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Genetic Association and Differential RNA Expression of Histone (De)Acetylation-Related Genes in Pemphigus Foliaceus—A Possible Epigenetic Effect in the Autoimmune Response

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Abstract: Pemphigus foliaceus (PF) is an autoimmune skin blistering disease characterized by antidesmoglein-1 IgG production, with an endemic form (EPF) in Brazil. Genetic and epigenetic factors have been associated with EPF, but its etiology is still not fully understood. To evaluate the genetic association of histone (de)acetylation-related genes with EPF susceptibility, we evaluated 785 polymorphisms from 144 genes, for 227 EPF patients and 194 controls. Carriers of *HDAC4_rs4852054*A* were more susceptible (OR = 1.79, $p = 0.0038$), whereas those with *GSE1_rs13339618*A* (OR = 0.57, $p = 0.0011$) and homozygotes for *PHF21A_rs4756055*A* (OR = 0.39, $p = 0.0006$) were less susceptible to EPF. These variants were not associated with sporadic PF (SPF) in German samples of 75 SPF patients and 150 controls, possibly reflecting differences in SPF and EPF pathophysiology. We further evaluated the expression of histone (de)acetylation-related genes in CD4⁺ T lymphocytes, using RNAseq. In these cells, we found a higher expression of *KAT2B*, *PHF20*, and *ZEB2* and lower expression of *KAT14* and *JAD1* in patients with active EPF without treatment compared to controls from endemic

regions. The encoded proteins cause epigenetic modifications related to immune cell differentiation and cell death, possibly affecting the immune response in patients with PF.

Keywords: pemphigus foliaceus; *fogo selvagem*; genetic polymorphisms; RNA expression; post-translational histone modifications

1. Introduction

Pemphigus foliaceus (PF) is an autoimmune blistering skin disease endemic in Brazil, where it is also known as *fogo selvagem* (“wild fire”) [1]. PF pathophysiology is distinguished by IgG1 and IgG4 pathogenic autoantibodies produced mainly against desmoglein 1 (DSG1), a transmembrane cell adhesion protein found in keratinocyte cell junction (desmosomes) [1,2]. The skin blisters in PF are caused by keratinocyte separation, mostly in the epidermal granular layer, a process known as acantholysis [2]. Studies trying to unveil the breakdown of the immunological tolerance in PF etiology indicate associations with environmental, genetic, and epigenetic factors [3–5]. Continued exposure to mosquito bites is among the candidate environmental factors for EPF [3]. Haplotypes of major histocompatibility complex (MHC) class II genes stand out as one of the most important genetic components: *DR1_DQw1* and *DR4_DQw3* haplotypes have been associated with susceptibility to EPF, while *DR7_DQw2* and *DR3_DQw2* have been associated with resistance against EPF [6]. Hence, certain alleles of single nucleotide polymorphisms (SNPs) in immune system genes have been reported to alter PF susceptibility [4]. Long non-coding RNAs, several of which are involved in epigenetic regulation of gene expression, were also associated with PF susceptibility [7–9]. Furthermore, allelic variants of genes involved in epigenetic regulation, whose products are histone lysine demethylase and methyltransferases (*KDM4C*, *SETD7*, *MECOM*, and *PRDM16*), have been associated with PF susceptibility [5].

Epigenetic modifications can alter chromatin structure, triggering different patterns of gene expression. Chromatin comprises DNA and histone (H1, H2A, H2B, H3, H4, as well as histone variants) and nonhistone proteins. Covalent post-translational modifications (PTMs) on histone tails, such as (de)methylation, (de)acetylation, and (de)phosphorylation, are established and removed by chromatin-modifying enzymes that integrate multiunit complexes [10]. Among those enzymes, the activity of well-characterized histone acetyltransferases (HATs) and histone deacetylases (HDACs) is correlated with gene activation and repression, respectively [11].

Dynamic epigenetic modifications control immune cells’ development, activation, and differentiation, which affect the development of autoimmune diseases [12]. Abnormal histone acetylation (altered H3/H4 acetylation and/or HDAC expression patterns) has been implicated in autoimmune diseases affecting the skin, such as systemic lupus erythematosus [13,14], alopecia areata [15], and pemphigus vulgaris [16]. In this work, we investigated whether allelic variants of genes encoding HATs, HDACs, and members of complexes that interact with these enzymes influence PF susceptibility and whether these genes are differentially expressed in CD4⁺ T cells. Genetic association and differential RNA expression of histone (de)acetylation-related genes in EPF may indicate a possible epigenetic effect in its autoimmune response, especially related to immune cell differentiation and cell death.

2. Materials and Methods

2.1. Association Analysis Samples

Two samples were enrolled in this study—one of EPF and another of sporadic PF (SPF) (Figure 1). DNA from 227 EPF patients and 194 controls was extracted from peripheral blood mononuclear cells (PBMCs) by the phenol–chloroform–isoamyl alcohol method. They lived in Brazilian Midwest, Southeast, and South regions and were recruited in the Hospital

Adventista do Pênfigo (Campo Grande, Mato Grosso do Sul), Lar da Caridade—Hospital do Fogo Selvagem (Uberaba, Minas Gerais), Hospital das Clínicas—Universidade de São Paulo (Ribeirão Preto, São Paulo), Hospital de Clínicas—Universidade Federal do Paraná, Hospital de Dermatologia Sanitária São Roque, and Hospital Santa Casa de Misericórdia (Curitiba, Paraná). Patients and controls were unrelated, of predominantly European ancestry [17], and had a similar sex ratio and age distribution: in both groups, 52% were women and the mean age of patients was 40.9 (6–83) years and of controls, 44.8 (11–86) years. No patient had a history of other autoimmune diseases. None of the controls presented autoimmune diseases.

