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IL6/IL6R genetic diversity and plasma IL6 levels in bipolar disorder: An Indo-French study

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Abstract

Reports of association of genetic variants of *IL6* and its receptor (*IL6R*) with psychiatric disorders are inconsistent, and there are few population-based studies thus far in bipolar disorder (BD). We genotyped the *IL6 rs*1800795 and *IL6R rs*2228145 polymorphisms in two independent sets of patients exposed to different environmental stimuli such as climatic conditions or specific infectious burden − a French sample and a south Indian Tamil sample of BD with quantitation of circulating plasma IL-6 levels in the latter sub-sample.

In both populations, allele and genotype frequencies did not differ significantly between cases and controls for either polymorphism. Upon stratifying based on age at onset, we found no associations with the *IL6 rs*1800795 variant. However, the *IL6R rs*2228145 C allele and CC genotype were associated with early onset

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of disease in the French sample when compared to late onset BD. A similar trend was observed in the Indian population where we also found that plasma IL-6 levels were significantly higher in BD and also in patients who were in residual phase or remission both as compared to controls.

Our findings are in favour of a possible trans-ethnic implication of the IL6R genetic diversity in BD and reinforce the notion that IL-6 is an important marker of the operating inflammatory processes in the disease.

Keywords: Genetics, Immunology, Molecular biology, Clinical genetics, Psychiatry

1. Introduction

Bipolar disorder (BD) is a severe and chronic mental disorder standing among the leading causes of disability worldwide (Gore et al., 2011). BD is characterised by alternating mood states of mania and depression, interspersed with partial symptomatic recovery (euthymia). Although the precise etiopathological mechanism remains unclear, a potential role for dysfunctional immuno-inflammatory processes in BD has been postulated based on several observations, as recently reviewed (Sayana et al., 2017); some of the prominent ones being: (i) high prevalence of comorbid chronic conditions viz. cardiovascular disorders, type 2 diabetes mellitus, hypertension, obesity and autoimmune disorders (Leboyer et al., 2012); (ii) signs of central nervous system (CNS) inflammation, as evidenced by increased levels of interleukin (IL)1β in the cerebrospinal fluid, and IL1β, IL1 receptor (IL1R), nuclear factor kappa B (NF-kB) subunits p50 and p65 in BD post-mortem frontal cortex with decreased levels of transforming growth factor beta 1 (TGF-β1) (an anti-inflammatory cytokine) (Rao et al., 2010; Söderlund et al., 2011; Stertz et al., 2013); (iii) inflammatory activation of the T cell/monocyte-macrophage system (Breunis et al., 2003; Drexhage et al., 2011); (iv) a pro-inflammatory mRNA signature in monocytes (Padmos et al., 2008); (v) anti-inflammatory effect of antipsychotics/mood stabilisers which are the mainstay of treatment in BD (Maes et al., 1997; Padmos et al., 2008); (vi) high rate of infectious stigma for viruses or parasites with tropism for the CNS, for example, *Toxoplasma gondii* (Del Grande et al., 2017; Hamdani et al., 2015, 2013; Sutterland et al., 2015); (vii) implication of genetic factors that lead to defective immune regulation, and inefficient anti-infectious response in the modulation of BD susceptibility (Debnath et al., 2013a,b; Oliveira et al., 2014); (viii) elevated levels of acute-phase proteins and alterations in circulating levels of pro-inflammatory and anti-inflammatory cytokines, particularly IL6 (Maes et al., 1997; Modabbernia et al., 2013).

IL6, one of the often implicated pro-inflammatory cytokines in BD at the serological level is functionally pleiotropic, released both from peripheral immune cells as well as cells of the CNS including neurons and microglia (Liu et al., 2010). IL6 plays an

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essential role in the regulation of immune response, systemic inflammatory pathways, acute-phase reactions and hematopoiesis by its signalling through the human IL6 receptor (IL-6R) which exists in both membrane-bound (mIL-6R) and soluble forms (sIL-6R) (Sun et al., 2008). It is known that signalling by IL6 can be either pro-inflammatory or anti-inflammatory based on whether the IL-6R is membrane bound or soluble – the former being the classical anti-inflammatory signalling and the latter, pro-inflammatory trans-signalling (Hodes et al., 2016).

