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BRIEF REPORT

A Functional Polymorphism in IL-1B Is Associated With Immune Reconstitution Inflammatory Syndrome of Chronic Disseminated Candidiasis

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We investigated single nucleotide polymorphisms (SNPs) possibly involved in immune reconstitution inflammatory syndrome of chronic disseminated candidiasis (IRIS-CDC) through a candidate gene approach and a prospective matched-control study. We found that an SNP located in interleukin-1B at rs1143627 was significantly associated with the risk of developing IRIS-CDC.

Keywords. IL-1B; *Candida* spp; cytokines; genetic polymorphism; immune inflammatory reconstitution syndrome; invasive fungal diseases.

Immune reconstitution inflammatory syndrome (IRIS), an exaggerated host inflammatory response, is triggered by several invasive fungal diseases (IFDs) [1]. Initially described in an HIV-seropositive population with neuro-cryptococcosis [2], fungal IRIS is also encountered in patients with a solid organ transplantation and hematological malignancies [3]. Through a large prospective study on chronic disseminated candidiasis (CDC), our team has investigated immune response to CDC [4]. We have shown that CDC belongs to the spectrum of IRIS. IRIS of CDC (IRIS-CDC) is rare, accounting for <5% of patients managed for acute leukemia [5]. Consequently, individual susceptibility could have an impact on IRIS-CDC occurrence. The cytokine synthesis phenotype may have a strong effect on susceptibility to immune-mediated diseases [6]. Characterizing single nucleotide polymorphisms (SNPs) that regulate cytokine abundance and biological processes is a crucial step toward new insights in IRIS-CDC pathophysiology.

Using a candidate gene approach and a matched control study, our aim was to assess genetic polymorphisms that could be associated with the occurrence of IRIS-CDC.

METHODS

This was a matched, case–control, candidate–gene association study of variants associated with susceptibility to IRIS-CDC after intensive chemotherapy for the treatment of hematological diseases. Participants' data were extracted from the CANHPARI study (Ethics Committee Ile-de-France 2013-mai-13239) conducted in France from 2013 to 2017 (registered at http://www.clinicaltrials.gov as NCT01916057) and from a cohort of hematological patients at Lausanne University Hospital (Swissethics 2017–01975) [4, 7]. Cases and controls provided written consent. Cases were ≥18 years old and had probable or possible CDC according to European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group criteria in 20 and 24 cases, respectively [8]. Patients undergoing allogenic hematopoietic cell transplant (HSCT; n = 2) were excluded as blood samples reflect the donors' but not the recipients' genomes after engraftment. We excluded 2 non-Caucasian patients to avoid population stratification. One to 5 controls without CDC were matched to each case according to underlying disease (acute myeloid leukemia, acute lymphoblastic leukemia, or other), treatment type (induction or consolidation chemotherapy or autologous HSCT), antifungal prophylaxis, and, whenever possible, age group (18–34, 35–49, 50–64, ≥65) and inaugural vs relapse status.

A total of 17 SNPs from 6 genes involved in IRIS were selected, based on a literature review [4]. Selected genotypes or their proxies identified using the Ldproxy API (https://ldlink.nci.nih.gov/) were extracted from a genome-wide SNP chip data set (Illumina Infinium Global screening array GSAMD-24v1–0_20011747_A1). Hardy-Weinberg equilibrium (HWE) and linkage disequilibrium (LD) between SNPs were assessed using

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the "pwld" and "hwe" tests, respectively, both implemented in Stata (StataCorp, College Station, TX, USA). SNPs that were not at HWE ($P < .01$) were excluded. Among 17 SNPs selected, 3 pairs were in strong LD and 1 was not at HEW, so 13 SNPs were tested. The association between SNPs and disease was assessed by conditional logistic regression using the "clogit" program implemented in Stata. For the sake of simplicity, the associations were tested for the additive mode of inheritance, in which wild-type, heterozygous, and homozygous genotypes were coded 0, 1, and 2, respectively, within a single variable.