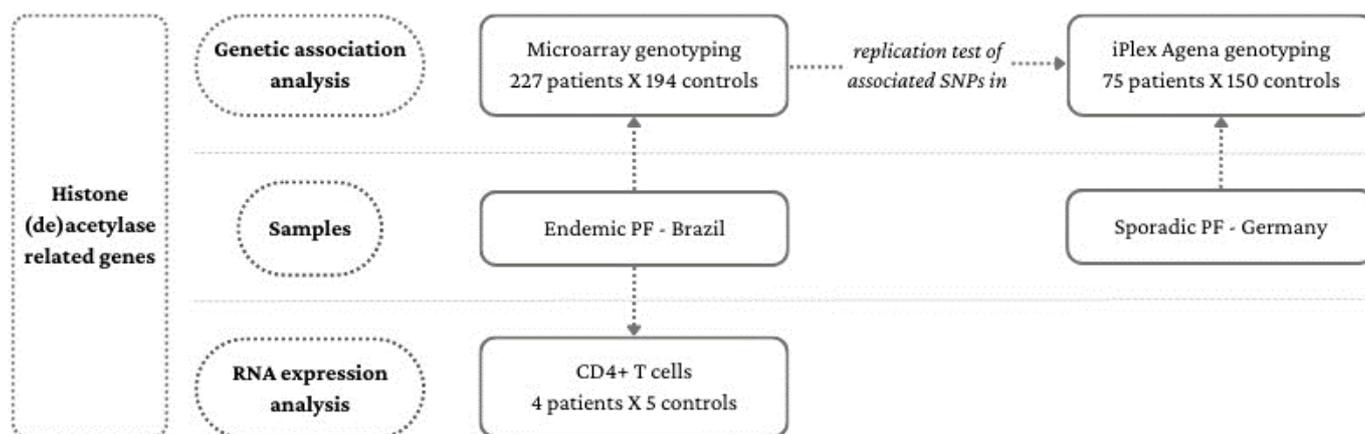


Figure 1. Flowchart of the study samples. The samples, composed of EPF and SPF patients from Brazil and Germany, respectively, and of controls were enrolled for experiments of genetic association with single nucleotide polymorphisms of (de)acetylation-related genes. EPF samples were also enrolled for RNA expression analyses of (de)acetylation-related genes.

DNA from 75 SPF patients and 150 controls was isolated from whole blood using the QIAamp DNA Maxi Blood Kit (Qiagen, Hilden, Germany). Patients and controls were all of European ancestry, predominantly of German origin, and recruited in German hospitals by the German Autoimmune Bullous Diseases Genetic Study Group. They had a similar sex ratio and age distribution: 46% of patients and 51% of controls were women and the mean age of patients was 60.1 (25–88) years, and of controls, 60.3 (21–77) years.

2.2. RNA Expression Analysis Samples

Total RNA was extracted from CD4⁺ T lymphocytes isolated from peripheral blood samples from four patients (three females and one male), before the start of oral corticosteroid treatment, who constantly presented new skin lesions and whose mean age was 36 (15–54) years, as well as from five controls (four females and one male) from EPF-endemic regions, whose mean age was 39.6 (22–58) years. The selection process of CD4⁺ T cells has been previously described by Bumiller-Bini Hoch et al. [18].

2.3. SNP Selection and Genotyping

Genotype data were available from a previous study using microarray hybridization (CoreExome-24, version 1.1, Illumina, San Diego, CA, USA) [19]. The genomic positions of 144 genes, encoding HATs (12) and HDACs (18) and members of histone acetylation (59) and deacetylation (55) complexes, were identified, considering 1000 base pairs downstream and upstream from the sequence for the longest transcript, according to the human genome version GRC37/hg19 (NCBI gene) [20] (Table S1). A total of 2486 SNPs located in these gene sequences were extracted from DNA microarray data of EPF samples.

SNPs associated with EPF were genotyped in the SPF samples using the iPLEX platform of the MassARRAY system (Agena Bioscience, San Diego, CA, USA). The primer sequences are available in Table S2. MassARRAY Typer software (v4.0) (Agena Bioscience,

San Diego, CA, USA) with standard settings was used to call the genotypes. The genotype distribution followed the Hardy–Weinberg equilibrium in patients, controls, and the set of participants (data not shown), except for rs13339618 ($p_{\text{controls}} = 0.049$; $p_{\text{all participants}} = 0.005$).

2.4. Association Analysis

Rare variants (minor allele frequency < 0.01) deviating from the Hardy–Weinberg equilibrium for controls ($p < 0.05$) or in high linkage disequilibrium (LD) with another SNP from the dataset ($r^2 \geq 0.80$) were excluded. After filtering, 785 SNPs remained for subsequent logistic regression association analysis with allele frequencies (additive model), frequencies of homozygotes for the minor allele (recessive model), and the sum of the frequencies of heterozygotes and homozygotes for the minor allele (dominant model) (PLINK version 1.1.9), correcting possible associations resulting from population stratification for two principal components of analysis and for sex. $p < 0.005$ was established as significant [21].

2.5. In Silico Analysis

Functional annotation available in reference public databases was used to explore the potential effects of the SNPs associated with PF. Gene and SNP annotations were performed with UCSC [22] and Ensembl [23] genome browsers. Gene expression was entrained with Protein Atlas [24], which, in addition to presenting its own database, also exhibits the Monaco dataset [25] and Schmiedel dataset [26]. Allelic variants' epigenetic annotations were entrained with the HaploReg v.4.1 database [27] and SNP Nexus tool [28], which filters many databases, including Roadmap and Encode [29,30]. LD between alleles was evaluated using LDLink [31], with European as a reference. The expression and splicing quantitative trait loci (eQTL and sQTL) effects were observed in Genehopper Qtlizer [32], which compiles information from several databases, such as Blood eQTL Browser [33], GRASP 2 Catalog [34], GTEx v8 [35], The Cardiogenics Project [36,37], and Zeller et al. [38]. Clinical significance was evaluated with ClinVar/NCBI [39].

2.6. RNAseq

Gene expression of CD4⁺ T lymphocytes was evaluated by RNA sequencing performed with the Illumina Hi-seq platform (San Diego, CA, USA) using a paired-end 150 bp protocol. The quality of RNAseq reads was investigated using FASTQC version 0.11.5. Reads were pseudoaligned to the human transcriptome (Ensembl version 93, GRCh38), using coding and non-coding genes. Expression was quantified using Salmon version 0.11.0 with 30 bootstrap cycles. Quantification files were imported to SLEUTH version 0.29.0 and pairwise comparisons between controls and EPF patients were performed. The Log2 fold change was obtained with the Wald test. All statistical analyses were performed using R version 3.4.4. $p < 0.005$ was established as significant [21].

