



Predicted high-affinity binding of *Porphyromonas gingivalis* peptides to 334 human leukocyte antigen (HLA) Class I and Class II molecules

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Abstract

Aim: To determine predicted binding affinities of peptides from *Porphyromonas gingivalis* (*P. gingivalis*) proteins and identify those binding with high-affinity to human leukocyte antigen (HLA) molecules.

Methods: We evaluated in silico binding affinities of all possible linear 9-mer and 15-mer peptides of 13 *P. gingivalis* proteins with 334 HLA alleles; strong predicted binding affinity ($IC_{50} < 50$ nM) was considered a “hit”.

Results: Predicted binding affinity of HLA molecules and *P. gingivalis* proteins varied substantially. We identified 798 unique 15-mer peptides that were predicted to bind strongly to Class II HLA molecules and did not overlap with any 15-mers of 83,607 human proteins and, thus, may be suitable candidates for *P. gingivalis* vaccine development.

Conclusions: Individual differences in HLA shape the adaptive immune system response to *P. gingivalis* and other antigens via variability in binding affinity, a crucial first step in mounting immune system responses aimed at neutralization or elimination of non-self antigens, assuming host immunocompetency otherwise. Various preventive and therapeutic strategies aimed at reducing the burden of *P. gingivalis* are under investigation; the current findings document specific HLA-peptide combinations that may be a useful starting point for ongoing efforts toward *P. gingivalis* vaccine development.

Keywords

Porphyromonas gingivalis, human leukocyte antigen (HLA), autoimmunity, binding affinity, predicted binding affinity



Introduction

Porphyromonas gingivalis (*P. gingivalis*)

P. gingivalis is a gram-negative bacterium that is widely implicated in the oral disease periodontitis [1]; however, the influence of *P. gingivalis* and its virulence factors extends well beyond damage to oral tissue [2]. *P. gingivalis* has been designated a keystone pathogen due to its ability to impair innate host immune defenses and reshape normal symbiotic microbiota into a dysbiotic state that contributes to a sustained inflammatory response in the absence of bacterial clearance [3, 4]. Various translocation mechanisms including degradation of the epithelial barrier, invasion of epithelial and endothelial cells, and dissemination via the blood permit systemic circulation of *P. gingivalis* periodontal pathogens and virulence factors with corresponding systemic implications [5–7]. To that end, mounting evidence suggests that *P. gingivalis* is a strong risk factor for Alzheimer's dementia and other conditions, including cardiovascular disease, rheumatoid arthritis, and various neurodegenerative disorders [6–14].

P. gingivalis produces several virulence factors, including gingipains and fimbriae, proteins that are involved in adhesion, tissue degradation, and disruption of immune system responses [15, 16]. Gingipains, the primary *P. gingivalis* virulence factors, are cysteine proteases that are essential for *P. gingivalis* survival and pathogenicity, playing critical roles in host colonization, inactivation of host defenses, iron and nutrient acquisition, and tissue destruction [17]. They comprise arginine gingipain-A (RgpA) and -B (RgpB) and lysine-specific gingipain (Kgp). Fimbriae are hair-like appendages that promote bacterial motility, adhesion, and invasion [16, 18]. They comprise several types of major (or long) fimbriae (FimA) and minor (or short) fimbriae (Mfa). These and other virulence factors (e.g., glycolipid lipopolysaccharide) subvert innate immune system responses aimed at elimination of *P. gingivalis* [19, 20], rendering *P. gingivalis* mostly resistant to the innate immune system responses targeting them and prompting activation of adaptive immune system responses as a secondary line of defense [17].

Adaptive immunity

The adaptive immune system utilizes lymphocytes (T and B cells) to attack specific pathogens and establish immunological memory to hasten immune response in the event of future exposure to that pathogen. Human leukocyte antigens (HLAs) are key to adaptive immunity. HLAs are cell-surface glycoproteins that play a critical role in presentation of peptides from bacterial proteins and other foreign antigens to T cells to promote their elimination. HLA-I (encoded by HLA-A, -B, -C genes) are expressed in all nucleated cells and bind short peptides (mostly 9-mer) of endogenous proteins for presentation to cytotoxic CD8⁺ T cells to signal destruction of infected cells. HLA-II (encoded by the HLA-DPB1, DQB1 and DRB1 genes) is expressed in professional antigen-presenting cells (APCs; e.g., macrophages, dendritic cells) and binds longer peptides (mostly 15-mer) of exogenous proteins for presentation to CD4⁺ helper T cells to stimulate B cell-mediated antibody production and enhance the activation of CD8⁺ T cells. Unlike the non-specific innate immune system responses, HLA-mediated adaptive immunity is highly specific to each foreign antigen encountered and rests on high-affinity binding of HLA molecules with foreign antigen peptides. HLA is extremely polymorphic [21] and most of the variability is localized in the binding groove [22–24], the region that binds peptides for transport to the cell surface for T cell presentation. Consequently, HLA molecules differ with regard to the repertoire of antigens that are suitable for high-affinity binding; that is, an interaction between a given HLA molecule and a given antigen peptide determines the adaptive immune system response such that strong, high-affinity HLA-peptide binding enhances immune responses targeting their elimination relative to the weak, low-affinity HLA-peptide binding, which is ineffective. The mechanisms of HLA-mediated antigen presentation to T lymphocytes are discussed in detail elsewhere [25, 26].