The *IL6* -174 G > C (*rs*1800795) is a common single nucleotide polymorphism (SNP; minor allele frequency of 0.14; https://www.ncbi.nlm.nih.gov/) located in the upstream of the gene, which has been shown to influence the circulating levels of both IL6 and C-reactive protein (CRP), with G allele being the high expressor allele for *IL6* (Brull et al., 2001; Eze et al., 2016; Sainz et al., 2008; Sanderson et al., 2009). The non-synonymous SNP of the *IL6R* gene (*rs*2228145) Asp358Ala has previously been shown to influence soluble IL-6R concentrations in an allele dependent manner (Ferreira et al., 2013; Galicia et al., 2004; Lourdusamy et al., 2012; Rafiq et al., 2007; van Dongen et al., 2014). IL-6 exerts its activity either by classical signalling upon binding to the membrane bound IL-6 receptor (mIL-6R) or by trans-signalling after interaction with its soluble variant (sIL-6R) issued from limited proteolytic cleavage and thereby shedding of the mIL-6R or by alternative mRNA splicing. The *IL6R rs*2228145 (A > C; Asp358Ala) variant in the exon 9 of the *IL-6R* gene on chromosome 1q21 was demonstrated to attenuate classical IL-6 signalling and to enhance trans-signalling, as the C allele (358Ala variant) is associated with a high rate of shedding of the IL-6R leading to a two-fold increase in sIL-6R levels (Garbers et al., 2014; Wypasek et al., 2014). Therefore, these functional polymorphisms could clearly influence the expression and levels of both *IL6* and *IL6R* and consequently, IL6 signalling.

Reports from different populations of the association of IL6 genetic variants and that of its receptor IL-6R with other psychiatric disorders are largely inconsistent (Debnath et al., 2013a,b; Kapelski et al., 2015a, 2015b; Mak et al., 2017; Srinivas et al., 2016; Sun et al., 2008) and there is a paucity of population-based IL6 genetic data in BD with very few reports thus far, to our knowledge (Clerici et al., 2009). Moreover, studies on the relationship between immunogenetic diversity and serological levels of inflammatory markers are scarce in BD, with only two studies exploring the genetics of MBL, MASP-2 and CRP production, but with negative results (Avramopoulos et al., 2015; Foldager et al., 2014).

The aims of the present study were: (i) to analyse the distribution of the *IL6* (-174 G > C) *rs*1800795 and *IL6R rs*2228145 polymorphisms in French and South Indian Tamil BD cohorts and (ii) to evaluate plasma levels of IL-6 in the Indian subsample and their potential relationship with IL-6 and IL-6R genotypes.

https://doi.org/10.1016/j.heliyon.2019.e01124

2. Methods

2.1. Study subjects

A sample of 565 French BD patients according to DSM-IV criteria (Dsm-iv-tr, 2000), admitted into three French university-affiliated psychiatry departments (Paris-Créteil, Bordeaux and Nancy), were interviewed by trained psychiatrists, using the French version of the Diagnostic Interview for Genetic Studies (DIGS version 3.0) (Nurnberger et al., 1994). Psychiatric evaluations were performed to assess the severity of symptoms and level of functioning of the subjects. Severity of manic symptoms were rated by using the Young's Mania Rating Scale (YMRS) (Young et al., 1978) and depressive symptoms by Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Furthermore, 201 healthy controls (HC) were recruited and interviewed with the DIGS to assess personal and family history of psychiatric disorders using the National Institute for Mental Health Family Interview for Genetic Studies (Maxwell, 1992 https://www.nimhgenetics.org/interviews/figs/). All patients and controls in this group were of French descent with at least three grandparents from mainland of France and were consecutively recruited between February 2006 and January 2010.

For the second sample, 152 south Indian Tamil patients who had a diagnosis of BD according to DSM-IV criteria (DSM-IV-TR, 2000) were consecutively recruited from out-patient and in-patient services of the Department of Psychiatry at Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, a major tertiary referral centre in South India. Detailed clinical and family history, as well as history of environmental exposures were obtained for each patient through structured interviews conducted by trained psychiatrists. Psychiatric evaluations were performed to assess the severity of symptoms and level of functioning of the subjects. Severity of manic symptoms was rated using the YMRS and MADRS. Remission was defined as a score of $\leq$7 on YMRS, and $\leq$10 on MADRS. One hundred and fifty-nine HC were also enrolled who were matched with respect to age, sex and ethnicity, and were without a personal or a first degree family history of psychiatric, neurological or autoimmune disorders. All subjects in this group were of south Indian Tamil ethnicity.