3. Results

3.1. Genetic Association of Histone (De)Acetylation-Related Genes in EPF

Three intronic SNPs in different genes were associated with EPF. One of these genes encodes an HDAC (*HDAC4*) and the other two, HDAC complex members—*GSE1* (Gse1 coiled-coil protein) and *PHF21A* (PHD zinc-finger protein 21A). Carriers of the *HDAC4* rs4852054*A intronic allele (OR = 1.79 [95%CI = 1.21–2.67], $p = 0.004$) presented increased susceptibility to EPF. The *GSE1* rs13339618*A regulatory allele (OR = 0.57 [95%CI = 0.41–0.80], $p = 0.001$) and the *PHF21A* rs4756055 A/A intronic genotype (OR = 0.391 [95%CI = 0.228–0.672], $p = 0.0006$) were associated with decreased EPF susceptibility. These associations were not replicated in SPF samples, suggesting different etiologies for EPF and SPF forms (Table 1). This may indicate distinctions in the pathogenesis of EPF and SPF.

Table 1. Genetic association analysis with endemic and sporadic pemphigus foliaceus.

Gene	SNP	Endemic Pemphigus Foliaceus								Sporadic Pemphigus Foliaceus							
		MAF (%)		Model	Control	Patients	OR	95% CI	<i>p</i>	MAF (%)		Model	Control	Patients	OR	95% CI	<i>p</i>
		Controls	Patients							Controls	Patients						
HDAC4 2q37.3 intron 1	rs4852054 G > a	30.67	39.82	ADD	119/269	180/272	1.525	[1.14–2.05]	0.0051	18.71	23.03	ADD	52/226	35/117	1.299	[0.80–2.11]	0.2891
				REC	19/175	32/194	1.536	[0.84–2.81]	0.1647			REC	05/134	04/72	1.489	[0.39–5.72]	0.5621
				DOM	78/148	94/100	1.794	[1.21–2.67]	0.0038			DOM	47/92	31/45	1.348	[0.76–2.40]	0.3097
GSE1 16q24.1 regulatory region downstream	rs13339618 G > a	29.64	19.42	ADD	115/273	87/361	0.571	[0.41–0.80]	0.0011	19.06	23.65	ADD	53/225	35/133	1.257	[0.81–1.96]	0.3108
				REC	16/178	5/219	0.261	[0.09–0.73]	0.0102			REC	09/130	07/67	1.509	[0.54–4.23]	0.4339
				DOM	99/95	82/142	0.578	[0.39–0.86]	0.0064			DOM	44/95	28/46	1.314	[0.73–2.37]	0.3643
PHF21A 11p11.2 intron 1	rs4756055 g > A	38.05	42.82	ADD	186/198	172/280	0.671	[0.50–0.90]	0.0079	45.32	37.50	ADD	126/152	57/95	0.740	[0.50–1.10]	0.1322
				REC	50/142	26/200	0.391	[0.23–0.67]	0.0007			REC	31/108	12/64	0.653	[0.38–1.36]	0.2559
				DOM	136/56	146/80	0.792	[0.52–1.21]	0.2831			DOM	95/44	45/31	0.672	[0.38–1.20]	0.1801

In bold, significant associations ($p < 0.005$). The minor alleles in our sample are given in lowercase; they are the reference for the associations. Abbreviations: ADD, additive model; CI, confidence interval; DOM, dominant model; GSE1, Gse1 coiled-coil protein; HDAC4, histone deacetylase 4; MAF, minor allele frequency; OR, odds ratio; PHF21A, PHD finger protein 21A; REC, recessive model; SNP, single nucleotide polymorphism.

3.2. Predicted Consequences of SNPs in Histone (De)Acetylation-Related Genes Associated with EPF

Concerning functional annotation, *HDAC4_rs4852054*A* and *GSE1_rs13339618*A* present regulatory features, being located on a promoter flanking region and an enhancer, respectively [23].

HDAC4 presents two similar transcripts (differing by five codons), expressed at similar levels in most tissues. In the blood, *HDAC4* is mostly expressed in granulocytes (neutrophils—47.0 normalized transcript per million, nTPM, and basophils—32.0 nTPM on the HPA dataset, 26.0 nTPM in the Monaco dataset), and much less so in the myeloid and lymphocytic lineages (very low in HPA, between 5 and 12 nTPM in monocytes and 1 and 10 nTPM in different kinds of T cells of the Monaco dataset) [24,25]. Its expression in the skin is rather low, at 11.1 nTPM in 1734 suprabasal keratinocyte cells [24]. Even so, the region containing *HDAC4_rs4852054*A* is enriched for enhancer- (H3K4me1 and H3K27ac) and promoter-associated histone marks (H3K9ac) and/or open-chromatin (H3K36, DNase) in immune (common myeloid progenitor CD34⁺ cells, monocytes, and T cells) and skin cells (fibroblasts, normal human keratinocytes, and melanocyte primary cells) (Table S3, with data from Haploreg v.4.1, Roadmap and ENCODE [27,29,30]). The region with this allelic variant is occupied by the NFIC regulatory protein in the myeloid K562 cell lineage [30]. Furthermore, *HDAC4_rs4852054*A* is in high LD ($r^2 > 0.90$) with six other *HDAC4* polymorphisms [31]. An *HDAC4* haplotype (composed of six SNPs in almost absolute LD) is associated with higher *HDAC4-AS1* (*HDAC4* antisense RNA 1) gene expression in skin and/or blood cells [35] (Table 2).

Table 2. Alleles in high LD with *HDAC4*, *GSE1*, and *PHF21A* alleles associated with EPF and their eQTL effect in relevant tissues and cells for PF pathophysiology.

