of Master Mix (TaqPath™ ProAmp™), 0.5 µl of forward and reverse primers-probes (TaqMan® SNP Genotyping Assay 20X), 1 µl of genomic DNA at 5 ng/µl concentration and 3.5 µl of Nuclease-Free Water. No-template controls (NTC) were used to identify polymerase chain reaction (PCR) contamination. For each SNP, the alleles were discriminated upon the presence of VIC or FAM reporter in 5′ and 3′-ends of probes. The PCR reactions were performed using the Light Cycler® 480 (Roche, Risch-Rotkreuz, Switzerland). Data was analyzed using the Light Cycler® 480 Software (Roche, Version 1.5.1.62).

2.8. Quality control and genotyping conditions

Hardy Weinberg Equilibrium (HWE) tests were performed in controls for all SNPs using a recommended SNPStats software (http://apps.biocompute.org.uk/hwe-mr-calc.html) (Rodriguez et al., 2009). To estimate genotyping quality, call rates were assessed. A call rate equal to or greater than 95 % indicates good-quality data and a call rate lower than the set value indicates poor-quality data. To limit genotyping error, negative controls were used and replication of 10% of the samples has been carried out as recommended (Pompanon et al., 2005). Lastly, the genotyping technician who conducted the procedures remained blinded to the relevant information. Samples with ambiguous or unknown genotypical status and duplicated subjects were excluded from the analysis. Three samples were excluded after quality control.

2.9. Statistical analysis

Data were expressed as frequency with percentage for categorical variables and mean and standard deviation (SD) for quantitative variables. Comparisons between groups were performed using chi-square (or Fisher's exact tests, if the expected frequency was less than 5) for categorical variables, and a one-way ANOVA for quantitative variables. We then analyzed the relationships between SNPs and 2-to-2 study groups (SAs *vs.* CTRL; SAs *vs.* non-SAs; non-SAs *vs.* CTRL). We used logistic regression models to estimate odds ratios (OR) and their 95% confidence intervals, adjusted for sex and origin of the sample (AOR: Adjusted odd ratio). The *p*-values (*p*) of the odds ratios were then corrected (*p*') to take account for the multiplicity of tests performed using the false discovery rate (FDR) method. Statistical analyses were performed using the SAS software version 9.4 (SAS Institute Inc.).**Genetic models**.

The association between selected SNPs and the study groups was assessed using codominant, dominant, and recessive models. For a SNP consist of alleles A and a, with A be the risk allele, three genotypes are expected: AA, Aa and aa. The dominant model assumes that either one or two copies of allele A are sufficient to increase risk of the disease. The genotypes AA and Aa are pooled and compared to the aa genotype [(AA + Aa) *vs.* aa]. The recessive model assumes that two copies of allele A are necessary to increase risk of the disease. The AA genotype is compared to the pooled Aa + aa genotype [AA *vs.* (Aa + aa). Finally, the codominant model assumes that the disease risk associated to Aa genotype is situated mid-way AA and aa (Lewis, 2002; Minelli et al., 2005).

3. Results

3.1. Description of the sample

Sociodemographic and clinical data of all participants are detailed in Table 1. The age and sex distributions differed significantly among the three groups. SAs and non-SAs were older than CTRL and more likely to be females. SAs were less likely to be in a relationship or employed, and they were also less likely to have achieved higher levels of education when compared to CTRL. Non SAs were situated between SAs and CTRL for most demographic features except sex and age.

3.2. Genotype and allele frequencies distribution of studied polymorphisms

The mean call rate for the five SNPs was 96.82 ± 0.90 indicating good quality data (genotyping-error rate <5 %). For the following SNPs: rs105323, rs7820268, rs10109853 and rs10988134, no deviation from HWE was found in CTRL group. Regarding rs2121337, the genotype distribution was not in accordance with HWE (Supplementary Table 3).

The distribution of genotype and allele frequencies between SAs, non-SAs and CTRL under codominant, dominant, and recessive models are summarized in Table 2.