The strongly bound peptide-HLA (pHLA) complex moves to the surface and engages CD8⁺ (pHLA-I complex) and CD4⁺ (pHLA-II complex) T cells by attaching to their $\alpha\beta$ T-cell receptor (TCR) [27–30]. Remarkably, a single pHLA-I complex is sufficient to activate a single CD8⁺ T-cell [31] with a bond lasting ~1 min [31, 32], leading to serial engagement of ~200 TCRs [33]. The pHLA-I/TCR occupancy correlates well with the release of interferon (IFN)- γ by the activated T cell [33], documenting the dependence of the

latter on the former. The number of pHLA-I complexes on the cell surface can vary from a few to a few thousand, depending on the cell and the peptides involved [34]. Given that (a) a single pHLA-I complex can successfully engage ~200 TCRs, and that (b) these engagements are functionally active, it follows that the overall T-cell activation initiated by a single APC can be very high and successful in eliminating infected cells by various killing mechanisms [35].

With respect to CD4+ T cell engagement, high-affinity-bound pHLA-II complexes traffic to the APC plasma membrane where they remain very stable. Such pHLA-II complexes can last very long (half-life of $t_{1/2} > 150$ h) [36]. Importantly, this pHLA-II half-life determines the in vivo immunogenicity of the bound epitope [36]. In summary, the degree of binding affinity of a peptide to an HLA-II molecule ultimately determines the magnitude of the biological effect of this pHLA-II complex, most probably due to the long time that an antigen is presented for CD4+ T cell engagement. pHLA-II complexes activate CD4+ T cells by binding to their TCR. This effect is extremely sensitive, since a single pHLA-II complex is sufficient to activate a CD4+ T cell [37]. This high sensitivity of CD4+ engagement and the associated long life of pHLA-II presentation [36] result in very strong and long-acting CD4+ T-cell activation. Although a unique role of the HLA-II system is to initiate, by the activation of CD4+ T cells, the production of antibodies by B cells against foreign antigens [38–40], an additional important role of CD4+ T cells is to augment the function of CD8+ T cells, with respect to both their cytotoxic action and the establishment of memory T-cells [41]. Finally, in addition to the binding of pHLA complex, successful activation and clonal expansion of CD8+ and CD4+ T cells in the presence of a pathogen requires the presence on APC surface of co-stimulatory signals B7.1 and B7.2, interfacing the combined action of innate and adaptive immune systems in pathogen elimination [42–47].

In summary, high-affinity pHLA binding is a necessary but not sufficient condition for a successful adaptive immunity, for which immunocompetency and well-functioning native immunity mechanisms are assumed. Conditions of immunosuppression (e.g., by the administration of immunosuppressant drugs, HIV infection, etc.) would compromise the mounting of an effective adaptive immunity. This is also true for *P. gingivalis*, which has been shown to suppress adaptive immunity for immunoevasion [48].

HLA and periodontitis

Both HLA Class I and Class II have been implicated in periodontitis [49–54]. Although several bacteria are associated with periodontitis, *P. gingivalis* is well-established as a major, primary contributor [15, 55, 56]. Compared to the wealth of literature evaluating HLA variation with regard to periodontal disease, relatively few studies have evaluated HLA with respect to *P. gingivalis* specifically. One recent study identified higher titres of anti-*P. gingivalis* antibodies related to specific HLA-DRB1 alleles in patients with rheumatoid arthritis [57]. *P. gingivalis* has adopted several immune evasion strategies [58, 59], including suppression of adaptive immunity [48]. Notwithstanding potential adaptive immune evasion, strong HLA-peptide binding of *P. gingivalis* proteins would be expected to induce an immune response aimed at pathogen elimination and reduce the development of periodontitis and systemic disease sequelae. Here we evaluated in silico the predicted binding affinity of 334 HLA alleles with proteins involved in *P. gingivalis* and identified specific epitopes characterized by high-affinity binding.

Materials and methods

P. gingivalis proteins

Thirteen proteins of *P. gingivalis* involved in its pathogenicity and structure were tested and are shown in Table 1. Their amino acid (AA) sequences were retrieved from the UniProt database (<https://www.uniprot.org/>) on December 25, 2025, and are given in Table S1.

HLA alleles

We investigated a total of 334 HLA common alleles [60], including 142 HLA-I alleles (Table S2; $N = 41, 72, 29$ of genes A, B, C, respectively) and 192 HLA-II alleles (Table S3; $N = 41, 35, 116$ of genes DPB1, DQB1, DRB1, respectively). Allele population frequencies are from [60].

Table 1. The 13 *P. gingivalis* proteins tested with 142 human leukocyte antigen (HLA)-I alleles and 192 HLA-II alleles.

Number	Protein	UniProt ID	Amino acid (AA)	HLA-I		HLA-II	
				<i>N</i> (9-mer)	<i>N</i> tested (142 HLA-I alleles)	<i>N</i> (15-mer)	<i>N</i> tested (192 HLA-II alleles)
1	Minor fimbrium subunit Mfa1	B2RHG1	563	555	78,810	549	105,408
2	Minor fimbrium anchoring subunit Mfa2	B2RHG2	324	316	44,872	310	59,520
3	Minor fimbrium tip subunit Mfa3	B2RHG3	446	438	62,196	432	82,944
4	Minor fimbrium tip subunit Mfa4	B2RHG4	333	325	46,150	319	61,248
5	Minor fimbrium subunit Mfa5	B2RHG5	1,228	1,220	173,240	1,214	233,088
6	Gingipain R2 (RgpA)	B2RKU0	736	728	103,376	722	138,624
7	Lys-gingipain (Kgp)	B2RLK2	1,723	1,715	243,530	1,709	328,128
8	Gingipain R1 (RgpB)	B2RM93	1,703	1,695	240,690	1,689	324,288
9	Major fimbrium subunit FimA	B2RH54	383	375	53,250	369	70,848
10	Major fimbrium subunit FimB	A0PA81	303	295	41,890	289	55,488
11	Major fimbrium subunit FimC	B2RH57	453	445	63,190	439	84,288
12	Major fimbrium subunit FimD	B2RH58	670	662	94,004	656	125,952
13	Major fimbrium subunit FimE	B2RH59	550	542	76,964	536	102,912
Total	-	-	-	9,311	1,322,162	9,233	1,772,736