RESULTS

Among 42 cases of IRIS-CDC, 38 were Caucasian and matched with 157 controls (Table 1). Cases had equal numbers of males and females, and their median age (interquartile range) was 50 (30–62) years. Most had acute myeloid (58%) or lymphoblastic (32%) leukemia. Cases were hospitalized for induction (74%) or consolidation (21%) chemotherapy, and a few were undergoing autologous HSCT (5%).

Among the 13 SNPs tested, the C allele of rs1143627 in interleukin (IL)-1B was associated with susceptibility to IRIS-CDC (odds ratio [OR], 2.43; 95% CI, 1.37–4.32; $P = .002$). The association was still significant when Bonferroni correction for multiple testing was applied (P after correction for multiple testing = .03) (Table 2). There was also a trend toward an association between SNP rs1805015 in IL-4RA and susceptibility to IRIS-CDC ($P = .08$) and a trend toward a protective effect of SNP rs2430561 in interferon (IFN)γ against IRIS-CDC ($P = .07$).

Table 1. Characteristics of Patients With Chronic Disseminated Candidiasis and Matched Controls

	Cases (n = 38)		Matched Controls[a] (n = 157)	
Characteristics	N	F	N	F
Male sex	19	0.50	105	0.67
Median age (IQR),[a] y	50	(30–62)	52	(22–62)
Underlying disease[a]	…	…	…	…
AML	22	0.58	107	0.68
ALL	12	0.32	39	0.25
Other[b]	4	0.11	11	0.07
Chemotherapy[a]	…	…	…	…
Induction	28	0.74	117	0.75
Consolidation	8	0.21	31	0.20
Autologous HCT	2	0.05	9	0.06
Antifungal prophylaxis[a]	3	0.08	15	0.10
Relapse[a]	9	0.25	29	0.18

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HCT, hematopoietic cell transplantation; IQR, interquartile range.

[a]For each case, 1 to 5 controls were matched for underlying disease, treatment type, antifungal prophylaxis, and, whenever possible, age group (18–34, 35–49, 50–64, ≥65) and relapse status.

[b]Non-Hodgkin lymphoma in 2 cases and 10 controls; Hodgkin lymphoma in 1 case and 1 control; other/undefined in 2 cases.

[c]Any antifungal agent with activity against yeasts (eg, fluconazole, posaconazole).

DISCUSSION

In this paper, we observed a significant association between an SNP in IL-1B and the risk of developing CDC among hematological patients. Single nucleotide polymorphisms in ILRA and IFNγ tended to be associated with an increased and decreased risk of IRIS-CDC, respectively. No associations were found for SNPs selected in IL-4, IL-2, IL-17A, and IL-6.

IL-1β, an effector of the NLRP3 inflammasome produced mainly by monocytes, macrophages, and neutrophils, is involved in the pathogenesis of many chronic inflammation–related diseases and affects both the innate and adaptive arms of the immune response [9]. Like other pro-inflammatory cytokines, IL-1β can play different and sometimes opposed roles in immunity. On the one hand, it can promote resistance against offending pathogens by inducing antimicrobial peptides at the site of infection and/or by promoting T-cell expansion and differentiation. On the other hand, prolonged production of this cytokine in chronically infected patients may induce local inflammation and tissue damage, thereby contributing to the clinical manifestations of the infection and/or its severity.

The IL-1B rs1143627 T allele (which is the most frequent in South Asian populations) has been linked with different infection-associated phenotypes. Carriers of the T allele of IL-1B rs1143627 have an increased risk of developing gastric cancer in the presence of *Helicobacter pylori* infection, which has been attributed to increased (although not yet demonstrated) IL-1β production [10]. In a subsequent study of patients with tuberculosis, monocytes from T allele carriers produced increased amounts of IL-1β after stimulation with mycobacterial stimuli, which correlated with an increased risk of developing active disease, as well as severe and/or extrapulmonary lesions resulting from local accumulation of neutrophils [11]. Consistent with this observation, investigators found that the rs1143627 T allele was more frequent among patients infected with the influenza virus during the 2009 H1N1 pandemic than among healthy controls, suggesting that higher IL-1β production in these individuals may have contributed to the development of symptomatic disease [12].