SNPs	r^2	eQTL	Tissues and Cells
<i>HDAC4_rs4852054*A</i> (Susceptibility)	-	<i>HDAC4-AS1</i>	Blood (ES = 0.15; $p = 1.5 \times 10^{-4}$)
			Skin not sun-exposed (ES = 0.17; $p = 3.4 \times 10^{-3}$)
<i>HDAC4_rs4852053*C</i>	1.0	<i>HDAC4-AS1</i>	Blood (ES = 0.17, $p = 4.7 \times 10^{-5}$)
			Skin sun-exposed (ES = 0.16; $p = 5.0 \times 10^{-3}$)
<i>HDAC4_rs55932933*T</i>	0.99	<i>HDAC4-AS1</i>	Blood (ES = 0.17; $p = 6.3 \times 10^{-5}$)
			Skin sun-exposed (ES = 0.16; $p = 5.0 \times 10^{-3}$)
<i>HDAC4_rs56064197*T</i>	0.99	<i>HDAC4-AS1</i>	Blood (ES = 0.17; $p = 5.8 \times 10^{-5}$)
			Skin sun-exposed (ES = 0.16; $p = 5.0 \times 10^{-3}$)
<i>HDCA4_rs1476321*T</i>	0.99	<i>HDAC4-AS1</i>	Blood (ES = 0.15; $p = 1.9 \times 10^{-4}$)
			Skin not sun-exposed (ES = 0.17; $p = 3.4 \times 10^{-3}$)
<i>HDCA4_rs10182344*A</i>	0.99	<i>HDAC4-AS1</i>	Blood (ES = 0.14; $p = 3.5 \times 10^{-4}$)
<i>HDCA4_rs58332998*A</i>	0.93	-	-
<i>GSE1_rs13339618*A</i> (Protection)		<i>GSE1</i>	Blood (ES = 5.37; $p = 7.9 \times 10^{-8}$)
<i>GSE1_rs13339626*A</i>	1.0	<i>GSE1</i>	Blood (ES = 5.37; $p = 7.9 \times 10^{-8}$)
<i>GSE1_rs13329722*C</i>	1.0	<i>GSE1</i>	Blood (ES = 5.40; $p = 6.9 \times 10^{-8}$)
		<i>TRIM35</i>	Monocytes (EF = -; $p = 9.2 \times 10^{-6}$)
<i>GSE1_rs7498141*A</i>	1.0	<i>GSE1</i>	Blood (EF = 5.40; $p = 6.9 \times 10^{-8}$)
		<i>TRIM35</i>	Monocytes (ES = -; $p = 9.0 \times 10^{-6}$)
<i>GSE1_rs4843505*G</i>	1.0	<i>GSE1</i>	Blood (ES = 5.40; $p = 6.9 \times 10^{-8}$)
<i>GSE1_rs13332576*A</i>	0.99	<i>GSE1</i>	Blood (ES = 5.31; $p = 1.1 \times 10^{-7}$)
<i>GSE1_rs8060638*A</i>	0.89	-	-

Table 2. Cont.

SNPs	r ²	eQTL	Tissues and Cells
<i>GSE1_rs28671512*T</i>	0.99	-	-
<i>PHF21A_rs4756055*A/A</i> (Protection)	-	<i>CRY2</i>	Blood (ES = 3.64; $p = 2.7 \times 10^{-4}$)
		<i>PEX16</i>	Blood (ES = -3.16; $p = 1.0 \times 10^{-3}$)
		<i>PHF21A</i>	Blood (ES = -; $p = 2.8 \times 10^{-4}$)
		<i>HNRNPH1</i>	Macrophages (ES = 0.08; $p = 5.8 \times 10^{-6}$)
<i>PHF21A_rs1976182*A</i>	0.98	<i>HNRNPH1</i>	Macrophages (ES = 0.08; $p = 5.4 \times 10^{-6}$)
<i>PHF21A_rs923530*T</i>	0.87	<i>CRY2</i>	Monocytes (ES = -0.04, $p = 3.8 \times 10^{-4}$)
		<i>HNRNPH1</i>	Macrophages (ES = 0.08, $p = 7.6 \times 10^{-6}$)
		<i>SLC37A1</i>	Macrophages (EF = -0.05, $p = 2.3 \times 10^{-6}$)
<i>PHF21A_rs11374563*T</i>	0.87	-	-
<i>PHF21A_rs7109480*T</i>	0.93	<i>CRY2</i>	Blood (ES = 3.46, $p = 5.4 \times 10^{-4}$)
		<i>HNRNPH1</i>	Macrophages (EF = 0.08; $p = 6.8 \times 10^{-6}$)
		<i>CRY2</i>	Monocytes (ES = -0.04, $p = 3.2 \times 10^{-4}$)
<i>PHF21A_rs7107550*C</i>	0.86	<i>HNRNPH1</i>	Macrophages (ES = 0.08, $p = 9.3 \times 10^{-6}$)
		<i>SLC37A1</i>	Macrophages (EF = -0.05, $p = 4.3 \times 10^{-6}$)
		<i>CRY2</i>	Blood (ES = 3.41; $p = 6.4 \times 10^{-4}$)
<i>PHF21A_rs950105*A</i>	1.0	<i>HNRNPH1</i>	Macrophages (EF = 0.08; $p = 9.1 \times 10^{-6}$)
		<i>CRY2</i>	Monocytes (ES = -0.04, $p = 5.8 \times 10^{-4}$)
<i>PHF21A_rs74366855*A</i>	0.87	<i>HNRNPH1</i>	Macrophages (ES = 0.08, $p = 8.0 \times 10^{-6}$)
		<i>SLC37A1</i>	Macrophages (EF = -0.05, $p = 5.7 \times 10^{-6}$)

High LD ($r^2 > 0.80$) between SNPs in the European population was evaluated with LDLink [31]. eQTL effect ($p \leq 5.0 \times 10^{-3}$) was observed in GeneHopper Qtlizer [32], which compiles information from Blood eQTL [33], GRASP 2 Catalog [34], GTEx v8 [35], The Cardiogenics Project [36,37], and Zeller et al. [38]. “-” indicates missing/unfound data. Abbreviations: CRY2, cryptochrome circadian regulator 2; ES, effect size; EPF, endemic pemphigus foliaceus; eQTL, expression quantitative trait loci; GSE1, Gse1 coiled-coil protein; HDAC4, histone deacetylase 4; HDAC4-AS1, HDAC4 antisense RNA 1; HNRNPH1, heterogeneous nuclear ribonucleoprotein H1; LD, linkage disequilibrium; PEX16, peroxisomal biogenesis factor 16; PE, pemphigus foliaceus; PHF21A, PHD finger protein 21A; SLC37A1, solute carrier family 37 member 1; SNP, single nucleotide polymorphism; TRIM35, tripartite motif containing 35.