In silico determination of predicted binding affinities

Predicted binding affinities were obtained for antigen peptides using the Immune Epitope Database (IEDB) NetMHCpan (ver. 4.1 BA) tool [61, 62]; accessed on January 7, 2026. More specifically, we used the sliding window approach [63–65] to test all possible linear 9-mer and 15-mer peptides for HLA-I and HLA-II predictions, respectively; the method is illustrated in Figure 1 for 9-mer and 15-mer peptides of the Gingipain R1 protein. Peptides of 9- and 15-mer length were tested because these are the dominant peptide lengths for binding to HLA-I [66, 67] and HLA-II molecules [67–69], respectively. DPB1 and DQB1 alleles were paired with highly frequent alpha chains, namely DPA*01:03 and DQA*01:01, respectively. For each pair of pHLA molecules tested, this tool gave, as an output, the IC₅₀ of the predicted binding affinity; the smaller the IC₅₀, the stronger the binding affinity. An IC₅₀ value of < 50 nM was regarded as strong [70–73] and was called a “hit”. Given a protein of *N* AA length and a peptide length of *k* AA, there are *N* - *k* + 1 binding affinity predictions returned by the prediction tool. The numbers of 9-mer (HLA-I) and 15-mer (HLA-II) peptides tested for each protein are given in Table 1.

Statistical analyses

Standard statistical methods (e.g., Pearson and Spearman correlations) were used to analyze the data using the IBM-SPSS statistical package (version 31). All *P*-values reported are 2-sided, and statistical significance was set at *P* < 0.05.

Results

The number of hits per HLA and protein is shown in Table 2. It can be seen that 249 of the 334 alleles tested (74.6%) showed at least one hit, whereas the remaining 85/334 (25.4%) alleles (Table 3) showed no hit for any protein. Figure 2 shows the normalized (Z-score) variation of hits across proteins and alleles.

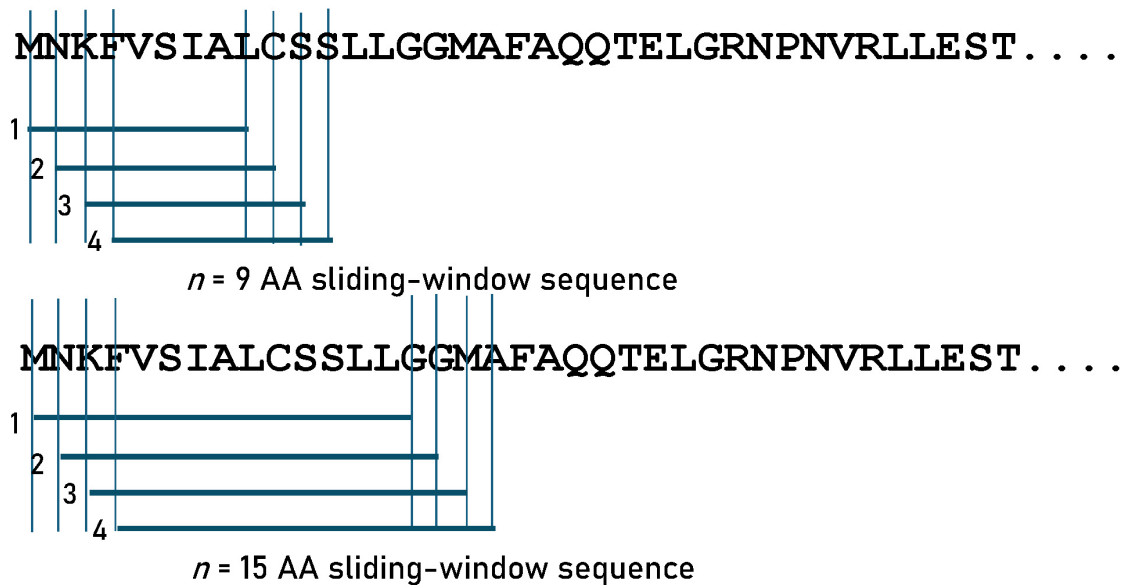


Figure 1. Schematic diagram illustrating the 9- and 15-mer sliding window approach for testing all linear 9- and 15-mer peptides of the Gingipain R1 (RgpB) protein of *P. gingivalis* exhaustively. The full amino acid (AA) sequence of this protein is given in [Table S1](#). The same approach was used for all 13 *P. gingivalis* proteins ([Table 1](#)).

Table 2. Number of hits (cases with predicted $IC_{50} < 50$ nM) per human leukocyte antigen (HLA) allele and *P. gingivalis* protein.

