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GENÉTICA:

Molecular, humana e médica

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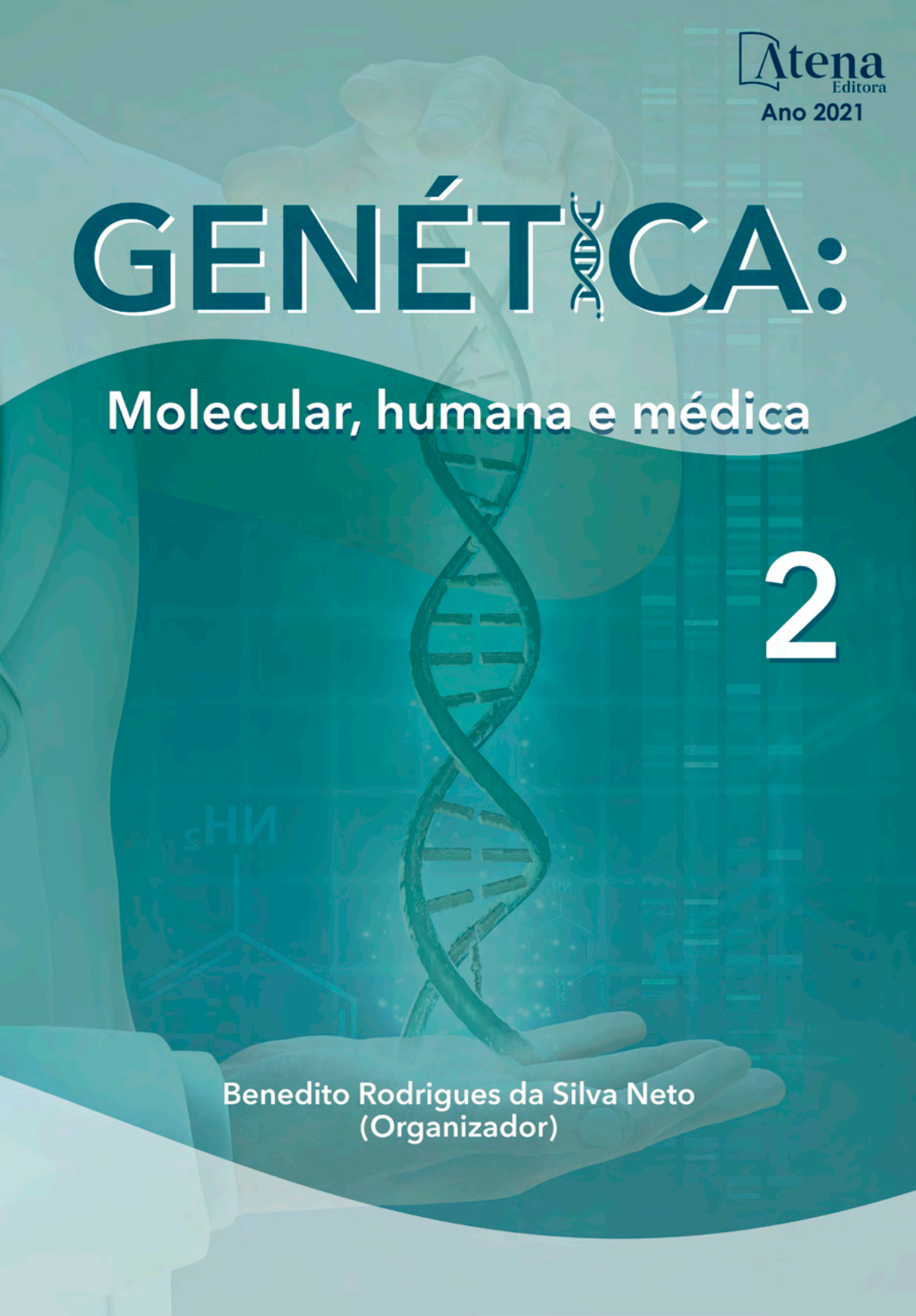