GSE1 encodes five transcripts in the skin, whose expression is not significantly affected by sun exposure [35]. In the skin, *GSE1* is expressed in suprabasal keratinocytes (29.1 nTPM in 1734 cells), B cells (28.8 nTPM in 268 skin B cells), and macrophages (31.2 nTPM in 961 skin macrophages, 24.5 nTPM in 1776 Langerhans cells). In lymph nodes, its expression in two B cell populations doubles (50.7–53.6 nTPM, 2283–2025 B cells) [24]. The region containing *GSE1_rs13339618*A* is enriched with enhancer- (H3K4me1 and H3K27ac) and/or promoter-associated histone marks (H3K4m3) in skin cells (fibroblasts and melanocyte primary cells) (Table S3). It is also occupied by the ZBTB33 and REST regulatory proteins in the K562 myeloid cell lineage [30]. *GSE1_rs13339618*A* presents high LD with seven other *GSE1* alleles (Table 2) [31]. These alleles, except *GSE1_rs8060638*A* and *GSE1_rs28671512*T*, are associated with five times higher *GSE1* gene expression in blood cells [33]. *GSE1_rs13329722*C* and *GSE1_rs7498141*A* are also associated with *TRIM35* (tripartite motif containing 35) gene expression in monocytes [38] (Table 2).

PH21A presents a moderate expression of five transcript variants in the skin, regardless of sun exposure. Skin-resident Langerhans cells, T and B cells, as well as macrophages, all present similar expression of this gene (varying from 12.6 to 16.5 nTPM in Langerhans cells and T cells, respectively). Its expression is relatively higher in lymph node B cells (27.4–48.1 nTPM) and T cells (20.0–34.2 nTPM) [24]. The *PHF21A_rs4756055*A* re-

gion is enriched with enhancers (H3K4me1 and H3K27ac), promoters (H3K4me3 and H3K9ac), and/or open-chromatin (DNase) in immune (neutrophils, monocytes, and mononuclear, natural killer, T and B cells) and skin cells (fibroblasts, keratinocytes, and melanocytes) [27,29] (Table S3). This region is also occupied by myocyte enhancer factor 2B (MEF2B), paired box 8 (PAX8), and nuclear factor of activated T cells 3 (NFATC3) regulatory proteins in the GM12878 cell line [30]. *PHF21A_rs4756055*A* is in high LD with seven other *PHF21* alleles (Table 2) [31]. These SNPs, excepting *PHF21A_rs11374563*T*, are associated with slightly higher *HNRNPH1* (heterogeneous nuclear ribonucleoprotein H1) gene expression in macrophages [37]. Three SNPs in strong LD, including the one associated with lower susceptibility to EPF, are also associated with three times higher *CRY2* (cryptochrome circadian regulator 2) expression in blood cells [33]. Three other SNPs displaying a somewhat lower LD ($0.8 < r^2 < 0.9$) are associated with slightly lower *CRY2* expression in monocytes [36]. *PHF21A_rs923530*T*, *PHF21A_rs7107550*C*, and *PHF21A_rs74366855*A* are associated with lower *SLC37A1* (solute carrier family 37 member 1) gene expression in macrophages [37]. *PHF21A_rs4756055*A* is also associated with lower *PEX16* (peroxisomal biogenesis factor 16) gene expression [33] and altered *PHF21A* gene expression [34] in blood cells (Table 2).

To date, no clinical significance has been reported for these variants [39].

3.3. Differential RNA Expression of Histone (De)Acetylation-Related Genes in EPF

Of the 144 genes encoding HATs and HDACs, and members of histone (de)acetylation complexes, 139 were analyzed by RNAseq. Five genes were found to be differently expressed in CD4⁺ T cells from patients with EPF without oral corticoid treatment and presenting active disease, compared to controls from PF endemic regions: *ZEB2* (zinc finger E-box binding homeobox 2), *KAT2B* (lysine acetyltransferase 2B), and *PHF20* (PHD finger protein 20) were overexpressed in patients, while *KAT14* (lysine acetyltransferase 14) and *JADE1* (jade family PHD finger 1) were underexpressed (Table 3). Interestingly, *ZEB2* expression is elevated in T cells from bone marrow (229.6 nTPM), as well as from peripheral blood (248.6 nTPM). In turn, *KAT2B* is highly expressed in memory CD4⁺ T helper (Th) 1/Th17 cells, in contrast to *PHF20* (303.5 vs. 47 TPM, respectively, in the Schmiedel dataset [26]). Both may reach 80–100 nTPM in T cells of vascular tissue. *JADE1* also is highly expressed in memory CD4⁺ Th1/Th17 cells (100.2 nTPM in the Monaco dataset [25], although its expression in memory CD4⁺ T cells in the HPA dataset was lower—18.4 nTPM). *KAT14*, however, is less expressed in T cells (in these cells, its higher expression occurs in naïve CD4⁺ cells—37.3 nTPM) [24].

Table 3. (De)acetylation-related genes differently expressed in CD4⁺ T cells of endemic pemphigus foliaceus patients compared to controls.

Gene	Full Name	Fold Change	p-Value
<i>ZEB2</i>	zinc finger E-box binding homeobox 2	1.08	6.2×10^{-6}
<i>KAT2B</i>	lysine acetyltransferase 2B	0.55	2.8×10^{-5}
<i>PHF20</i>	PHD finger protein 20	0.41	8.6×10^{-5}
<i>KAT14</i>	lysine acetyltransferase 14	−0.59	2.0×10^{-4}
<i>JADE1</i>	jade family PHD finger 1	−0.31	2.6×10^{-3}

PF patients presented new skin lesions coming up constantly, before starting oral corticosteroid treatment. Controls were from endemic areas for PF.