Number	Allele	FimB	Mfa2	Mfa4	FimA	Mfa1	FimC	Mfa3	RgpA	FimE	FimD	RgpB	Mfa5	Kgp	Hits
1	A*01:01	1	1	0	1	0	0	1	0	2	1	2	0	1	10
2	A*02:01	5	2	4	2	4	5	1	5	8	5	14	8	20	83
3	A*02:02	7	4	5	6	5	9	7	9	15	7	21	18	23	136
4	A*02:05	3	1	5	4	4	7	5	9	9	6	18	7	18	96
5	A*02:06	5	3	4	6	4	7	5	9	13	7	23	11	26	123
6	A*02:17	0	0	2	0	1	1	0	0	2	0	0	0	0	6
7	A*02:30	5	2	4	2	4	5	1	5	8	5	14	8	20	83
8	A*02:35	4	3	3	2	3	4	1	4	7	3	10	6	17	67
9	A*02:63	7	4	5	6	5	9	7	9	15	7	21	18	23	136
10	A*02:77	5	2	4	2	4	5	1	5	8	5	14	8	20	83
11	A*03:01	0	2	1	2	1	1	0	2	0	2	3	2	5	21
12	A*03:02	0	2	2	2	2	2	0	2	0	1	4	4	5	26
13	A*03:81	0	2	1	2	1	1	0	2	0	2	3	2	5	21
14	A*11:01	0	2	4	3	3	2	4	3	4	7	7	8	10	57
15	A*11:02	0	2	4	3	3	2	4	3	4	7	7	8	10	57
16	A*23:01	1	0	2	2	2	0	3	1	0	3	2	3	6	25
17	A*24:02	1	0	2	2	1	0	4	0	0	2	2	3	6	23
18	A*24:03	4	3	3	3	4	1	6	4	4	5	8	9	13	67
19	A*25:01	0	0	0	0	0	0	0	1	0	0	1	0	0	2
20	A*26:01	1	0	0	0	0	0	1	1	0	2	2	1	1	9
21	A*26:08	1	0	0	0	0	0	0	1	0	0	1	1	1	5
22	A*26:12	1	0	0	0	0	0	0	1	0	2	1	2	0	7
23	A*29:01	2	0	1	2	2	1	2	5	4	7	12	3	12	53
24	A*29:02	2	0	1	2	2	1	2	5	4	7	12	3	12	53
25	A*30:01	0	2	3	6	8	9	1	1	4	8	5	8	12	67
26	A*30:02	0	1	2	3	0	2	2	0	1	3	4	3	9	30

Table 2. Number of hits (cases with predicted IC₅₀ < 50 nM) per human leukocyte antigen (HLA) allele and *P. gingivalis* protein. (continued)

Number	Allele	FimB	Mfa2	Mfa4	FimA	Mfa1	FimC	Mfa3	RgpA	FimE	FimD	RgpB	Mfa5	Kgp	Hits
27	A*31:01	1	0	5	1	2	3	2	6	2	3	7	5	9	46
28	A*32:01	2	2	1	1	1	3	0	2	3	2	2	2	3	24
29	A*33:01	0	1	0	0	0	0	5	4	0	2	3	0	3	18
30	A*33:03	1	1	1	1	2	1	4	6	1	3	5	2	5	33
31	A*34:01	1	0	0	0	0	0	0	0	0	1	1	1	0	4
32	A*34:02	0	1	1	1	1	1	2	2	1	5	2	2	2	21
33	A*36:01	0	0	0	0	0	0	0	0	0	0	1	0	0	1
34	A*68:01	4	4	3	3	7	4	5	8	5	10	10	13	13	89
35	A*68:02	3	4	3	5	8	6	4	10	5	8	15	11	15	97
36	A*68:37	4	4	3	3	7	4	5	8	5	10	10	13	13	89
37	A*74:01	0	0	0	0	0	0	0	0	0	0	1	0	1	2
38	A*74:03	0	0	0	0	0	0	0	0	0	0	1	0	1	2
39	A*80:01	0	0	1	0	0	1	0	1	1	1	2	1	2	10
40	B*07:02	2	0	3	0	0	1	0	3	1	2	4	5	5	26
41	B*07:04	1	0	0	0	0	1	0	0	1	1	0	1	2	7
42	B*07:05	2	0	3	1	1	2	0	5	2	2	10	8	11	47
43	B*08:01	0	1	0	1	0	0	1	0	0	0	0	3	2	8
44	B*14:01	0	0	0	0	0	0	0	0	0	0	0	0	1	1
45	B*14:02	0	0	0	0	0	0	0	0	0	0	0	0	1	1
46	B*15:01	2	1	1	1	2	3	2	4	1	2	5	6	11	41
47	B*15:03	6	6	6	9	7	11	8	18	10	15	31	26	45	198
48	B*15:07	0	0	0	0	1	1	0	1	0	0	1	0	2	6
49	B*15:16	0	0	0	0	1	1	0	0	0	0	0	0	0	2
50	B*15:17	2	6	8	9	6	9	9	13	6	14	27	14	30	153
51	B*15:35	0	0	0	0	0	1	0	0	0	0	0	2	2	5
52	B*18:01	0	0	0	0	0	1	0	0	1	1	4	1	6	14
53	B*27:05	0	2	0	1	0	1	1	1	1	0	1	2	0	10
54	B*27:07	2	1	2	1	1	2	3	3	2	3	4	4	4	32
55	B*27:08	0	0	0	0	0	1	0	0	0	0	0	0	0	1
56	B*35:01	3	1	4	3	3	3	5	7	5	5	13	8	13	73
57	B*35:02	2	0	1	1	1	1	0	1	1	0	5	4	5	22
58	B*35:03	1	0	0	0	1	0	0	0	1	0	1	3	1	8
59	B*35:08	1	0	0	0	1	0	2	1	2	0	5	4	5	21
60	B*35:17	2	0	1	0	1	0	1	2	2	2	8	4	7	30
61	B*37:01	0	0	0	0	0	0	1	0	0	0	0	0	0	1
62	B*39:01	1	0	1	0	1	2	0	0	1	0	0	2	0	8
63	B*39:02	0	2	0	0	2	1	1	1	2	2	1	3	1	16
64	B*39:05	0	0	0	0	0	0	0	0	1	0	0	0	0	1
65	B*39:06	0	0	0	1	0	1	0	0	0	1	1	1	0	5
66	B*39:24	0	0	1	0	1	2	0	0	1	0	0	1	1	7
67	B*40:01	1	2	0	1	4	2	1	1	4	3	2	1	1	23
68	B*40:02	0	3	1	1	2	2	0	3	3	4	1	2	1	23
69	B*41:01	1	2	2	3	1	2	1	3	2	2	6	1	4	30
70	B*41:02	0	3	1	1	2	2	2	4	4	3	1	2	1	26
71	B*42:02	1	0	0	0	0	0	0	0	1	1	1	0	1	5
72	B*44:02	0	1	1	0	0	0	1	0	2	0	1	2	1	9
73	B*44:03	0	1	1	0	0	0	1	1	2	0	1	2	1	10
74	B*44:04	0	0	0	0	0	0	0	0	0	0	0	1	0	1
75	B*44:07	0	1	1	0	0	0	1	1	2	0	1	2	1	10