The allelic and genotypic distribution of the *KMO* rs1053230 SNP demonstrated multiple associations with SAs when compared with CTRL, namely a higher frequency of the T allele (28.5 % *vs.* 21.8 %; *p'* = 0.012; AOR = 1.50; IC 95 % [1.16–1.93]) and the TT genotype (10.7 % *vs.* 4.2 %; *p'* = 0.03; AOR = 2.82; IC 95 % [1.50–5.32]). Under a recessive model (TT *vs.* CT + CC), rs1053230 was also associated with SAs compared to CTRL (89.25 % *vs.* 95.75 %; *p'* = 0.02; AOR = 2.58; IC 95 % [1.39–4.80]). All these differences remained significant after correction for multiple testing. When comparing SAs *vs.* non-SAs, the T allelic frequency of rs1053230 was higher among SAs (25.8 % *vs.* 19.7 %; *p* = 0.04; adjusted OR (AOR) = 1.54; IC 95 % [1.02–2.32]), but this difference did not remain significant after statistical correction (*p'* = 0.12).

Regarding the *IDO2* rs10109853 SNP, the genotype frequency of TT under a recessive model (TT *vs.* CT + CC) was higher in non-SAs compared to CTRL (35.7 % *vs.* 20.8 %; *p'* = 0.05; AOR = 2.03; IC 95 % = [1.19–3.46]). In a codominant model (CT vs CC and TT *vs.* CC), there were also statistical differences in genotype frequencies between non-SAs and CTRL (*p'* = 0.02; CC: 39.8% *vs.* 50.5%; TT: 35.7% *vs.* 20.8%, respectively), but those differences were not significant in one-by-one comparisons (AOR = 0.80; 95% CI = [0.43–1.47] and AOR = 1.76; 95% CI = [0.92–3.38]). In SAs *vs.* CTRL as well as in SAs *vs.* non-SAs comparison, no significant association was found.

Analysis of *ACMSD* rs2121337 SNP revealed that under a recessive model (CC *vs.* CT + TT), the genotype frequency of CC was lower in SAs compared to CTRL (7.1% *vs.* 12.6%; *p'* = 0.05; AOR = 0.50; IC 95 % [0.28–0.88]). In addition, in a codominant model (CC *vs.* TT and CT *vs.* TT) the CC and CT genotype frequencies were different in SAs compared to CTRL (*p'* = 0.03; 7.1 % *vs.* 12.6 % and 40.2 % *vs.* 32.3 %, respectively). However, one-by-one comparisons were not significant (AOR =

Table 2
SNP association analyses of *KMO*, *ACMSD*, *IDO1*, *IDO2*, *KAT1* polymorphisms between the three groups.