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(Organizador)

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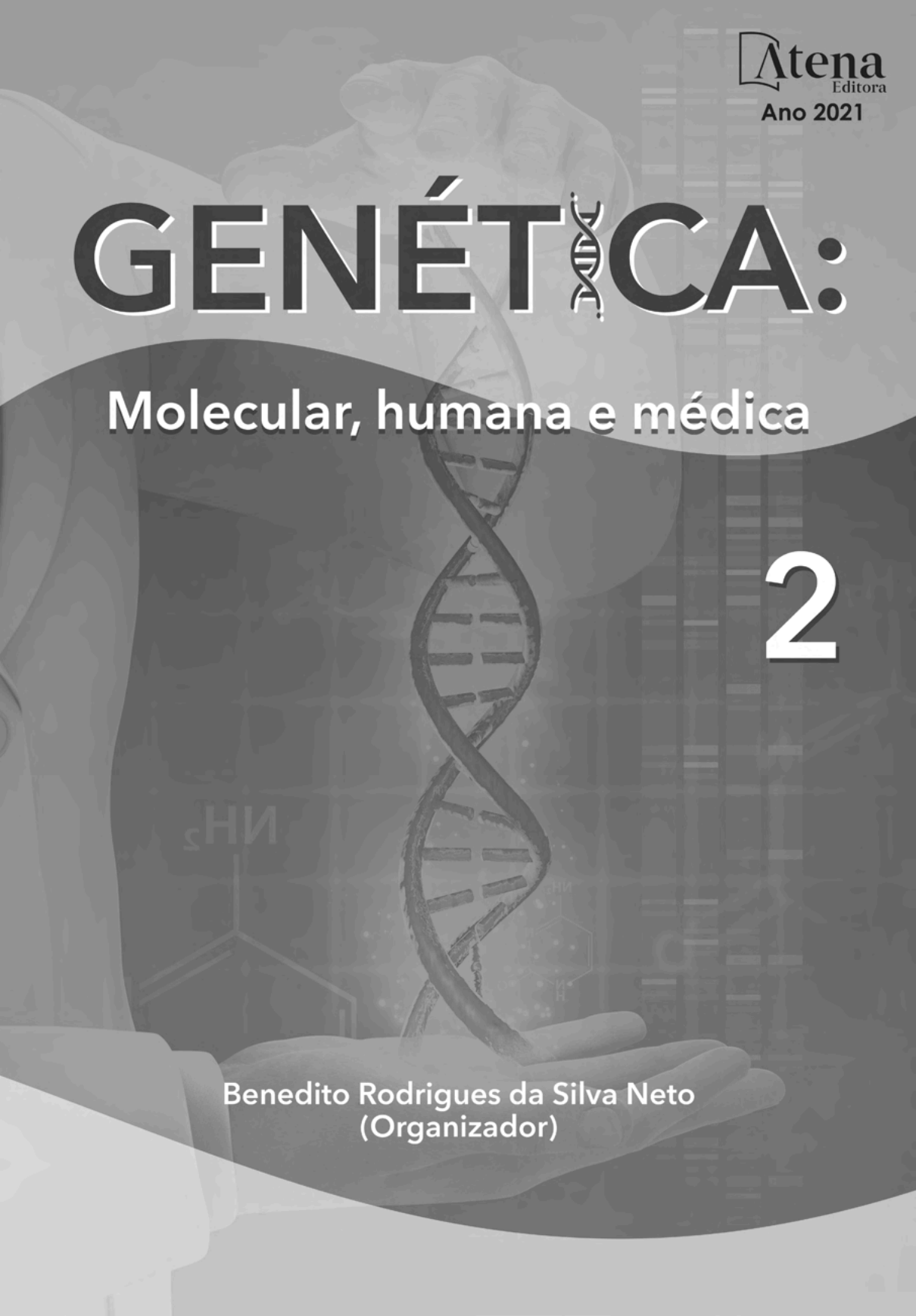