Table 2. Number of hits (cases with predicted IC₅₀ < 50 nM) per human leukocyte antigen (HLA) allele and *P. gingivalis* protein. (continued)

Number	Allele	FimB	Mfa2	Mfa4	FimA	Mfa1	FimC	Mfa3	RgpA	FimE	FimD	RgpB	Mfa5	Kgp	Hits
76	B*44:27	0	1	1	0	0	0	1	0	2	0	1	2	1	9
77	B*45:01	0	0	0	2	1	0	0	1	2	0	2	1	2	11
78	B*47:01	0	0	0	0	0	0	0	0	0	0	0	0	1	1
79	B*48:01	0	0	0	0	0	0	0	0	0	0	0	1	0	1
80	B*49:01	0	0	0	0	0	1	0	0	0	0	0	0	0	1
81	B*50:01	0	0	1	0	1	0	0	2	1	1	1	0	1	8
82	B*50:02	0	0	0	1	0	0	0	1	0	0	1	0	1	4
83	B*53:01	0	0	0	0	0	0	0	1	2	0	4	4	2	13
84	B*54:01	1	0	1	1	0	2	3	4	0	0	6	4	9	31
85	B*55:01	0	0	0	0	0	0	1	1	0	0	1	0	1	4
86	B*56:01	0	0	0	0	0	0	1	1	0	0	3	1	5	11
87	B*57:01	0	0	0	1	1	0	0	1	3	0	2	3	0	11
88	B*57:02	0	0	0	1	0	2	0	1	1	0	1	1	0	7
89	B*57:03	0	0	0	2	1	2	0	3	2	0	5	1	1	17
90	B*58:01	1	0	1	2	4	3	0	2	3	2	7	3	8	36
91	B*81:01	1	0	0	0	0	0	0	0	0	0	0	1	1	3
92	C*01:02	0	0	0	2	0	0	1	3	0	0	5	1	1	13
93	C*02:02	1	1	1	1	0	0	0	0	0	0	1	1	1	7
94	C*02:10	1	1	1	1	0	0	0	0	0	0	1	1	1	7
95	C*03:02	1	7	3	7	7	8	4	7	3	7	16	12	20	102
96	C*03:03	2	4	3	4	4	4	2	6	2	6	18	11	16	82
97	C*03:04	2	4	3	4	4	4	2	6	2	6	18	11	16	82
98	C*05:01	1	1	1	0	0	0	1	1	1	0	3	2	4	15
99	C*06:02	0	0	0	0	0	0	0	1	0	1	1	2	0	5
100	C*07:01	0	0	0	0	0	0	0	0	0	0	1	0	0	1
101	C*07:02	0	0	0	0	1	0	0	0	0	1	0	0	1	3
102	C*08:01	0	1	1	0	0	0	0	1	0	0	0	1	0	4
103	C*08:02	0	1	1	0	0	0	1	1	1	0	0	1	0	6
104	C*08:03	0	1	1	0	0	0	0	1	0	0	0	1	0	4
105	C*12:02	1	2	2	2	1	1	1	1	0	1	5	4	6	27
106	C*12:03	1	6	3	4	4	6	2	5	2	6	13	9	17	78
107	C*14:02	2	4	3	5	7	6	8	4	7	6	13	13	24	102
108	C*15:02	1	2	1	0	1	0	1	0	1	3	4	4	4	22
109	C*15:04	1	3	1	1	2	2	2	1	1	2	5	4	6	31
110	C*15:05	0	0	0	0	0	0	0	0	0	0	0	1	0	1
111	C*15:06	0	4	1	0	1	0	0	0	0	1	3	4	4	18
112	C*15:09	1	3	1	1	2	2	2	1	1	2	5	4	6	31
113	C*16:01	2	9	4	9	4	7	4	10	3	9	21	11	25	118
114	C*16:02	0	4	1	2	1	2	0	1	1	1	5	6	8	32
115	C*16:04	1	7	1	3	2	2	1	4	1	4	7	8	10	51
116	C*17:01	0	2	1	1	0	1	0	1	0	1	3	1	3	14
117	DPB1*01:01	0	0	6	0	0	0	0	0	0	0	6	0	6	18
118	DPB1*02:01	0	1	16	1	0	0	0	6	9	3	18	6	25	85
119	DPB1*02:02	0	1	18	1	1	0	0	6	9	6	19	6	26	93
120	DPB1*03:01	0	5	5	2	4	0	6	3	0	1	1	0	0	27
121	DPB1*04:01	0	0	16	0	0	0	0	6	5	2	14	6	18	67
122	DPB1*06:01	0	0	0	0	0	0	3	0	0	0	0	0	0	3
123	DPB1*104:01	0	5	5	2	4	0	6	3	0	1	1	0	0	27
124	DPB1*124:01	0	5	5	2	4	0	6	3	0	1	1	0	0	27