In patients chronically infected with the hepatitis B virus (HBV), carriage of the rs1143627 TT genotype was associated with reduced infection-induced fibrosis compared with others [13]. The authors suggest that this phenotype results from reduced baseline serum levels of IL-1β in TT genotype carriers compared with TG or GG carriers. However, baseline levels can vary over time and might not be correlated with the differences in cytokine expression or production, which occur after appropriate cell stimulation in vitro. As described above, investigators have found increased but not reduced production of this cytokine in monocytes from T allele carriers after stimulation with mycobacterial products [11]. Decreased fibrosis in

Table 2. Association of Variants in Genes Encoding IRIS-Associated Cytokines With Susceptibility to Chronic Disseminated Candidiasis

Gene, Variant[a]	Genotype	Cases (n = 38)		Matched Controls (n = 157)		OR	95% CI	*P*
		N	F	N	F			
TLR, rs13150331[b,c]	AA	11	0.32	58	0.39	0.93	(0.51–1.72)	.8
…	AG	22	0.65	70	0.47	…	…	…
…	GG	1	0.03	21	0.14	…	…	…
TLR2, rs4696480[c]	TT	12	0.32	46	0.29	0.82	(0.48–1.39)	.4
…	TA	20	0.54	73	0.47	…	…	…
…	AA	5	0.14	37	0.24	…	…	…
IFNγ, rs2069705	AA	17	0.45	78	0.50	1.52	(0.87–2.65)	.1
…	AG	16	0.42	70	0.45	…	…	…
…	GG	5	0.13	8	0.05	…	…	…
IFNγ, rs2430561	AA	19	0.50	44	0.28	0.61	(0.36–1.04)	.07
…	AT	11	0.29	77	0.50	…	…	…
…	TT	8	0.21	34	0.22	…	…	…
IL-1B, rs1143627[d]	TT	10	0.26	82	0.52	**2.43**	**(1.37–4.32)**	**.002**[f]
…	TC	21	0.55	64	0.41	…	…	…
…	CC	7	0.18	11	0.07	…	…	…
IL-1B, rs1143633	GG	15	0.39	61	0.39	0.72	(0.41–1.29)	.3
…	GA	22	0.58	70	0.45	…	…	…
…	AA	1	0.03	25	0.16	…	…	…
IL-1B, rs1143634	GG	22	0.58	89	0.57	0.85	(0.44–1.64)	.6
…	GA	15	0.39	60	0.38	…	…	…
…	AA	1	0.03	8	0.05	…	…	…
IL-2, rs2069762	AA	12	0.32	73	0.46	1.44	(0.84–2.45)	.2
…	AC	23	0.61	67	0.43	…	…	…
…	CC	3	0.08	17	0.11	…	…	…
IL-4RA, rs1805015	AA	22	0.58	111	0.71	1.8	(0.93–3.51)	.08
…	AG	13	0.34	43	0.27	…	…	…
…	GG	3	0.08	3	0.02	…	…	…
IL-4, rs2070874	GG	28	0.74	114	0.74	1.15	(0.52–2.52)	.7
…	GA	10	0.26	39	0.25	…	…	…
…	AA	0	0.00	2	0.01	…	…	…
IL-6, rs1800795	CC	14	0.37	60	0.38	1.15	(0.65–2.01)	.66
…	CG	16	0.42	78	0.50	…	…	…
…	GG	8	0.21	19	0.12	…	…	…
IL-6, rs1800796	CC	32	0.84	134	0.86	1.18	(0.49–2.87)	.7
…	CG	5	0.13	22	0.14	…	…	…
…	GG	1	0.03	0	0.00	…	…	…
IL-17A, rs1999673[e]	CC	27	0.71	105	0.67	0.76	(0.40–1.44)	.4
…	CA	10	0.26	42	0.27	…	…	…
…	AA	1	0.03	10	0.06	…	…	…

The study had >50% power to detect a genetic effect of 3.0, 2.5, and 2.0 for minor allele frequencies of 0.1, 0.2, and 0.3, respectively.

Abbreviations: HWE, Hardy-Weinberg equilibrium; IFN, interferon; IL, interleukin; IRIS, immune reconstitution inflammatory syndrome; LD, linkage disequilibrium; OR, odds ratio; SNP, single nucleotide polymorphism; TLR, Toll-like receptor.