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APRESENTAÇÃO

Podemos definir a genética como a parte da ciência que estuda a hereditariedade, assim como a estrutura e função dos genes e a variação dos seres vivos. Através da genética podemos compreender os mecanismos e leis que regem a transmissão das características através das gerações. Essa genética clássica quando aprofundada revela outras subáreas, como a genética molecular que tem as suas fundações na genética clássica, mas dá um enfoque maior à estrutura e função dos genes ao nível molecular, abordando o DNA, genes e o genoma que controlam todos os processos vivos, nos ajudando na compreensão da biologia humana em saúde e doença.

Outra subárea de importância é a genética humana, que tem como estratégia descrever o estudo da transmissão genética em seres humanos, englobando a genética clássica propriamente dita, a citogenética, a bioquímica , genética populacional, genética do desenvolvimento etc. Por fim a genética médica ou genética clínica é a especialidade que lida com o diagnóstico, tratamento e controle dos distúrbios genéticos e hereditários. É uma área que enfoca não só o paciente, mas também toda a família, principalmente por meio do aconselhamento genético.

Além das três subáreas que destacamos acima a genética compreende um leque outras áreas específicas, no entanto ao mencionar a genética humana, molecular e médica estamos abrindo caminho para o segundo volume do livro publicado dentro do contexto dessas definições.

É muito nítido que nos últimos anos a genética tem influenciado diversas pesquisas promissoras em todo o mundo, contribuindo de forma significativa em diversas áreas e principalmente na saúde e aliada à revolução tecnológica essa tem contribuído muito com o avanço no campo da pesquisa.

Assim, esperamos que mais uma vez o conteúdo deste material possa somar de maneira significativa aos novos conceitos aplicados à genética, influenciando e estimulando cada vez mais a pesquisa nesta área em nosso país. Desejamos que seja mais um volume que anteceda inúmeros outros dentro desse contexto. E por fim parabenizamos cada autor pela teoria bem fundamentada aliada à resultados promissores, e principalmente à Atena Editora por permitir que o conhecimento seja difundido e disponibilizado para que as novas gerações se interessem cada vez mais pelo ensino e pesquisa em genética.

Desejo a todos uma excelente leitura!

Benedito Rodrigues da Silva Neto

SUMÁRIO

CAPÍTULO 5

DNA REPAIR GENES POLYMORPHISMS: INFLUENCE UPON SYSTEMIC LUPUS ERYTHEMATOSUS AND ITS CLINICAL MANIFESTATIONS

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ABSTRACT: DNA repair genes polymorphisms can contribute for increase damage in autoimmune diseases, considering that accumulated DNA damage promotes chronic inflammatory processes. Systemic Lupus Erythematosus (SLE) is an autoimmune disorder characterized by chronic inflammatory response and a wide spectrum of clinical manifestations. SLE patients display an inefficient DNA repair mechanism and some genes have been associated with this process. *LIG4* and *SKT17A* are genes involved in the main pathways to repairing DNA damage. Therefore, we assessed five Single Nucleotide Polymorphisms (SNPs) in the DNA repair *LIG4* and *STK17A* genes, and its possible association in SLE development and clinical manifestations. Genotyping was performed using fluorogenic probes Taqman® in 202 SLE patients and 190 healthy individuals from the Northeast Brazilian population. We observed a protective factor for *LIG4* SNP rs3093740 G/T genotype (OR = 0.32, p = 0.018) against nephrite development and for *STK17A* SNP rs2330875 in A (OR= 0.47, p = 0.007) allele and A/A genotype (OR = 0.15, p = 0.010) to malar rash development in SLE patients. Our results suggested that DNA repair genes *LIG4* and *STK17A* polymorphisms are associated with some clinical SLE features

highlighting the important role of DNA repair pathways upon disease's course.
KEYWORDS: DNA repair genes; *LIG4*; *STK17A*; Systemic Lupus Erythematosus; SNPs