Table 2. Number of hits (cases with predicted IC₅₀ < 50 nM) per human leukocyte antigen (HLA) allele and *P. gingivalis* protein. (continued)

Number	Allele	FimB	Mfa2	Mfa4	FimA	Mfa1	FimC	Mfa3	RgpA	FimE	FimD	RgpB	Mfa5	Kgp	Hits
125	DPB1*126:01	0	0	16	0	0	0	0	6	5	2	14	6	18	67
126	DPB1*14:01	0	4	1	0	3	0	5	0	0	0	0	0	0	13
127	DPB1*15:01	0	0	10	0	0	0	0	0	5	1	6	0	11	33
128	DPB1*16:01	0	0	3	0	0	0	0	0	4	0	1	0	1	9
129	DPB1*20:01	0	5	2	0	0	0	4	0	0	0	0	0	0	11
130	DPB1*23:01	0	0	16	0	0	0	0	6	5	2	14	6	18	67
131	DPB1*33:01	2	8	36	6	8	5	8	28	28	22	42	18	66	277
132	DPB1*34:01	0	0	3	0	0	0	0	0	2	0	6	1	11	23
133	DPB1*35:01	0	2	0	0	0	0	0	0	0	0	0	0	0	2
134	DPB1*39:01	0	0	16	0	0	0	0	6	5	2	14	6	18	67
135	DPB1*40:01	0	0	1	0	0	0	0	0	0	0	6	0	10	17
136	DPB1*41:01	0	0	1	0	0	0	0	0	6	0	1	3	1	12
137	DPB1*46:01	0	1	16	1	0	0	0	6	9	3	18	6	25	85
138	DPB1*47:01	0	1	18	1	1	0	0	6	9	6	19	6	26	93
139	DPB1*71:01	2	8	36	6	8	5	8	28	28	22	42	18	66	277
140	DPB1*72:01	0	0	16	0	0	0	1	8	6	7	19	6	24	87
141	DPB1*81:01	0	1	16	1	0	0	0	6	9	3	18	6	25	85
142	DPB1*91:01	0	5	2	0	0	0	4	0	0	0	0	0	0	11
143	DRB1*01:01	46	33	26	56	62	67	45	71	80	66	150	124	205	1,031
144	DRB1*01:02	7	11	0	12	3	14	10	33	4	19	19	32	48	212
145	DRB1*01:03	1	4	0	4	0	0	0	0	0	0	0	0	3	12
146	DRB1*01:11	21	11	6	16	9	26	14	27	14	23	24	39	79	309
147	DRB1*01:18	48	36	32	67	75	81	54	96	96	86	162	141	214	1,188
148	DRB1*01:20	39	28	20	65	64	60	51	83	73	66	105	113	137	904
149	DRB1*01:24	24	13	9	19	14	29	20	33	15	28	39	51	97	391
150	DRB1*01:29	24	14	8	22	21	34	21	40	25	27	53	62	110	461
151	DRB1*03:01	13	0	0	0	0	9	2	16	5	9	24	10	22	110
152	DRB1*03:04	13	0	0	0	0	9	2	16	5	9	24	10	22	110
153	DRB1*03:05	2	1	0	0	0	0	0	0	1	0	0	0	0	4
154	DRB1*03:11	17	6	9	2	7	36	11	24	11	22	31	28	27	231
155	DRB1*03:13	13	0	0	0	0	9	2	16	5	9	24	10	22	110
156	DRB1*03:15	5	0	0	0	1	0	0	8	4	8	11	8	14	59
157	DRB1*04:01	7	6	16	15	7	11	17	3	28	8	8	17	17	160
158	DRB1*04:02	0	2	0	4	0	0	0	0	0	0	0	5	0	11
159	DRB1*04:03	0	0	0	0	0	0	0	0	0	0	0	2	0	2
160	DRB1*04:04	1	13	8	14	11	13	20	10	12	7	13	28	20	170
161	DRB1*04:05	3	4	1	3	6	6	19	6	17	2	13	6	19	105
162	DRB1*04:06	0	0	0	0	0	0	0	0	0	0	0	2	0	2
163	DRB1*04:07	0	0	0	0	0	0	1	0	4	0	0	0	0	5
164	DRB1*04:08	4	8	13	14	9	6	16	3	18	8	6	19	16	140
165	DRB1*04:10	1	8	2	1	0	4	13	1	0	0	5	8	3	46
166	DRB1*04:44	0	8	4	4	0	0	7	1	0	2	1	9	2	38
167	DRB1*04:53	0	3	0	0	0	0	0	0	0	0	0	4	0	7
168	DRB1*04:56	0	7	4	4	0	0	9	0	0	0	1	14	2	41
169	DRB1*04:72	2	0	5	0	0	9	14	0	16	3	4	12	8	73
170	DRB1*07:01	24	10	8	6	27	29	8	27	34	16	36	48	70	343
171	DRB1*08:01	6	0	0	0	0	0	7	0	0	0	0	0	0	13
172	DRB1*08:02	0	3	0	2	0	0	4	0	1	0	0	4	2	16
173	DRB1*08:03	0	3	0	0	0	0	3	0	0	0	0	0	0	6