While genotype analyses were carried out in both the French and south Indian Tamil samples, IL6 levels in plasma were measured only in the latter group, which remained on medication during enrolment into the study. Among them, 88% were on mood stabilizers (either of lithium, valproate, or carbamazepine). About 82% of the patients were treated with antipsychotic medication at least once during their lifetime, including typical (22.7%), atypical (43.7%), and a combination of both (33.6%) antipsychotics. Also, 9% of the patients were treated with antidepressants, 56% with anxiolytics, and 9% of the patients had at least once undergone electroconvulsive therapy.

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In both samples, age at onset (AAO) was defined as the age at which the first mood episode (depressive, manic or hypomanic) occurred. The threshold for early-onset BD (AAO before the age of 22 years) was defined on the basis of previous admixture analyses in eight independent samples (Geoffroy et al., 2013).

The power of the study, analysed using the Genetic Association Study (GAS) Power Calculator that is used to compute statistical power for one-stage genetic association studies, was found to be >70% assuming the genotype relative risk at 1.5 and the significance level set to 0.05.

In both the Indian and the French sample, all participants provided written informed consent for participation in the study, which had previously been reviewed and approved by the respective institutional ethics committees.

2.2. *IL6* and *IL6R* genotyping

Genomic DNA was extracted from peripheral blood leukocytes (Miller et al., 1988). Polymorphisms in the upstream promoter region of the *IL6* gene -174 G > C (*rs*1800795) and in the coding region of *IL6R* gene (*rs*2228145) Asp358Ala were analysed by allelic discrimination method (Step One Plus™ Real Time PCR System, Applied Biosystems, FosterCity, CA, USA) with TaqMan 5′ Nuclease Assays using allele specific fluorogenic oligonucleotide probes − C__1839697_20 and C__16170664_10 respectively, following manufacturer's instructions.

2.3. Plasma measurement

The plasma levels of IL6 were assessed using the "Human IL-6 ELISA Kit" (Diaclone, Besançon, France) following manufacturer instructions.

2.4. Statistical analysis

Categorical variables were expressed as frequencies and percentages, and continuous variables were expressed in terms of median values for each group. The distribution of allele and genotype frequencies was compared between BD cases and healthy controls using chi-square test with Bonferroni correction. The odds ratio (OR) with 95% confidence interval was determined for each allele and genotype. Shapiro-Wilk's test was performed to check for normal distribution of the data. The differences in plasma IL-6 levels between cases and controls were analysed using two-tailed Mann-Whitney U test and Kruskal-Wallis test. A corrected *p*-value (two tailed) <0.05 was considered significant. IBM SPSS v16 software was used for performing linear regression analyses with age, gender, BMI, smoking status, symptom severity as covariates. Winpepi COMPARE 2 v3.85 software was used to test for genotypic associations, and GraphPad Prism 6 was used to compare plasma IL6 levels between cases and controls.

https://doi.org/10.1016/j.heliyon.2019.e01124

3. Results

Demographic characteristics of the study subjects are as shown in Table 1.

Two polymorphisms − one in the promoter region of the *IL6* gene (*rs*1800795) and one in the *IL6R* gene (*rs*2228145) − were characterized in BD patients and HC from two different populations − French, and south Indian Tamil. The genotype and allelic frequencies shown in Tables 2, 3 and 4 were found to be in Hardy Weinberg equilibrium in both cases and controls except for the polymorphism *IL6R rs*2228145 in the French BD group.

We found that allele and genotype frequencies did not differ significantly between cases and controls for both polymorphisms in the French population. In the Indian sample, comparison of the *IL-6* and *IL-6R* allele and genotype distribution showed that the frequency of the *IL-6R rs*2228145 CA genotype was higher in HC than in patients (P = 0.04, Pc = 0.12), while that of the *IL-6R* CC genotype was higher in cases as compared to HC (P = 0.06, Pc = 0.18), albeit failing to reach statistical significance after correction for multiple comparisons (Table 2). The same trend was

Table 1. Demographic & clinical characteristics.