1 | INTRODUCTION

DNA repair genes are known to be impaired in SLE individuals causing excessive DNA damage accumulation, which may increase clinical features in disease (Bassi et al., 2008; Choi et al., 2012; Jahantigh et al., 2015; Mireles-Canales et al., 2018). Double strand breaks (DSB) are the most critical damage to the cells and is a marker of environmental stress in which both strands of DNA are affected inducing loss of genetic material, mutagenesis, apoptosis and disease activity in lupus (Danoy et al, 2008; Rastogi et al., 2010; Namas et al., 2016). Systemic Lupus Erythematosus (SLE) is an autoimmune disorder presenting diverse clinical manifestations with involvement of several organ and systems. SLE is a disease characterized by deregulated inflammatory response, in which the immune system fails to distinguish self from non-self (Magalhães et al., 2003; Tsokos 2011).

Altered immune responses, including the loss of self-tolerance with subsequent deregulation of the immune system are the result of genetic, hormonal and environmental factors (Tsokos 2011; Liu and Lu 2020). Ultraviolet (UV) light exposure is an environmental factor that produces reactive oxygen species (ROS) that might induce DNA damage (Hanssen-Bauer et al., 2012). Accumulation of DNA damage leads to the production of autoreactive antibodies and immune complexes that accumulate in various tissues and organs increasing the damage and inflammation (Braunwald et al., 2011; Jahantigh et al., 2015). In this context, Tumurkhuu et al. (2020) observed that oxidative DNA damage accelerates skin inflammation in lupus-induced mice model.

Those cells with DNA damage can follow two major DNA repair pathways: homologous recombination (HR) and non-homologous end-joining (NHEJ) (Sonoda et al., 2006). DNA ligases protein family are involved in DNA-end-joining mechanisms in DSB repair. DNA *LIG4*, located on 13q33.34, encodes LIGIV protein, which forms complexes with XRCC4 protein acting directly in NHEJ pathway (Burma et al., 2006; Davies et al., 2012) being the most used DSB repair mechanism. NHEJ pathway promotes DNA DSB repair in cells deficient of HR, and there is evidence that it operates at all stages of the cell cycle (Yu et al., 2020).

The gene serine/threonine kinase 17a (*STK17A*), located on chromosome 7p13, encodes a nuclear protein autophosphorylated also known as DRAK1 (protein kinase related apoptosis inducing PAD1) (Ashurst et al., 2005). *STK17A* knockdown in human embryonic carcinoma results in decreased reactive oxygen species (ROS) associated with increased expression of antioxidant genes (Mao et al., 2011). *STK17A* regulates nuclear processes in response to DNA damage in the cascade of intracellular protein kinase (Sanjo et al., 1998) and its related with several cell death signaling pathways (Mao et al., 2011).

Therefore, oxidative stress performs a crucial role in SLE (Shah et al., 2014; Fujii et al., 2015) and *LIG4* and *SKT17A* are main genes involved in the DSB repair mechanisms into DNA (Bassi et al., 2008). Association studies between *LIG4* and *SKT17A* and DNA repair/damage are well established in some diseases such as cancer, however, only a few studies evaluated the association of these genes in autoimmune diseases (Da Silva Fonseca et al., 2013; De Azevêdo Silva et al., 2014; Wei and Liu 2020).

In this study, we assessed SNPs in *LIG4* and *SKT17A* in SLE patients and healthy controls in a Northeast Brazilian population in order to understand the relationship between development or clinical manifestations of SLE and DNA repair genes.