SNP ID (*GENE*)	Model	Comparison	SAs n (%)	Non-SAs n (%)	CTRL n (%)	SAs vs. CTRL (ref)			SAs vs. Non-SAs (ref)			Non-SAs vs. CTRL (ref)		
						AOR [95%]	*p*	*p'*	AOR [95%]	*p*	*p'*	AOR [95%]	*p*	*p'*
rs1053230 (*KMO*)	Allele	C	439 (71.5%)	151 (80.3%)	663 (78.2%)	ref			ref			ref		
		T *vs.* C	175 (28.5%)	37 (19.7%)	185 (21.8%)	**1.50 [1.16; 1.93]**	**0.002**	**0.012**	**1.54 [1.02;2.32]**	**0.04**	0.12	0.78 [0.50; 1.21]	0.27	0.78
	Codominant	CC	165 (53.7%)	61 (64.9%)	257 (60.6%)	ref			ref			ref		
		CT *vs.* CC	109 (35.5%)	29 (30.9%)	149 (35.1%)	1.26 [0.90; 1.76]	**0.005**	**0.03**	1.32 [0.78; 2.22]	0.14	0.42	0.83 [0.49; 1.42]	0.55	0.83
		TT *vs.* CC	33 (10.7%)	4 (4.3%)	18 (4.2%)	**2.82 [1.50; 5.32]**			2.79 [0.93; 8.38]			0.52 [0.14; 1.89]		
	Dominant	(CT + TT) *vs.* CC	142 (46.25%)	33 (35.11)	167 (39.39)	1.44 [1.05; 1.98]	0.02	0.12	1.50 [0.91; 2.46]	0.11	0.57	0.79 [0.47; 1.32]	0.36	0.93
	Recessive	CT + CC	274 (89.25%)	90 (95.75%)	406 (95.75%)	ref			ref			ref		
		TT *vs.* (CT + CC)	33 (10.7%)	4 (4.3%)	18 (4.2%)	**2.58 [1.39; 4.80]**	**0.003**	**0.02**	2.52 [0.85; 7.47]	0.10	0.30	0.55 (0.15; 1.99]	0.36	0.72
rs2121337 (*ACMSD*)	Allele	T	453 (72.8%)	135 (74.2%)	587 (71.2%)	ref			ref			ref		
		C *vs.* T	169 (27.2%)	47 (25.8%)	237 (28.8%)	0.93 [0.73; 1.92]	0.56	0.98	1.02 [0.69; 1.49]	0.94	0.97	0 0.91 [0.61; 1.35]	0.64	0.96
	Codominant	TT	164 (52.7%)	50 (54.95%)	227 (55.1%)	ref			ref			ref		
		CT *vs.* TT	125 (40.2%)	35 (38.5%)	133 (32.3%)	1.35 [0.97; 1.89]	**0.01**	**0.03**	0.97 [0.59; 1.61]	0.96	0.99	1.39 [0.82; 2.35]	0.11	0.33
		CC *vs.* TT	22 (7.1%)	6 (6.6%)	52 (12.6%)	0.56 [0.32; 1.01]			1.12 [0.42; 3.00]			0.49 [0.18; 1.33]		
	Dominant	(CT + CC) *vs.* TT	147 (47.3%)	41 (45.05)	185 (44.90%)	1.13 [0.82; 154]	0.46	0.87	0.99 [0.61; 1.61]	0.97	0.99	1.13 [0.69; 1.86]	0.63	0.93
	Recessive	CT + TT	289 (92.9%)	85 (93.4%)	360 (87.4%)	ref			ref			ref		
		CC *vs.* (CT + TT)	22 (7.1%)	6 (6.6%)	52 (12.6%)	**0.50 [0.28;0.88]**	**0.02**	**0.05**	1.13 [0.42; 2.97]	0.80	0.91	0.44 (0.17 1.15)	0,09	0.27
rs7820268 (*IDO1*)	Allele	C	434 (67.6%)	133 (67.2%)	570 (67.2%)	ref			ref			ref		
		T vs. C	208 (32.4%)	65 (32.8%)	278 (32.8%)	0.95 [0.7; 1.20]	0.69	0.98	0.99 [0.70; 1.41]	0.97	0.97	1.01 [0.70; 1.44]	0.98	0.98
	Codominant	CC	149 (46.4%)	46 (46.5%)	195 (46%)	ref			ref			ref		
		CT *vs.* CC	136 (42.4%)	41 (41.4%)	180 (42.5%)	0.98[0.70; 1.36]	0.91	0.98	1.02 [0.62; 1.67]	0.99	0.99	1.03 [0.62; 1.73]	0.99	0.99
		TT *vs.* CC	36 (11.2%)	12 (12.1%)	49 (11.6%)	0.90 [0.54; 1.49]			0.97 [0.45; 2.06]			0.99 [0.45; 2.16]		
	Dominant	CT + TT *vs.* CC	172(53.58%)	53 (53.54%)	229 (54.01%)	0.96 [0.70; 1.31]	0.77	0.87	1.00 [0.63; 1.61]	0.99	0.99	1.02 [0.63; 1.66]	0.93	0.93
	Recessive	CT + CC	285 (88.8)	87 (87.9)	375 (88.4)	ref			ref			ref		
		TT *vs.* CT + CC	36 (11.2%)	12 (12.1%)	49 (11.6%)	0.91 [0.56; 1.47]	0.80	0.97	0.96 (0.47,197)	0.91	0.91	0.97 (0.46; 2.04)	0.94	0.99
rs10109853 (*IDO2*)	Allele	C	344 (53.8%)	87 (44.4%)	432 (54%)	ref			ref			ref		
		T *vs.* C	296 (46.3%)	109 (55.6%)	368 (46%)	0.93 [0.74; 1.16]	0.49	0.98	0.68 [0.49; 0.95]	0.02	0.12	1.37 [0.97; 1.93]	0.08	0.48
	Codominant	CC	96 (30%)	24 (24.5%)	115 (28.8%)	ref			ref			ref		
		CT *vs.* CC	152 (47.5%)	39 (39.8%)	202 (50.5%)	0.79 [0.55; 1.13]	0.43	0.86	0.94 [0.52; 1.70]	0.04	0.24	0.80 [0.43; 1.47]	**0.003**	**0.02**
		TT *vs.* CC	72 (22.5%)	35 (35.7%)	83 (20.8%)	0.89 [0.57; 1.38]			0.50 [0.27; 0.94]			1.76 [0.92; 3.38]		
	Dominant	CT + TT *vs.* CC	224 (70%)	74 (75.51%)	285 (71.25%)	0.82 [0.58; 1.15]	0.24	0.72	0.74 [0.43; 1.26]	0.27	0.57	1.08 [0.62; 1.88]	0.79	0.93
	Recessive	CT + CC	248 (77.5)	63 (24.28)	317 (79.25)									
		TT *vs.* CT + CC	72 (22.5%)	35 (35.7%)	83 (20.8%)	1.03 [0.70; 1.50]	0.90	0.97	0.52 (0.31; 0.87)	0.01	0.06	**2.03 (1.19;3.46)**	**0.009**	**0.05**
rs10988134 (*KAT1*)	Allele	C	447 (72.8%)	142 (76.3%)	515 (72.5%)	ref			ref			ref		
		T *vs.* C	167 (27.2%)	44 (23.7%)	195 (27.5%)	1.03 [0.78; 1.30]	0.98	0.98	1.13 [0.76; 1.69]	0.54	0.81	0.83 [0.55; 1.27]	0.39	0.78
	Codominant	CC	161 (52.4%)	55 (59.1%)	182 (51.3%)	ref			ref			ref		
		CT *vs.* CC	125 (40.7%)	32 (34.4%)	151 (42.5%)	0.95 [0.68; 1.33]	0.88	0.98	1.29 [0.77; 2.17]	0.61	0.92	0.74 [0.43; 1.26]	0.53	0.83
		TT *vs.* CC	21 (6.8%)	6 (6.5%)	22 (6.2%)	1.13 [0.57; 2.25]			0.99 [0.36; 2.71]			0.88 [0.35; 2.34]		
	Dominant	CT + TT *vs.* CC	146 (47.56%)	38 (40.86%)	173 (48.73%)	0.97 [0.70; 1.35]	0.87	0.87	1.25 [0.76; 2.04]	0.38	0.57	0.76 [0.45; 1.26]	0.28	0.93
	Recessive	CT + CC	286 (93.16%)	87(93.55%)	333 (93.80%)	ref			ref			ref		
		TT *vs.* CT + CC	21 (6.8%)	6 (6.5%)	22 (6.2%)	1.15 [0.59; 2.26]	0.68	0.97	0.89 (0.33; 2.39)	0.82	0.91	1.01 (0.35; 2.89)	0.99	0.99