[a]Among 17 selected SNPs, 3 pairs were in strong LD (IL1B rs1143627 with rs16944 [$R^2 = 0.82$], IL4 rs2070874 with rs2243250 [$R^2 = 1.0$], and IL6 rs1800795 with rs1800797 [$R^2 = 0.91$]), and 1 was not at HWE (TLR2 rs3804099, $P < .001$), so 13 remaining independent associations were tested.

[b]TLR2 rs13150331 was used as a proxy for rs1898830 ($R^2 = 0.69$).

[c]TLR2 rs13150331 and rs4696480 were in partial LD ($R^2 = 0.54$).

[d]Reverse/complement alleles T and C were used instead of A and G, respectively, to be consistent with the literature.

[e]IFNG rs1999673 was used as a proxy for rs1974226 ($R^2 = 0.68$).

[f]For $P = .03$ after Bonferroni correction for multiple testing, considering 13 independent tests.

rs1143627 T allele carriers may result from better control of HBV infection rather than lower inflammation. In the present study, we found that carriage of the C and T alleles was associated with higher and lower susceptibility to CDC, respectively. It is possible that reduced IL-1β production in rs1143627 C allele carriers results in increased fungal colonization in the gut and infection of organs during neutropenia, with subsequent clinical manifestations of IRIS during immune recovery.

Conversely, T allele carriers may have better control fungal colonization and/or infection during neutropenia, resulting in fewer manifestations of IRIS after neutrophil recovery.

CDC is particularly apt to decipher IRIS mechanisms in a non-HIV population. However, individual susceptibility to CDC has rarely been studied. One study investigated 40 CDC patients and found that a common haplotype of IL-4 (1098T/589C/33C) was overrepresented among patients with CDC ($P = .010$), whereas another common haplotype (1098T/589T/33T) was underrepresented ($P = .018$) [14]. In the other study on the same cohort of patients, the authors failed to find an association between CDC and the selected gene polymorphisms [15].

The strength of our study relies on the relevant choice of genes that have been demonstrated to code for cytokine production involved in fungal diseases and/or IRIS-CDC [4]. We also chose to test for IL-4 gene polymorphisms due to the results mentioned above [14]. In the Journal, we have demonstrated that significantly higher levels of IL-6, sCD25, IL-1β, IL-10, IL-2, and tumor necrosis factor–α were present in the plasma of IRIS-CDC patients compared with age- and disease-matched controls. In addition, *Candida*-specific IFNγ+ T cells were significantly higher in IRIS-CDC cases than in controls, with higher proportions of VD2+ T cells expressing CXCR3, which is typically associated with IFNγ [4].

We tested IL-17 gene polymorphisms insofar as IL-17 is crucial in preventing the passage from *Candida* mucosal colonization to dissemination [16]. IL-17 stimulates accumulation, activation, and enhanced IL-17 responsiveness in circulating neutrophils. Here, IL-17 SNPs were not associated with IRIS-CDC. This finding correlated with *Candida*-specific IL-17+ T cells that were detected in similar proportion between IRIS-CDC cases and controls [4].

Like other candidate gene association studies, our work had limitations. The relatively small number of cases (in the setting of IRIS-CDC, which has become less frequent due to expanded antifungal prophylaxis in hematology) did not allow for genome-wide association study and/or analysis of a large number of variants within candidate genes. We decided to focus on a very limited number of variants within the genes involved in the mechanisms of IRIS. Despite these limitations, one of the associations was still significant after correction for multiple testing. Unfortunately, there are very few studies on IRIS-CDC with appropriate controls and appropriate samples allowing for validation. Large cohorts of patients with systematic sampling and careful clinical characterization of disease and risk factors would be mandatory to further identify and validate similar associations in the future. Furthermore, functional studies are needed to confirm the biological mechanisms underlying this genetic association.

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Patient consent. a. The patient's written consent was obtained, b. The design of the work has been approved by local ethical committees (Ethics Committee Ile-de-France 2013-mai-13239 and Swissethics 2017–01975).

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