2 I MATERIAL AND METHODS

2.1 Patients and controls

We performed a case-control study enrolling 202 SLE patients (96.1% females and 3.9% males), mean age 34,05 years SD± 8.74 years, selected from Nephrology Division from the Clinical Hospital at Federal University of Pernambuco (UFPE) between August 2015 and July 2017. All were >18 years of age, unrelated, with the criteria of Systemic Lupus International Collaborating Clinics/American College of Rheumatology - Damage Index (SLICC/ACR). The following laboratorial and clinical data regarding the SLE patients were collected: hematological alterations (hemolytic anemia, leucopenia, lymphopenia, thrombocytopenia), immunological alterations (Anticardiolipin, Anti-Sm, Anti-RNP), presence of antinuclear antibodies (ANA), photosensitivity, serositis (pleuritis, pericarditis), arthritis, cutaneous manifestations (malar or discoid rashes), oral ulcers, neuropsychiatric disorder (seizures, headache, psychosis) and nephritic disorder. The diagnosis of the nephrite was histologically confirmed by renal biopsy.

The control group consisted of 190 healthy individuals (75.8% females and 24.2% males), mean age 32 years old (SD± 13 years old), from Metropolitan region of Recife, Pernambuco, Northeast of Brazil.

All individuals provided written informed consent and the local ethics committee (CAAE n° 24374913.0.0000.5208) approved this study.

Clinical manifestations regarding sex and age described in our SLE group are show in Table 1.

Demographic and clinical / laboratorial characteristics	SLE n=202
Sex	
Male	3.96%
Female	96.03%
ACR Characteristics	
Malar Rash	67.82%
Discoid Rash	33.66%
Photosensitivity	70.29%
Arthritis	60.39%
Oral Ulcerations	59.90%
Serositis	35.15%
Hematological alterations	23.76%
Nephritic disorder	45.05%
Neuropsychiatric disorder	38.12%
ANA+	49.50%
Immunological alterations	60.89%

Table 1. Clinical features from the SLE patients studied.

2.2 DNA/RNA Isolation and cDNA Synthesis

Genomic DNA was isolated from whole blood samples in both assessed groups using the Salting Out method (Sambrook and Russell, 2006). Total RNA was isolated using Trizol Reagent (Invitrogen, USA) according to manufacturer's instructions. RNA integrity was verified by 1.5% agarose gel electrophoresis and the RNA quantification/quality was verified by Nanodrop ND 1000 spectrophotometer (Nanodrop Technologies Inc, Delaware, USA). The cDNA synthesis was performed with 500 ng of RNA input from each sample and using GoScript™ Reverse Transcription System (Promega, USA) following the manufacturer's instructions.

2.3 Polymorphisms Analysis

SNPs were selected using SNPBrowser software (Applied Biosystems, Foster City, CA, USA) and National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov) according the following criteria: Minor Frequency Allele (MAF), TagSNPs and gene coverage. The SNPs rs10131, rs1805388, rs3093740 (*LIG4*) and rs7805969, rs2330875 (*STK17A*) were genotyped with Taqman SNP Genotyping Assay (Thermo Fisher Scientific, MA, USA) using the ABI 7500 Real-Time PCR System (Thermo Fisher Scientific, MA, USA).

The chi-square test ($\chi 2$) was used to assess the Hardy-Weinberg equilibrium in the studied population. The data analysis was performed by Fisher's exact test, along with SNPStats tool and the R version 3.0.2 program (http://cran.r-project.org/mirrors.html).

3 | RESULTS

A total of 392 subjects were genotyped, including 202 SLE patients (51.53%) and 190 healthy controls (48.47%). All frequencies assessed were in Hardy-Weinberg Equilibrium (HWE) in SLE patients and health control groups except for rs1805388 (*LIG4*) and rs2330875 (*STK17A*) in both groups ($p<0.05$).