	French subjects		South Indian Tamil subjects	
	BD (*n* = 565)	**HC (*n* = 201)**	**BD (*n* = 152)**	**HC (*n* = 159)**
Age at inclusion (years)				
Mean ± SD	42.5 ± 12.9	42.2 ± 11.9	32.49 ± 10.63	33.79 ± 11.02
Median (Range)	42 (18−80)	44 (19−64)	31 (18−60)	30 (18−63)
Gender				
Male, n (%)	235 (41.6)	119 (59.2)	75 (49.4)	88 (55.3)
Age at onset (years)[a]				
Mean ± SD	24.9 ± 9.9		23.83 ± 6.99	
Median (Range)	22 (6−67)		22 (13−51)	
Plasma IL-6 Levels (pg/mL)[a]				
Median			6.38	5.05
Interquartile range			3.5−9.1	3.1−8.0
Mean ± SD			7.6 ± 9.3	6.1 ± 5.2
Symptom severity				
YMRS				
Acute phase			18.1 ± 10.3	
Residual/remission phase			1.9 ± 2.5	
MADRS				
Acute phase			12.3 ± 12.2	
Residual/remission phase			2.2 ± 6.0	

BD: bipolar disorder; HC: healthy controls; SD: standard deviation; pg/mL: picograms per milliliter.

[a] Data not available for all subjects (Age at onset data missing for 35 BD subjects in the French sample and 30 in the Indian sample; IL-6 levels: not measured in the French sample and data missing for 2BD and 6 HC subjects in the Indian sample).

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Table 2. Frequency distribution *IL6 rs*1800795 and *IL6R rs*2228145 genotypes.

***IL6 rs*1800795**	**French sample**							**South Indian Tamil sample**							
	BD n = 565	**%**	**HC n = 201**	**%**	**P**	**OR**	**95% CI**	**BD n = 152**	**%**	**HC n = 159**	**%**	**P**	**Pc**	**OR**	**95% CI**
Genotype															
CC	213	37.9	71	36.4	0.71			6	3.9	8	5.0	0.64			
GC	253	45.0	93	47.7	0.52			42	27.6	42	26.4	0.80			
GG	96	17.1	31	15.9	0.70			104	68.4	109	68.6	0.98			
Allele															
C	679	60.4	235	60.3	-			54	17.8	58	18.2	-			
G	445	39.6	155	39.7	0.96			250	82.2	260	81.8	0.87			
***IL6R rs*2228145**															
Genotype															
AA	203	36.2	67	34.5	0.68			87	57.2	82	51.6	0.31			
CA	246	43.8	99	51.0	0.08			50	32.9	70	44.0	0.04	0.12	0.62	0.38−1.01
CC	112	20.0	28	14.4	0.09			15	9.9	7	4.4	0.06	0.18	2.36	0.87−7.04
Dominant model															
Allele															
A	652	58.1	233	60.1	-			224	73.7	234	73.6	-			
C	470	41.9	155	39.9	0.41			80	26.3	84	26.4	0.97			

Missing genotypes represent less than 5% of the sample. BD: bipolar disorder; HC: healthy controls; P: *p*-value; Pc: corrected *p*-value; OR: odds ratio; CI: confidence interval.

Table 3. Frequency distribution *IL6 rs*1800795 genotypes in early- and late-onset bipolar disorder.

IL6 rs 1800795	EOBD n = 232	%	LOBD n = 333	%	French sample HC n = 201	%	P^1	P^2	P^3	OR^1 95% CI	OR^2 95% CI	OR^3 95% CI
Genotype												
CC	90	39.3	123	36.9	71	36.4	0.57	0.54	0.90			
GC	99	43.2	154	46.2	93	47.7	0.48	0.36	0.75			
GG	40	17.5	56	16.8	31	15.9	0.84	0.67	0.78			
Allele												
C	279	60.9	400	60.1	235	60.3	-	-	-			
G	179	39.1	266	39.9	155	39.7	0.77	0.84	0.95			