SNP: single nucleotide polymorphism; SAs: suicide attempters; Non-SAs: depressed non-attempters; CTRL: non-psychiatric controls; ref: reference: AOR: adjusted odd ratio for sex and country; KMO: kynurenine monooxygenase; ACMSD: amino-carboxy muconate semialdehyde decarboxylase; IDO1: idoleamine-2,3- dioxygenase 1; IDO2: idoleamine-2,3- dioxygenase 2; KAT1: kynurenine-aminotransferase 1; *p*: p-value adjusted for sex and country; *p'*: adjusted p-value for sex and country and multiple comparisons (FDR). Significant values are in bold.

0.56; IC 95 % = [0.32–1.01] and AOR = 1.35; IC 95 % = [0.97–1.89]). In non-SAs *vs*. CTRL as well as in SAs *vs.* non-SAs comparison, no significant association was found.

Finally, the allelic and genotypic frequencies of *IDO*1 rs7820268 and *KAT1* rs10988134 polymorphisms were not significantly different between the groups.

4. Discussion

Accumulating evidence suggests that the metabolic dysregulation of the KYN pathway plays a role in the physiopathology of SB (Bryleva and Brundin, 2017). It is important to gain a deeper understanding of the underlying mechanisms at play. We investigated the relationship between several SNPs located in genes encoding for the major enzymes involved in the KYN pathway and their association with lifetime SB and depression. The main finding of our study indicates that the T allele of the *KMO* rs1053230 SNP is associated with a history of suicide attempts almost independently of the model (only in the dominant model statistical significance is lost after FDR correction). However, it cannot be ruled out that a similar association exists between non-SAs and CTRL, as the relatively small size of the non-SAs group may have limited the statistical power to find a difference. *ACMSD* rs2121337 SNP may also have a connection with a history of suicide attempts, although the association appears to be less robust. On the other hand, the genotype TT of the *IDO2* rs10109853 SNP is associated with an increased risk of lifetime depression, but not SB, in codominant and recessive models. These associations were observed for the first time, representing novel contributions to the field. For the other SNPs, *IDO1* rs7820268 and *KAT1* rs10988134, SNP association analyses were negative at the allelic level as well as at the genotypic level.