The allele and genotypic frequencies for *LIG4* and *STK17A* SNPs were assessed and no significant association was observed for polymorphisms tested with SLE development (Table 2). When considering clinical features we identified two polymorphisms with protection for SLE patients (Table 3). For *LIG4* SNP rs3093740, we observed association between G/T genotype (OR = 0.32, CI = 0.10-0.89, p = 0.018) with lower susceptibility to nephrite development. *STK17A* SNP rs2330875 was associated with A allele (OR = 0.47, CI = 0.27-0.84, p = 0.007) and A/A genotype (OR = 0.15, CI = 0.02-0.78, p = 0.010) with lower susceptibility to malar rash. No association was observed for remaining clinical manifestations tested ($p>0.05$).

GENE	SNP		Controls		Patients		OR	CI (95%)	P
			N*	%	N*	%			
LIG4	rs1805388	G	289	84.5	331	87.56	1.00		
		A	53	15.49	47	12.43	0.77	0,49 – 1.21	0.238
		GG	119	69.6	142	75.1	1.00		
		AG	51	29.8	47	24.9	0.77	0.47 – 1.26	0.288
		AA	1	0.6	0	0	NA	NA – 32,96	0.458
			HWE *p*=0.083		HWE *p*=0.084				
	rs10131	C	236	84.53	231	85.55	1.00		
		T	43	15.46	39	14.44	0.93	0.56 – 1.52	0.811
		CC	101	72.7	98	72.6	1.00		
		CT	33	23.7	35	25.9	1.09	0.61 – 1.97	0.780
		TT	5	3.6	2	1.5	0.41	0.04 – 2.60	0.446
			HWE *p*=0.32		HWE *p*=0.74				
	rs3093740	T	331	85.3	359	92.52	1.00		
		G	25	7.02	29	7.47	1.07	0.59 – 1.94	0.888
		TT	155	87.1	167	86.1	1.00		
		GT	21	11.8	25	12.9	1.10	0.57 – 2.17	0.875
		GG	2	1.1	2	1	0.93	0.07 – 12.95	1.000
			HWE p=0.2		HWE p=0.28				
STK17A	rs7805969	G	138	39.65	142	37.36	1.00		
		A	210	60.34	238	62.63	1.11	0.81 – 1.51	0.542
		GG	68	39.1	74	39	1.00		
		AG	74	42.5	90	47.4	1.12	0.69 – 1.80	0.647
		AA	32	18.4	26	13.7	0.75	0.38 – 1.44	0.436
			HWE *p*=0.15		HWE *p*=1				
	rs2330875	T	90	27.77	76	22.7	1.00		
		A	234	72.22	258	77.24	1.30	0.90 – 1.89	0.151
		TT	89	54.9	100	59.9	1.00		
		AT	56	34.6	58	34.7	0.92	0.56 – 1.51	0.812
		AA	17	10.5	9	5.4	0.47	0.18 – 1.19	0.096
			HWE *p*=0.08		HWE *p*=0.83				

Table 2. Genotype and allele frequencies from LIG4 and STK17A in Systemic Lupus Erythematosus patients (SLE) and healthy controls (HC).

* Due to technical issues, some samples were not genotyped. OR - Odds Ratio; CI - Confidence Interval; P - p-value; HWE – Hardy-Weinberg Equilibrium; NA - Not Available.

GENE (SNP)	CLINICAL FEATURE (CL)		Patients without CL		Patients with CL		OR	CI (95%)	P
			N	%	N	%			
LIG4 (rs3093740)	Nephrite	T	187	90	172	96	1.00		
		G	21	10	8	4	0.41	0.15 – 1.01	0.051
		TT	84	81	83	92	1.00		
		GT	19	18	6	7	**0.32**	**0.10 – 0.89**	**0.018**
		GG	1	1	1	1	1.01	0.01 – 80.32	1
STK17A (rs2330875)	Malar Rash	T	66	67	192	81	1.00		
		A	32	33	44	19	**0.47**	**0.27 – 0.84**	**0.007**
		TT	23	47	77	65	1.00		
		AT	20	41	38	32	0.57	0.26 – 1.24	0.139
		AA	6	12	3	3	**0.15**	**0.02 – 0.78**	**0.010**

Table 3. Clinical features associated with SNPs from *LIG4* and *STK17A* in Systemic Lupus Erythematosus by Fisher's exact test.