	EOBD n = 55	%	LOBD n = 67	%	South Indian Tamil sample HC n = 159	%	P^1	P^2	P^3	OR^1 95% CI	OR^2 95% CI	OR^3 95% CI
Genotype												
CC	1	1.8	5	7.5	8	5.0	0.15	0.31	0.47			
GC	15	27.3	19	28.3	42	26.4	0.89	0.90	0.76			
GG	39	70.9	43	64.2	109	68.6	0.43	0.74	0.52			
Allele												
C	17	15.5	29	21.6	58	18.2	-	-	-			
G	93	84.5	105	78.4	260	81.8	0.21	0.50	0.40			

EOBD: early onset bipolar disorder; LOBD: late onset bipolar disorder; HC: healthy controls; P: *p*-value; Pc: corrected *p*-value; OR: odds ratio; CI: confidence interval.
P^1, P^2 and P^3 corrected *p*-values correspond to EOBD vs LOBD, EOBD vs controls and LOBD vs controls comparisons, respectively.
OR^1, OR^2 and OR^3 odds ratios correspond to EOBD vs LOBD, EOBD vs controls and LOBD vs controls comparisons, respectively.

observed in the French sample. The *IL6R rs*2228145 heterozygous CA genotype was more frequent in controls (P = 0.08, Pc = 0.24), and the CC genotype was more frequent in cases (P = 0.09, Pc = 0.27), although the differences were not statistically significant. Altogether, these observations suggest a possible recessive susceptibility status of the *IL6R rs*2228145 C allele.

Upon stratifying both populations based on the age at onset as early onset BD (EOBD) and late onset BD (LOBD), in the French population, we found no associations with the *IL6 rs*1800795 variant. The *IL6R rs*2228145 C allele and CC genotype frequencies were significantly higher in EOBD as compared to LOBD (P = 0.01, Pc = 0.03, OR = 1.73, 95% CI = 1.14−2.63) and to HC (P = 0.006, Pc = 0.018, OR = 2.36, 95% CI = 0.87−7.04). A similar trend, although statistically non-significant, was observed in the Indian sample with respect to *IL6R*

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Table 4. Frequency distribution of *IL6R rs*2228145 genotypes in early- and late-onset bipolar disorder.

*IL6R rs*2228145	EOBD n = 232	%	LOBD n = 333	French sample						OR[2] 95% CI	OR[3] 95% CI
				%	HC n = 201	%	P[1]	P[2]	P[3]	OR[1] 95% CI	
Genotype											
AA	74	32.2	129	39.0	67	34.5	0.10	0.61	0.31		
CA	98	42.6	148	44.7	99	51.0	0.62	0.08	0.16		
CC	58	25.2	54	16.3	28	14.4	0.01	0.006	0.57	1.73 (1.14−2.63)	2.00 (1.22−3.32)
Allele											
A	246	53.5	406	61.3	233	60.1	-			-	-
C	214	46.5	256	38.7	155	39.9	0.008	0.05	0.97	1.38 (1.08−1.76)	1.31 (0.99−1.72)
				South Indian Tamil sample							
	EOBD n = 55	%	LOBD n = 67	%	HC n = 159	%	P[1]	P[2]	P[3]	OR[1] 95% CI	OR[2] 95% CI	OR[3] 95% CI
Genotype											
AA	33	60.0	36	53.7	82	51.6	0.49	0.28	0.76		
CA	16	29.1	25	37.3	70	44.0	0.34	0.05	0.35	0.52 (0.25−1.05)	
CC	6	10.9	6	9.0	7	4.4	0.72	0.08	0.18	2.66 (0.70−9.69)	
Allele											
A	82	74.5	97	72.4	234	73.6	-	-	-		
C	28	25.5	37	27.6	84	26.4	0.70	0.84	0.79		

EOBD: early onset bipolar disorder; LOBD: late onset bipolar disorder; HC: healthy controls; P: *p*-value; Pc: corrected *p*-value; OR: odds ratio; CI: confidence interval.
P[1], P[2] and P[3] corrected *p*-values correspond to EOBD vs LOBD, EOBD vs controls and LOBD vs controls comparisons, respectively.
OR[1], OR[2] and OR[3] odds ratios correspond to EOBD vs LOBD, EOBD vs controls and LOBD vs controls comparisons, respectively.