KMO is a key enzyme in the metabolism of the KYN pathway. In humans, the *KMO* gene is located on the long arm of chromosome 1. The rs1053230 polymorphism is situated in exon 15 of the KMO gene. This polymorphism involves a substitution of arginine with cysteine at position 452 in the enzyme's amino-acid sequence. Although the exact influence of the rs1053230 SNP on KMO enzyme activity has not been fully demonstrated, previous research has shown that this polymorphism is associated not only with psychiatric disorders such as depression, bipolar disorder, and schizophrenia but also with alterations in the catalytic activity of the KMO enzyme and changes in the levels of certain KYN pathway metabolites. In a study by Holtze et *al*., the T allele of *KMO* rs1053230 SNP was strongly associated with increased cerebrospinal fluid (CSF) KYNA levels in both subjects with schizophrenia and controls (Holtze et al., 2012). In a Swedish sample of individuals with bipolar disorder, with or without psychotic features, it has been found that the C allele of the rs1053230 SNP was more common in those with psychotic features, particularly manic episodes. Using an independent sample, the same study revealed that the C allele was associated with elevated CSF KYNA levels in individuals with bipolar disorder and reduced KMO expression in lymphoblastoid cell lines and hippocampal biopsies (Lavebratt et al., 2014). Additionally, a study conducted on Chinese women suffering from postpartum depressive symptoms found an association with the rs1053230 polymorphism: the AG (CT) genotype carriers were more susceptible to develop postpartum depressive symptoms than GG (CC) carriers (Wang et al., 2017). Significantly, the same study also demonstrated that the peripheral levels of 3-HK and 3-HK/KYN ratio (a biomarker of KMO activity) were higher in AG carriers than in GG carriers. Taken together, these findings suggest that the *KMO* rs1053230 SNP may contribute to the metabolic deregulation of the KYN pathway in individuals with psychiatric disorders.

Regarding SB, the impact of *KMO* rs1053230 SNP on the metabolic balance in the KYN pathway has not been explored previously. Nonetheless, the shifts in levels of various neurotoxic and neuroprotective metabolites within the pathway (like KYN, KYNA, QUIN, and PIC) among individuals with a history of suicide attempts, as previously documented, could potentially arise from an unevenness in the activity of KYN pathway enzymes, including KMO (Bay-Richter et al., 2015; Brundin et al., 2016; Carlborg et al., 2013; Erhardt et al., 2013; Sublette et al., 2011). KMO enzyme is situated at the crossroads of the neuroprotective and neurotoxic branches of the KYN pathway (Fig. 1). Any change in the activity of the KMO enzyme could lead to a shift in the KYN catabolism. Although the influence of rs1053230 on the expression and/or catalytic efficiency of the KMO enzyme has not been demonstrated by functional analyses, our results suggest that *KMO* rs1053230 SNP might have a role in this regard.

Regarding *IDO2* rs10109853 SNP, the relationship between this variant and psychiatric disorders has never been examined previously. This study is the first to report an association between this variant and a psychiatric disorder, namely depression. Unlike rs1053230, the *IDO2* rs10109853 SNP is much less documented due to its recent discovery. Relation of rs10109853 with some pathological somatic conditions, such as susceptibility to Crohn's disease, multiple sclerosis, and myeloma, have been examined previously. Two studies failed to find a link between the functional polymorphism with the risk of Crohn's disease (Lee et al., 2014) or multiple sclerosis onset and progression (Agliardi et al., 2017). More recently, Kasamatsu et *al*. found that the *IDO2* C/T (named R/W by the authors) was associated with a higher risk of multiple myeloma (Kasamatsu et al., 2021).

In humans, the *IDO2* gene is constitutively expressed in brain and peripheral organs such a liver, thyroid and B cells (Platten et al., 2019). Like IDO1, the IDO2 enzyme is also able to catalyze the first rate-limiting step allowing the conversion tryptophan into KYN (Fig. 1). The two enzymes are encoded by two paralogous genes arranged in tandem on chromosome 8 and due to their structural similarity, it was long thought that IDO1 and IDO2 enzymes played redundant functions. Enzymatic assays have shown that the catalytic activity of IDO2 enzyme is much weaker compared to that of IDO1 (Qian et al., 2012). In addition, a recent work suggested a distinct and opposite immuno-regulatory functions during the inflammatory response. In an auto-immune context, IDO2 would be involved in the pro-inflammatory response mediated by B cells, while IDO1 would modulate the suppressive effect of T cells (Merlo et al., 2020).