* Due to technical issues, some samples were not genotyped; OR - Odds Ratio; CI - Confidence Interval; *P* - p-value.

4 | DISCUSSION

Genetic factors may confer a predisposition to development of SLE by the combined effect of polymorphisms in a large number of genes involved in various pathways, among these DNA repair genes pinpoint their importance in disease development (Bassi et al., 2008; Jahantigh et al., 2015; Mireles-Canales et al., 2018). In this study, we evaluated the possible association between *LIG4* and *STK17A* and SLE development and clinical features.

In this study we identified a G/T genotype association between *LIG4* SNP rs3093740 and nephrite in SLE patients indicating lower susceptibility to this clinical feature. The *LIG4* SNP rs3093740 is a TagSNP and is tagged by rs1805388, which in our study was not associated with the disease or its clinical characteristics. Polymorphisms in DSB repair genes could influence individually or in combination on the efficacy of DSB repair processes, or even act as a protective factor (Yin et al., 2012; Mumbrekar et al., 2016). Unresolved DSB lead to apoptosis with subsequent accumulation of immune complexes in tissue organs, including

kidneys, being a more important cause associated with worsening SLE (Tsokos 2011, Liu et al., 2013). When DNA repair mechanisms as HR are defective, alternative pathways as NHEJ are triggered (Yu et al., 2020). Our results suggest that SNPs in *LIG4*, involved directly in NHEJ repair, might influence clinical features development in SLE patients. Jahantigh et al. (2015) performed a genetic association study with DNA repair genes XRCC5, XRCC6 and XRCC7, also involved in NHEJ pathway, and observed that the genotypes with XRCC5 VNTR 0R allele (rs6147172) and XRCC7 6721G allele (rs7003908) could be risk factors for SLE susceptibility.

The A allele and A/A genotype of *STK17A* SNP rs2330875 were associated to lower susceptibility to malar rash in SLE patients. Agreeing to our results, another *STK17A* polymorphism (rs7805969) also was associated with lower susceptibility to cutaneous alterations in a Southeast Brazilian population, although a risk to SLE and others clinical features, as arthritis and immunological alterations were observed for authors (Da Silva Fonseca et al., 2013). UV light exposure is capable of producing DSB, leading to direct or subsequent DNA oxidative damage (Rastogi et al., 2010; Souliotis et al., 2019). STK17A regulates nuclear processes in response to DNA oxidative damage and is involved in apoptotic pathway, being activated in response to environmental factors, such as UV light exposition (Sanjo et al., 1998; Mao et al 2011). Oxidative stress performs a crucial role in SLE, being used as biomarker to the disease (Shah et al., 2014; Fujii 2015; Tumurkhuu et al., 2020). Individuals with SLE show increased cutaneous manifestations in response to DNA breaks, induced by immune response due to apoptotic bodies' deposition and subsequent immune complexes formation (Meas et al., 2017), justifying inflammation and rash after UV light skin exposition.

Although exposure to UV radiation has been shown as related to development of various clinical manifestations in SLE, in the present study in Northeast Brazilian population, the *LIG4* and *STK17A* were photoprotective factors to SLE clinical features. Northeast Brazilian population often had a higher UV-light exposure when compared to the other regions in Brazil, resulting in a higher melanin production. Melanin, in turn, acts as a natural protection from sunlight exposition (Bohm et al., 2005). In addition, smaller quantities of ROS induce less DSB formation and less recruitment of DNA repair proteins.

5 | CONCLUSIONS

We identified that polymorphisms within DNA repair genes might influence SLE susceptibility and its clinical features such as malar rash and nephrite highlighting the importance of studying another DNA repair genes polymorphisms and the potential role of DNA repair pathway impairment upon disease's course.

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