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*rs*2228145 CC genotype on comparing EOBD to controls (P = 0.05, Pc = 0.15, OR = 1.52, 95% CI = 0.25−1.05); however, the difference was not replicated at the allelic level, or when comparing EOBD with LOBD (Table 3).

In the South Indian population, we found that plasma IL-6 levels were significantly higher in BD as compared to HC (median: 6.38 pg/mL *vs* 5.05 pg/mL, P = 0.007 in patients and HC respectively) (Fig. 1). Comparison of plasma IL-6 levels between BD cases in acute phase and those in remission/residual phase of the disease, or with controls did not show any significant differences (Fig. 2). However, when the levels of subjects enrolled at remission/residual phase were compared with healthy controls, we observed that the IL-6 levels were significantly higher in patients than in the controls (median: 7.68 pg/ml *vs* 5.23 pg/ml, P = 0.005 in patients and HC respectively). The plasma IL-6 levels were not influenced by the *IL-6* and *IL-*

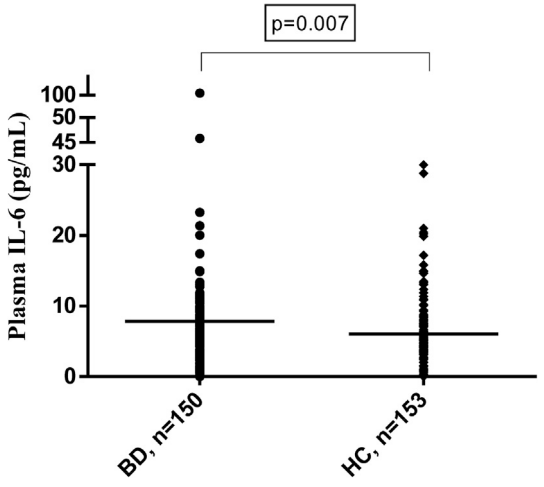

Fig. 1. Median plasma IL-6 levels between BD cases and controls.

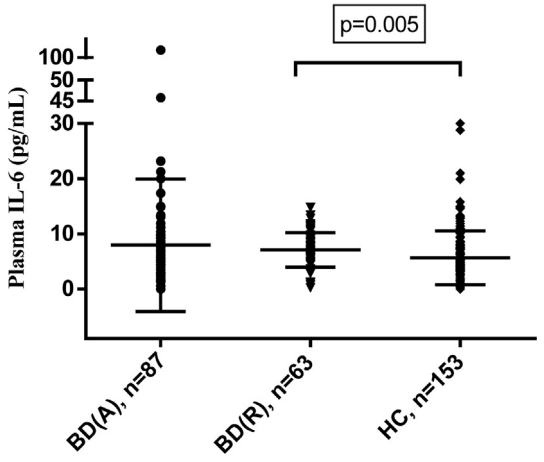

Fig. 2. Median plasma IL-6 levels between BD cases in Acute phase [BD(A)], Residual Phase/Remission [BD(R)] and controls (SNC).

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6R alleles/genotypes both in BD and in controls (data not shown). Linear regression analyses showed that IL-6 levels were not influenced by age, gender, BMI, smoking status, or severity of symptoms as assessed by the MADRS or the YMRS clinical assessments.

4. Discussion

Converging evidences point towards the involvement of inflammatory mechanisms, at least in a subset of patients, in BD. Overall, BD could be viewed as a multi-system inflammatory disease, owing to the high burden of comorbid disorders associated with inflammation and immune abnormalities (Leboyer et al., 2012). As a marker of such dysimmunity, IL6 was amply studied and implicated in the risk to develop BD.

In the present study, we observed that the French and the south Indian Tamil cohorts differ in terms of allelic frequencies for both *IL6* rs1800795 and the *IL6R* rs2228145 polymorphisms. The minor G allele of the IL6 rs1800795 variant was found almost three times more frequent in the French sample (60%) as compared to the south Indian Tamil sample (18%). However the frequencies were comparable to that of 1000 Genomes reference data (The 1000 Genomes Project Consortium et al., 2015) for European (35−51%) and South Asian ancestries (11−17%) respectively. Similarly, for the IL6R rs2228145 polymorphism, the frequency of the minor C allele was comparable to the reference data of European ancestry (25−41%) for our French sample (40%), and with the South Asian ancestry (27−31%) for our south Indian Tamil sample (26%), although widely different between the two studied samples.