None of them coincided with genes presenting EPF-associated variants. This is not surprising, since the associated polymorphisms do not have an eQTL effect in lymphocytes. However, HDAC4 and *KAT2B* are known to co-occur (may physically interact). Furthermore, HDAC4, *KAT2B*, and *ZEB2* are known to be coexpressed, as well as *HNRNPH1*, *PHF21A*, and *GSE1* (Figure 2).

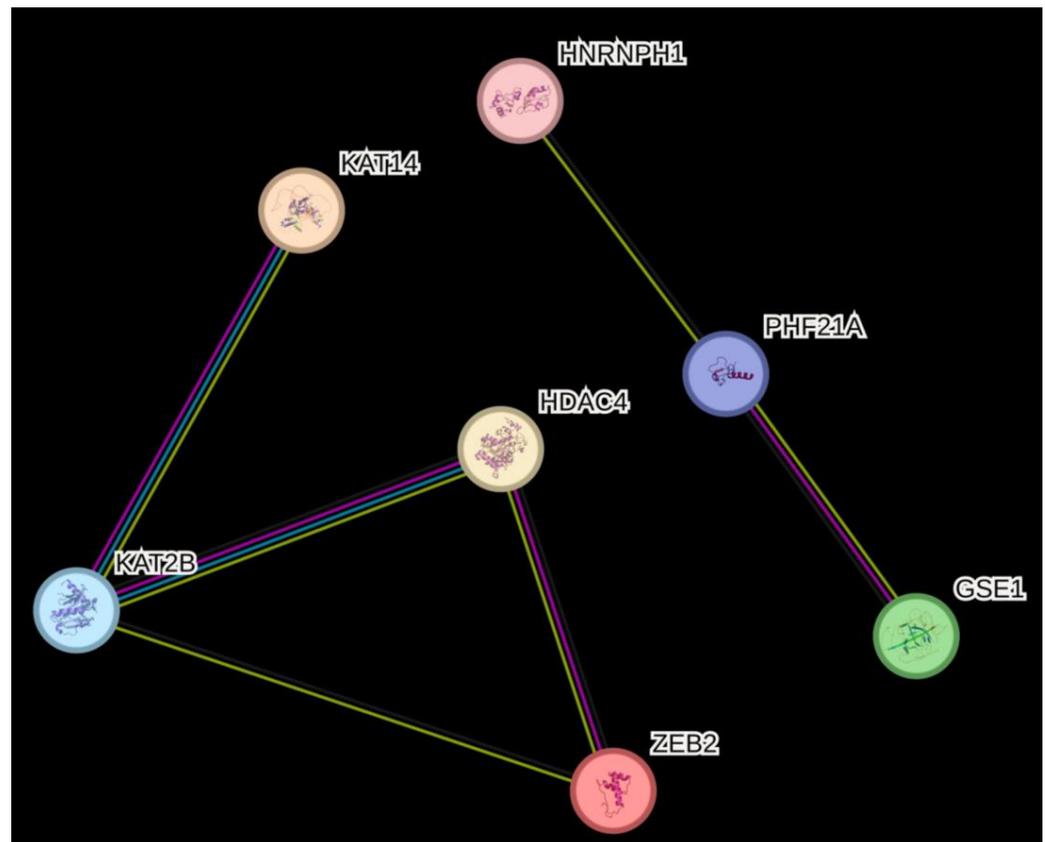


Figure 2. Interactions among proteins encoded by genes whose polymorphisms were associated with EPF susceptibility (*HDAC4*, *GSE1*, and *PHF21A*), have an eQTL effect (*HNRNPH1*), or which were differently expressed in EPF patients' CD4⁺ T cells (*KAT14*, *ZEB2*, *KAT2B*). The interactions map was drawn using STRING (stringdb.org; accessed on 28 November 2023). The edges present a protein–protein association. Blue and purple edges indicate interactions with known co-occurrence and experimental evidence, respectively. Black and yellow edges indicate co-expression and textmining evidence, respectively. All the 3D protein structures are known or predicted.

4. Discussion

Dysregulated homeostasis in autoimmune diseases is closely associated with epigenetic modifications [13]. Altered DNA methylation and histone PTMs are known to break immune tolerance [40], but their role is still poorly understood in PF. In this work, we identified HATs, HDACs, and interacting proteins either genetically associated with EPF or differentially expressed in CD4⁺ T cells (Figure 3). Three variants within three genes related to histone deacetylase were associated with altered EPF susceptibility. The lack of association in SPF may be related to different pathophysiological pathways (reviewed in [41]).

One of the herein associated genes encodes HDAC4, a member of the human class II histone deacetylases, known to silence the transcription of genes related to the immune response [42–44]. It represses myocyte enhancer factors 2 A (MEF2A), C (MEF2C), and D (MEF2D) [43–45]. Moreover, the caspase-cleaved amino-terminal fragment of HDAC4 (independently from the HDAC4 deacetylase domain) has been shown to repress MEF2C, triggering cell death [46]. It modulates thymocyte apoptosis and T and B cell differentiation and trafficking, by regulating the expression of the steroid receptor *Nur77* [45,47] and *KLF2* (Krüppel-like factor 2) [48,49]. These HDAC4 interactions indicate a possible role for cell death in EPF physiopathology, reinforced by our results and by others [50,51]. HDAC4 is also associated with B-cell lymphoma 6 (BCL6), a repressor protein essential for germinal center B cells and T follicular helper cells (Tfh), known to be increased in the blood of

bullous pemphigoid patients [52–54]. By the way, DNA binding sites for MEF2A and BCL6 were significantly enriched in systemic lupus erythematosus susceptibility loci [55]. HDAC4 is also associated with regulatory factor X-associated ankyrin-containing protein and class II MHC transactivator (CIITA) protein, and represses CIITA-mediated MHC class II gene expression [56]. Moreover, *CIITA_rs3087456*G* carriers present an increased susceptibility to EPF [57]. This variant is also an eQTL for lower CIITA expression in sun-exposed skin [35]. Finally, HDAC4 forms a complex with GATA binding protein 3 and yin-yang 1 protein and downregulates *IL5* (interleukin 5) expression [58], thus influencing Th2 cell differentiation and function. In the initial phase of the EPF immune response, Th1 and Th2 cytokines have been proposed to drive IgG1 and IgG4 anti-DSG1 production, while during the second phase, Th2 cytokines seem to drive IgG4 anti-DSG1 production [59,60].

