SHORT COMMUNICATION

Frequency of TNFalpha, *IL17RA*, and *Act1* Genetic Polymorphisms in a Population with Psoriasis Compared with Healthy Individuals: Results in a Multiracial Population in Rio de Janeiro, Brazil

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Psoriasis is a chronic systemic inflammatory disease with genetic underpinnings, affecting approximately 2–3% of Caucasian Europeans (1) and an estimated 1.3% of Brazilians, with regional variability (2). The disease arises from dysregulation of innate and adaptive immune responses, with the Th17/Th23 axis playing a pivotal role in its pathogenesis (3, 4). Genetic predisposition is a significant determinant of disease risk and severity (5), often influencing treatment strategies based on metrics like the Psoriasis Area Severity Index (PASI), Body Surface Area (BSA), and Dermatology Life Quality Index (DLQI) (6). While psoriasis can manifest at any age, there are 2 notable peaks of incidence: in young people around 30 and above 60 years old (3).

Genome-wide studies have identified over 109 loci associated with psoriasis susceptibility (7). However, genetic variation among populations remains underexplored, particularly in Brazil's diverse, multiracial context. In Rio de Janeiro, genetic influences include Native Amerindians, Iberian (Portuguese), and African descent, potentially affecting psoriasis profiles compared with Latin America.

*HLA-C*06:02*, which is linked to autoantigen recognition and inflammation, stands out as a major contributor (8). Similarly, the TNF-α gene, extensively studied for its role in immune regulation, contains promoter region mutations associated with psoriasis. Notably, specific SNPs, including TNF alleles – rs361525 (238G/A) and rs1800629 (308G/A) – influence its gene expression. The A allele of rs361525 has been implicated in increased risk of type 1 psoriasis (9), though findings have been inconsistent across studies (10). A Brazilian study conducted in 2010 found the -238G/G genotype to be more frequently associated with severe psoriasis (11). Polymorphisms in the *IL17RA* gene, which encodes the interleukin 17A receptor, have also been linked to a higher incidence of psoriasis in a Spanish population. These polymorphisms exhibit linkage disequilibrium with *HLA-C*06* and are associated with improved response to certain therapies, such as TNF-α blockers (12). The *Act1* gene, also known as *TRAF3IP2* or *CIKS*, is essential for IL-17 receptor intracellular signalling within the NF-κB pathway, a key mediator of inflammation in psoriasis. A specific SNP, SNP-D10N (rs33980500), leads to hyperactivation of the Th17 inflammatory response (13) and is related to the disease in a Polish population (14).

In this study, we investigated 3 SNPs commonly associated with psoriasis pathophysiology in global populations, focusing on a mixed-race Brazilian cohort. These SNPs included rs361525 (A/G) in the TNF-α promoter region, rs4819554 (A/G) in the IL17RA gene, and rs33980500 (C/T) in the TRAF3 gene, which is involved in the NF-κB inflammatory cascade (**Table I**), the intracellular inflammatory pathway mediated by IL17. We examined their prevalence in healthy individuals and psoriatic patients, stratifying disease severity into mild or moderate-to-severe categories based on PASI ≥10 or current/previous systemic therapy and age of onset of the disease.

MATERIALS AND METHODS

We recruited 121 plaque psoriasis patients (81% with PASI ≥10) and 121 healthy controls matched for sex and ethnicity (Table I). Informed consent was obtained, and the study was approved by the Research Ethics Committee of Pedro Ernesto University Hospital (CAAE: 31055720.9.0000.5259). Genomic DNA was extracted, and SNPs were genotyped using TaqMan probes (Table SI). Statistical analysis included Hardy–Weinberg Equilibrium (HWE) testing, χ^2 tests for allele and genotype comparisons, and odds ratios (OR) with confidence intervals (CI). Mann–Whitney tests assessed correlations between SNP frequencies and disease severity and age onset. A p-value <0.05 was considered significant. Genotypic variables were analysed using the method described by Liu et al. (15), comparing additive, dominant, recessive, and codominant models.