The *IDO2* rs10109853 (C > T; R248W) SNP is known as a non-synonymous substitution that consists of the substitution of arginine (R; C allele) to tryptophan (W; T allele) thus reducing catalytic the activity of IDO2 enzyme by 90 % (Metz et al., 2007). The homozygote genotype TT (W/W) confers to IDO2 the lowest catalytic activity compared to CT (RW) and CC (RR) genotypes, and it is associated to depression according to our results. Furthermore, a meta-analysis comparing metabolite levels in the KYN pathway between depressed patients and controls revealed that depression was associated with reduced levels of KYN and KYNA (Ogyu et al., 2018). Taken together, these findings suggest that a reduction in the catalytic activity of the IDO2 enzyme caused by a variation of rs10109853 SNP may contribute to the pathogenesis of the illness.

We have also established a connection between the *ACMSD* rs2121337 SNP and a history of suicide attempts, but caution is warranted due to a deviation from Hardy-Weinberg equilibrium for this SNP. Supporting evidence for this association can be found in a prior study, which demonstrated diminished ACMSD activity in individuals who had attempted suicide (Brundin et al., 2016). Coherently, they also reported reduced PIC levels and a decreased PIC/QUIN ratio in both CSF and plasma among suicide attempters. It is worth noting that, contrary to our findings, they observed a higher prevalence of the C allele in suicide attempters compared to healthy controls.

4.1. Limitations

Our results should be considered in light of several limitations. First, the SAs group consisted of subjects affected by diverse psychiatric disorders. This point is important since numerous mental disorders are associated with SB (Nock et al., 2010) and diagnostic heterogeneity may

introduce a bias in the results. However, it should be noted that no participant was diagnosed with a psychotic or bipolar disorder. Secondly, some of the above-mentioned SNPs have been associated with specific disorders. rs7820268 SNP with IFNα-induced depressive symptoms (Smith et al., 2012), rs1053230 (Lezheiko et al., 2016) and rs10988134 (Wigner et al., 2018) SNPs with depression. Given the high prevalence of MDD (major depressive disorder) within the SAs group, there was a risk of false positive associations. Third, it appears that the genetic predisposition for violent SB is different from that of non-violent SB (Bayle et al., 2003; Courtet et al., 2005). In our SAs group, most suicide attempts were non-violent (e.g., poisoning) and the inclusion of subjects who had made violent suicide attempts could yield different results. Fifth, we studied cohorts which seem to be homogenous from the point of view geographical origin and their belonging to the European genetic ancestry group. However, we cannot extrapolate the results on other genetic ancestry group due the fact that the distribution of the studied SNPs could be different. Finally, the deviation from HWE observed for *ACMSD* rs2121337 SNP forces us to interpret the related results with caution. The deviation can be caused by several factors including mutation, natural selection, genetic drift and population structure (Waples, 2015).

5. Conclusion

In summary, genetic variations impacting the IDO2 and KMO enzymes may play a role in the metabolic changes observed in the KYN pathway in individuals with depression and suicidal behavior, respectively. Functional analyses on the *IDO2* rs10109853 and *KMO* rs1053230 variants are required to confirm our hypotheses by studying the gene expression profiles of *IDO2* and *KMO*, as well as the catalytic efficiency of the IDO2 and KMO enzymes in the presence of these two variants. These investigations should also consider the interactions between the immune system and the KYN pathway. Several pro and anti-inflammatory cytokines have the capability to regulate the expression of enzymes positively or negatively in this pathway. Therefore, evaluating the influence of cytokines on these enzymes, especially IDO2 and KMO, in the context of depression and SB would be of great interest.

CRediT authorship contribution statement

Rabah Tamimou: Writing – original draft, Investigation, Conceptualization. **Christine Montout:** Methodology, Data curation. **Thibault Mura:** Writing – review & editing, Methodology. **Ismael Conejero:** Writing – review & editing. **Alexandre Evrard:** Writing – review & editing. **Philippe Courtet:** Writing – review & editing, Resources. **Pablo Bonilla-Escribano:** Writing – review & editing, Methodology. **Carlos Riaza:** Writing – review & editing, Resources. **Concepción Vaquero-Lorenzo:** Writing – review & editing, Resources. **Enrique Baca-Garcia:** Writing – review & editing, Supervision, Resources. **Fabrice Jollant:** Writing – review & editing, Resources. **Serge Lumbroso:** Writing – review & editing, Resources. **Kevin Mouzat:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Jorge Lopez-Castroman:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Availability of data

The data will be provided upon request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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