Then, we found that the *IL6R rs*2228145 C allele and CC genotype were associated with EOBD in a relatively large French sample, with similar trend being observed in the Indian population-group. Functionally, the *IL6R rs*2228145 attenuates classical IL-6 signalling and to enhances trans-signalling, as the C allele (358Ala variant) is associated with a high rate of shedding of the IL-6R leading to a two-fold increase in sIL-6R levels (Garbers et al., 2014; Wypasek et al., 2014). Indeed, trans- and not classical IL-6 signalling and thus IL6-related pro-inflammatory processes have been found to be associated with chronic immune/inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease (Garbers et al., 2014). This could partly explain the herein observed association between the *IL6R* C allele at homozygous state early-onset BD, which is considered as the more severe form (Oliveira et al., 2015).

The difference in IL-6 signalling was also reflected by the higher levels of circulating IL-6 observed in the Indian BD patients who were in residual phase or remission, in agreement with earlier reports (Hope et al., 2011; Kim et al., 2007; Tsai et al., 2012). However, we did not find any significant difference on comparing patients in acute

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phase with those in residual/remission phase or with controls. Also, no phasic differences in IL-6 levels within the disease groups were observed, and the alterations in the plasma IL-6 levels were independent of the studied *IL-6* and *IL-6R* genetic variants.

An earlier meta-analysis of 30 studies on cytokine alterations in BD found that concentrations of IL-6 and sIL-6R were significantly elevated in BD patients compared to healthy controls (Modabbernia et al., 2013). One study examined the phasic differences of cytokine levels in BD and found that IL-6 was elevated in acute mania and in acute depressive phases compared to healthy subjects (Brietzke et al., 2009). A finding of T-cell immune activation and increased B- cell numbers − markers of immune dysregulation in BD in an earlier study, was attributed to the stimulatory effect of IL-1 and IL-6 cytokines which were also found to be raised in this condition (Breunis et al., 2003). Hamdani *et al* found a correlation of IL-6 mRNA expression levels and cognitive deterioration index in BD patients infected with *Toxoplasma* gondii. Taking IL-6 as a marker of long-term exposure to inflammation, it has been proposed that *IL-6* expression could help design personalized treatment for BD by acting as a predictor of cognitive deterioration (Hamdani et al., 2013).

Based on data from twin families (n = 2360), van Dongen *et al* observed that the functional *IL-6R* SNP *rs*2228145 contributed 51% to the heritability of the sIL-6R which was estimated at 72% (van Dongen et al., 2014). Cetin *et al* reported that the sIL-6R levels were increased in BD patients with and without subsyndromal symptoms as compared to healthy control subjects. However, they did not find any differences between the two BD subgroups (Cetin et al., 2012).

There is paucity of comprehensive population based data on the *IL6* and *IL6R* genetic variant distribution and concerning their potential relationship with IL-6 expression in BD. Here, we addressed, for the first time to our knowledge, these aspects in two genetically distant population-groups − French and south Indian Tamil. In particular, being an understudied ethnicity compared to European and other populations, inclusion of genetic data from the south Indian Tamil population in a reasonable large sample adds to the novelty of our study. Despite the importance of the trans-ethnic aspect of the study, a limitation is the non-availability of IL-6 plasma level data of the French sample. Also in the south Indian Tamil cohort, all patients remained on medication during this study. This could be a potential limitation with respect to the IL-6 quantitation given that pro-inflammatory cytokines might be modified by the administration of psychoactive drugs (Modabbernia et al., 2013).

Nevertheless, the present study uncovers the possible association of the IL-6R genetic diversity with BD and replicates that of increased IL6 plasma levels. These trans-ethnic findings warrant further investigation and replication in larger cohorts.

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Declarations

Author contribution statement

Aparna Sundaresh: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

José Oliveira: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Raj Kumar Chinnadurai, Ravi Philip Rajkumar: Contributed reagents, materials, analysis tools or data.

Lylia Hani: Performed the experiments.

Rajagopal Krishnamoorthy: Analyzed and interpreted the data; Wrote the paper.

Marion Leboyer, Vir Singh Negi, Ryad Tamouza: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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