RESULTS AND DISCUSSION

No significant differences in genotype frequencies were observed between psoriatic patients and controls for the SNPs (**Table II**) in the population studied. The allele frequency analysis yielded results consistent with the genotype analysis, showing no significant differences in frequencies between healthy individuals and psoriasis patients, nor between patients with mild vs moderate to severe psoriasis and age onset (Table SII). The dominant, recessive, codominant, and additive models were also tested, and no statistical differences were found. However, we observed a trend suggesting that the IL-17RA

Table I. Demographic data and severity of psoriasis

Factor	Control (n=121)	Psoriasis (n=121)	p-value
Sex			
Male	62 (49.6%)	63 (50.4%)	NS
Female	59 (50.4%)	58 (49.6%)	
Age (years) at diagnostic onset	26 [17–58]	50 [39–82]	<0.001
		31 [5–74]*	<0.001
Colour/race auto-declaration			
White	60 (58.25%)	43 (41.75%)	NS
Multiracial	47 (45.19%)	57 (54.81%)	
Black	14 (40%)	21 (60%)	
Severity of psoriasis			
Mild psoriasis	–	23 (19%)	
Moderate to severe psoriasis	–	98 (81%)	

Healthy controls were volunteers with no history or current diagnosis of psoriasis or other inflammatory skin diseases, as well as no psychiatric disorders, intellectual disabilities, or visible skin conditions. Patients were recruited from the Dermatology Outpatient Clinics of Pedro Ernesto University Hospital (HUPE) or Piquet Carneiro University Policlinic (PPC), with selection criteria including a disease duration of more than 10 years and the absence of psychiatric disorders or intellectual impairments. Data are expressed as frequency or mean [min–max]. NS: non-significant, a p-value of less than 0.05 was considered statistically significant.

AG codominant genotype might be more frequent in the moderate to severe group (p=0.097).

Despite previous findings regarding TNF-α alleles in other regions of Brazil, we were unable to replicate these results in our population. This may be attributed to the highly mixed and diverse nature of the Brazilian population, which varies significantly between regions. Another factor to consider is the sample size, and further studies with larger samples are needed to confirm these findings. Additionally, we did not observe the same results for other alleles tested, such as IL17RA in Spain and Act1 (or TRAF3IP2) in Poland. These findings suggest unique genetic architecture in Brazil's multiracial population, differing from other regions inside the country and across the world. Contrary to prior reports emphasizing TNF-α and *HLA-C*06* in Brazilian psoriasis, our results of rs361525, rs4819554, and rs33980500 analysis showed no significant associations. However, trends for IL17RA warrant larger confirmatory studies.

Studies in multiracial populations such as in Brazil are crucial to understanding global genetic variability in psoriasis, informing personalized treatments. Future research should include larger cohorts and longitudinal studies examining genotype–phenotype correlations and treatment outcomes.

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Table II. IL-17RA, TNFα, and TRAF3 genotype and allele frequencies in controls versus psoriasis patients

SNP	Genotype allele	Controls	Psoriasis	χ^2	p-value	OR
rs4819554 (IL17RA)	AA	72 (64.9%)	77 (65.8%)	1.07	0.440	
	AG	36 (32.4%)	34 (29.1%)			
	GG	3 (2.7%)	6 (5.1%)			
	A	180 (81.08%)	188 (80.34%)	0.04	0.4216	1.04 (0.65–1.67)
	G	42 (18.92%)	46 (19.66%)			
rs361525 (TNFα promoter region)	GG	110 (90.9%)	103 (85.12%)	2.05	0.086	
	AG	10 (8.3%)	17 (14.0%)			
	AA	1 (0.8%)	1 (0.8%)			
	G	230 (95.04%)	223 (92.15%)	16.89	0.100	0.61 (0.29–1.29)
	A	12 (4.96%)	19 (7.85%)			
rs33980500 (TRAF3)	CC	93 (80.2%)	88 (75.2%)	0.89	0.184	
	CT	21 (18.1%)	27 (23.1%)			
	TT	2 (1.7%)	2 (1.7%)			
	C	207 (89.22%)	203 (86.75%)	0.67	0.208	1.26 (0.72–2.21)
	T	25 (10.78%)	31 (13.25%)			

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