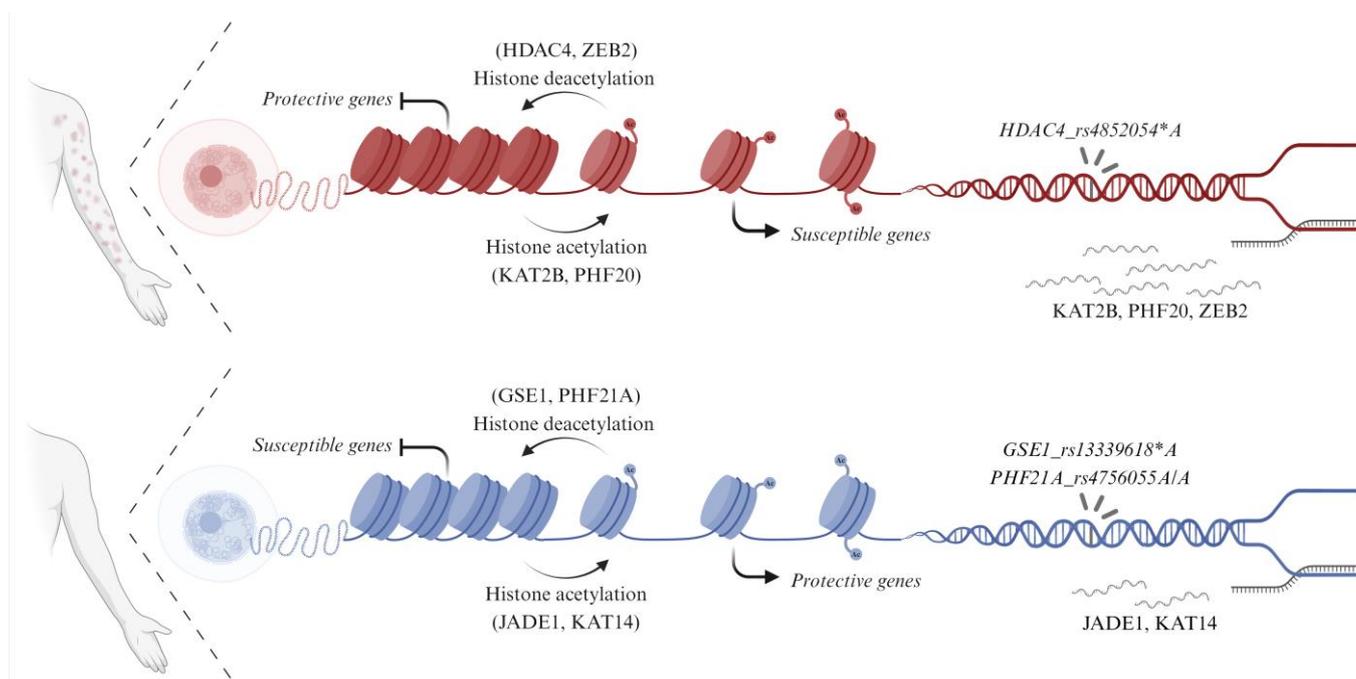


Figure 3. *HDAC4_rs4852054*A* was associated with increased EPF susceptibility, whereas *GSE1_rs13339618*A* and *PHF21A_rs4756055 A/A* were associated with decreased EPF susceptibility. In $CD4^+$ T cells from EPF patients, ZEB2, KAT2B, and PHF20 were overexpressed, and instead, KAT14 and JADE1 were underexpressed. By turning chromatin into a close state, deacetylation-related proteins whose polymorphisms were associated with increased EPF susceptibility (*HDAC4*) or which were overexpressed in patients' $CD4^+$ T cells (ZEB2) are thought to repress the expression of genes conferring protection to EPF in patients, whereas those associated with decreased EPF susceptibility (*GSE1* and *PHF21A*) are thought to repress the expression of genes conferring susceptibility to the disease in controls. Conversely, in turning chromatin into an open state, acetylation-related proteins encoded by genes overexpressed in patients' $CD4^+$ T cells (KAT2B and PHF20) are supposed to induce expression of genes conferring susceptibility to the disease in EPF patients, while those underexpressed (JADE1 and KAT14) are supposed to induce expression of genes conferring protection to EPF in controls.

*HDAC4_rs4852054*A* carriers were approximately 1.8 times more susceptible to EPF. This variant occurs within a five SNP haplotype consistently associated with higher expression of the *HDAC4-AS1* lncRNA in blood and skin cells [35]. On hypoxia, this antisense inhibits *HDAC4* expression in the human retinal pigment epithelial ARPE-19 cell line [61]. If this regulation also occurs in immune cells, higher *HDAC4-AS1* expression in these individuals may ultimately decrease *HDAC4* expression and activity, maintaining aberrant gene activation in the autoimmune response.

The other two polymorphisms associated with decreased EPF susceptibility are also associated with altered expression of histone deacetylase complex members, namely of two BRAF35-HDAC chromatin-remodeling complex components in blood: GSE1 and PHF21A [62,63]. *GSE1_rs13339618*A* is associated with greatly enhanced expression of *GSE1* in blood cells, probably of the myeloid lineage. This higher gene expression may increase the efficiency of acetyl group removal from histones in inflammatory genes, reducing the odds of autoimmunity. *GSE1_rs13339618*A* is also associated with altered *TRIM35* expression [38]. Interestingly, *TRIM35* negatively regulates type I interferon response by interacting with *IRF7*, promoting its ubiquitination and subsequent degradation [64]. Cells and pathways with a pathogenic role in autoimmunity can be activated by type I interferon [65].