Table 2. Number of hits (cases with predicted IC₅₀ < 50 nM) per human leukocyte antigen (HLA) allele and *P. gingivalis* protein. (continued)

Number	Allele	FimB	Mfa2	Mfa4	FimA	Mfa1	FimC	Mfa3	RgpA	FimE	FimD	RgpB	Mfa5	Kgp	Hits
174	DRB1*08:04	0	6	2	9	5	7	11	8	11	22	4	20	8	113
175	DRB1*08:24	0	1	0	2	0	0	3	0	4	6	8	3	5	32
176	DRB1*08:30	0	4	0	0	0	0	3	0	0	2	0	2	4	15
177	DRB1*08:36	0	3	0	0	0	0	3	0	0	0	0	0	0	6
178	DRB1*09:01	11	9	2	2	12	15	10	17	18	5	26	21	49	197
179	DRB1*09:02	0	0	0	0	0	0	0	0	1	0	0	4	2	7
180	DRB1*10:01	25	21	25	45	44	37	40	48	50	60	85	84	152	716
181	DRB1*11:01	7	7	0	12	13	0	23	6	15	12	21	33	29	178
182	DRB1*11:02	0	5	5	20	18	35	17	13	26	37	8	24	15	223
183	DRB1*11:03	1	3	0	15	15	26	20	14	29	34	15	33	15	220
184	DRB1*11:04	10	8	8	18	12	24	23	15	27	37	28	49	20	279
185	DRB1*11:06	0	3	0	3	0	0	0	0	0	3	0	1	0	10
186	DRB1*11:07	0	0	0	0	0	0	0	2	0	0	4	6	5	17
187	DRB1*11:08	3	4	3	4	8	2	18	2	14	13	8	17	11	107
188	DRB1*11:10	7	7	0	12	13	0	23	6	15	12	21	33	29	178
189	DRB1*11:11	0	0	0	4	4	0	5	1	6	7	5	7	6	45
190	DRB1*11:12	7	7	0	12	13	0	23	6	15	12	21	33	29	178
191	DRB1*11:13	5	6	16	21	12	34	16	21	26	36	15	29	20	257
192	DRB1*11:14	4	6	16	22	25	25	29	23	26	49	34	45	39	343
193	DRB1*11:19	0	4	0	0	0	0	4	1	0	0	0	2	4	15
194	DRB1*11:27	0	0	0	0	0	0	1	0	2	6	4	1	2	16
195	DRB1*11:28	7	7	0	12	13	0	23	6	15	12	21	33	29	178
196	DRB1*11:29	7	7	0	12	13	0	23	6	15	12	21	33	29	178
197	DRB1*11:37	0	0	0	3	0	0	5	0	6	6	11	11	9	51
198	DRB1*11:42	11	9	18	31	21	48	34	29	36	54	42	57	43	433
199	DRB1*11:46	10	8	8	18	12	24	23	15	27	37	28	49	20	279
200	DRB1*11:49	7	7	0	12	13	0	23	6	15	12	21	33	29	178
201	DRB1*11:54	0	0	0	0	0	0	0	0	0	1	0	0	0	1
202	DRB1*11:58	10	8	8	18	12	24	23	15	27	37	28	49	20	279
203	DRB1*11:62	7	7	0	12	13	0	23	6	15	12	21	33	29	178
204	DRB1*11:65	0	5	5	20	18	35	17	13	26	37	8	24	15	223
205	DRB1*11:74	7	7	0	12	13	0	23	6	15	12	21	33	29	178
206	DRB1*11:84	1	3	0	4	5	0	4	2	8	12	2	5	0	46
207	DRB1*12:01	0	5	3	2	0	3	0	0	0	0	0	0	4	17
208	DRB1*12:02	0	4	4	2	6	3	0	3	3	0	2	0	3	30
209	DRB1*12:03	0	5	6	8	6	11	0	11	4	2	9	0	20	82
210	DRB1*12:16	0	5	0	0	5	1	2	3	5	7	0	0	6	34
211	DRB1*13:01	0	5	5	20	18	35	17	13	26	37	8	24	15	223
212	DRB1*13:02	4	6	16	22	25	25	29	23	26	49	34	45	39	343
213	DRB1*13:03	2	0	0	0	0	0	3	0	0	0	0	0	0	5
214	DRB1*13:05	7	7	0	12	13	0	23	6	15	12	21	33	29	178
215	DRB1*13:07	0	0	0	3	0	0	5	0	6	6	11	11	9	51
216	DRB1*13:11	10	8	8	18	12	24	23	15	27	37	28	49	20	279
217	DRB1*13:12	2	0	0	0	0	0	2	0	0	0	0	0	0	4
218	DRB1*13:14	7	7	0	12	13	0	23	6	15	12	21	33	29	178
219	DRB1*13:21	6	6	0	3	14	3	17	10	15	12	28	18	22	154
220	DRB1*13:23	4	6	16	22	25	25	29	23	26	49	34	45	39	343
221	DRB1*13:26	0	0	0	0	0	0	0	0	2	4	0	0	0	6
222	DRB1*13:33	0	0	0	0	0	0	4	0	0	0	0	0	0	4