PHF21A regulates IL-1-induced gene expression [66] and is a core protein of the CoREST complex [67], whose inhibition impairs the suppressive function of regulatory T (Treg) cells [68]. These findings support the notion that dysfunctional Treg cells and cytokine production contribute to EPF pathophysiology. Furthermore, *PHF21A_rs4756055*A* and seven SNPs at LD are also associated with higher expression of the circadian *CRY2* and *HNRNPH1* genes in blood cells and macrophages, respectively, and with lower expression of *PEX16* and *SLC37A1* genes in the same types of cells. Thus, this region has a regulatory influence on several genes in immune cells, which may also be implicated in EPF. *CRY2* expression is also reduced in celiac disease [69], and *Cry* double knockout mice have an overactivated B cell receptor signaling pathway, contributing to high serum IgG concentrations and antinuclear antibodies, with severe lung and kidney involvement [70]. Thus, higher *CRY2* expression in *PHF21A_rs4756055*A* carriers may improve resistance to autoimmunity. Moreover, *HNRNPH1* has been shown to reduce *IL8* expression [71]. Interestingly, higher levels of IL-8 were found in the serum and blister fluids of patients with pemphigus [72]. The possible involvement of the other genes remains elusive.

Five genes were differentially expressed in CD4⁺ T cells from patients with active EPF without oral corticoid treatment. Three of these were overexpressed in patients—*ZEB2*, *KAT2B*, and *PHF20*, while the other two were underexpressed—*KAT14* and *JADE1*.

ZEB2, also known as Smad-interacting protein 1, is a member of two-handed zinc finger/homeodomain transcription factors [73], which binds E box sequences and interacts with several co-repressors containing HDACs [74]. *ZEB2* is essential for normal hematopoietic stem cell and hematopoietic progenitor cell differentiation and mobilization [75]. It interacts with T-Box Transcription Factor 21 and represses *IL7R* and *IL2* expression, promoting terminal differentiation of lymphocytes, especially of CD8⁺ T cells [76,77]. It also regulates dendritic cell differentiation [78]. The consequences of its overexpression in CD4⁺ T cells from EPF patients warrant further investigation.

Consistent with our findings, the HDAC *KAT2B* gene is also upregulated in PBMCs from rheumatoid arthritis patients [79], and its overexpression increases histone H4 acetylation on the enhancer of MHC class I promoters [80]. It is nevertheless also important in Treg cell development [68,81,82]. *KAT2B* interacts with *KLF10* and induces *FOXP3* transcription [68]. Indeed, decreased levels of CD4⁺ *FOXP3*⁺ T cells occur in *Kat2b*-deficient mice [82,83]. Moreover, *KAT2B* acetylates the *IL2* promoter, protecting Treg cells from undergoing apoptosis upon T cell receptor stimulation [81]. It even acetylates *FOXP3* itself [81] and *DEK* protein [84]. When overexpressed, *KAT2B* acetylates *DEK*, reducing its affinity for DNA and impairing its transcription repression function [84]. Interestingly, anti-*DEK* autoantibodies have been identified in juvenile rheumatoid arthritis [85] and other inflammatory diseases [86]. Thus, *KAT2B* overexpression in T lymphocytes may maintain a deregulated immune response in EPF patients.

In contrast to *ZEB2* and *KAT2B*, which are related to histone deacetylation, *PHF20* is a component of the NSL (non-specific lethal) complex, which has HAT activity [87]. *Phf20* knockout impairs thymocyte differentiation and maturation in mice [88]. Moreover, the second Tudor domain and the PHD finger of *PHF20* recognize dimethylated lysines on p53, promoting nuclear factor kappa B (NF-κB) transcriptional activity [88–90], by

stabilizing p53 [91] and avoiding its acetylation by the NSL complex [90]. PHF20 further regulates autophagy genes [92]. Its higher expression possibly implicates this protein in EPF autoimmune activation.

Among the two genes with lower expression in CD4⁺ T lymphocytes of patients, KAT14 is a subunit of the ADA2A-containing acetyltransferase complex, essential for mammalian development, exerting a role in cell cycle progression and apoptosis [93]. Its impact on EPF autoimmune activation should be further investigated.

Jade family PHD finger 1 (JADE1, also known as PHF17) belongs to a subfamily of PHD zinc finger proteins, which contain two PHD zinc finger domains. JADE1 is subjected to post-transcriptional regulation and polyadenylation, resulting in multiple transcripts and two protein isoforms: the major isoform JADE1L and the truncated isoform JADE1S [94]. JADE1 is a transcriptional co-activator associated with HAT activity specific for histone H4 [95]. It interacts with lysine acetyltransferase 5 and 7 (KAT5 and KAT7, known as TIP60 and HBO1, respectively), which are close homologs, but is only able to induce transcription with KAT7 [95,96]. Essential roles of JADE1 in cell cycle regulation [97], and also as a consequence on apoptosis [98], have been described.

5. Conclusions

This is the first study suggesting that disruption of histone (and other proteins) (de)acetylation is involved in EPF pathophysiology, indicating a possible epigenetic effect in the autoimmune response.

We suggest that by turning chromatin into a close state, deacetylation-related proteins associated with increased EPF susceptibility (HDAC4) or overexpressed in patients' CD4⁺ T cells (ZEB2) repress the expression of protective genes. Conversely, those associated with decreased EPF susceptibility (GSE1 and PHF21A) may repress the expression of genes conferring susceptibility to the disease. In the opposite direction, by turning chromatin into an open state, acetylation-related proteins overexpressed in patients' CD4⁺ T cells (KAT2B and PHF20) may induce the expression of genes conferring susceptibility to the disease. Furthermore, those underexpressed (JADE1 and KAT14) induce the expression of protective genes. Some of these genes, whose expression is supposedly regulated by histone (de)acetylase-related proteins, seem to be essential genes in immune cell differentiation and cell death processes (Figure 3).

In conclusion, our findings highlight the importance of histone (de)acetylation dynamic processes, and its crosstalk with other histone PTMs, such as (de)methylation, in the autoimmune pathophysiology of EPF. Experiments evaluating the chromatin state may increase our understanding of epigenetic alterations in PF.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/life14010060/s1>, Table S1: Genomic position of HATs, HDACs and histone (de)acetylation complexes members; Table S2: Primer sequences used for investigating genetic association in sporadic pemphigus foliaceus samples; Table S3: Epigenomic annotation of allelic variants associated with PF in immune and skin cells.

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Informed Consent Statement: Written informed consent has been obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions.

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