Table 2. Number of hits (cases with predicted IC₅₀ < 50 nM) per human leukocyte antigen (HLA) allele and *P. gingivalis* protein. (continued)

Number	Allele	FimB	Mfa2	Mfa4	FimA	Mfa1	FimC	Mfa3	RgpA	FimE	FimD	RgpB	Mfa5	Kgp	Hits
223	DRB1*13:50	7	7	0	12	13	0	23	6	15	12	21	33	29	178
224	DRB1*13:61	0	3	0	4	8	12	3	0	5	6	0	1	1	43
225	DRB1*13:66	2	0	0	0	0	0	6	0	0	7	0	0	1	16
226	DRB1*13:96	1	5	13	3	14	19	15	2	18	36	3	9	15	153
227	DRB1*13:97	4	6	16	22	25	25	29	23	26	49	34	45	39	343
228	DRB1*14:01	0	4	10	0	5	10	1	0	0	0	0	0	3	33
229	DRB1*14:02	0	3	1	0	0	1	6	0	4	6	0	3	5	29
230	DRB1*14:03	0	3	0	0	0	0	4	0	0	0	0	0	4	11
231	DRB1*14:04	0	3	5	0	1	8	0	0	0	0	0	0	3	20
232	DRB1*14:06	0	5	1	5	6	14	9	3	10	20	1	10	4	88
233	DRB1*14:07	0	0	0	0	0	0	1	0	0	0	0	0	1	2
234	DRB1*14:12	0	4	0	4	4	2	0	1	4	10	0	3	0	32
235	DRB1*14:32	0	6	13	15	8	25	8	17	27	18	12	9	18	176
236	DRB1*14:38	0	0	4	0	0	0	0	0	0	0	0	0	0	4
237	DRB1*14:54	0	4	10	0	5	10	1	0	0	0	0	0	3	33
238	DRB1*15:01	12	10	0	6	0	4	9	16	14	8	9	15	19	122
239	DRB1*15:02	2	3	0	0	3	1	2	5	10	11	6	1	17	61
240	DRB1*15:03	4	5	0	4	0	2	0	5	7	4	3	8	7	49
241	DRB1*15:06	12	10	0	6	0	4	9	16	14	8	9	15	19	122
242	DRB1*15:07	3	6	0	4	0	1	0	7	6	2	2	9	7	47
243	DRB1*15:15	5	5	0	4	9	4	14	9	6	7	9	11	21	104
244	DRB1*15:37	2	3	0	0	0	0	0	4	4	0	0	4	1	18
245	DRB1*16:01	8	5	0	1	5	6	13	10	7	4	6	7	16	88
246	DRB1*16:02	12	5	2	0	10	11	11	11	16	4	8	12	27	129
247	DRB1*16:04	3	3	0	0	3	0	5	2	4	0	4	3	4	31
248	DRB1*16:05	3	3	0	0	0	0	4	3	4	0	4	3	9	33
249	DRB1*16:09	9	5	0	4	7	4	14	11	8	4	8	4	18	96
Total hits	-	725	792	856	1,095	1,118	1,296	1,442	1,472	1,719	1,814	2,487	2,620	3,490	20,926

Table 3. List of the 85 human leukocyte antigen (HLA) alleles without hits for any of the 13 *P. gingivalis* proteins.

Number	Allele	Number	Allele	Number	Allele
1	A*30:04	31	DPB1*105:01	61	DQB1*05:11
2	A*66:01	32	DPB1*11:01	62	DQB1*06:01
3	B*13:02	33	DPB1*13:01	63	DQB1*06:02
4	B*14:03	34	DPB1*17:01	64	DQB1*06:03
5	B*15:09	35	DPB1*19:01	65	DQB1*06:04
6	B*15:10	36	DPB1*26:01	66	DQB1*06:07
7	B*15:18	37	DPB1*28:01	67	DQB1*06:08
8	B*15:24	38	DPB1*30:01	68	DQB1*06:09
9	B*18:09	39	DPB1*49:01	69	DQB1*06:11
10	B*27:02	40	DPB1*55:01	70	DQB1*06:14
11	B*27:04	41	DPB1*85:01	71	DQB1*06:15
12	B*27:10	42	DQB1*02:02	72	DQB1*06:18
13	B*38:01	43	DQB1*03:01	73	DQB1*06:19
14	B*44:05	44	DQB1*03:02	74	DQB1*06:22
15	B*48:07	45	DQB1*03:03	75	DQB1*06:27
16	B*51:01	46	DQB1*03:04	76	DQB1*06:32
17	B*51:02	47	DQB1*03:05	77	DRB1*03:02
18	B*51:07	48	DQB1*03:10	78	DRB1*03:41

Table 3. List of the 85 human leukocyte antigen (HLA) alleles without hits for any of the 13 *P. gingivalis* proteins. (continued)

Number	Allele	Number	Allele	Number	Allele
19	B*51:09	49	DQB1*03:14	79	DRB1*04:11
20	B*52:01	50	DQB1*03:17	80	DRB1*04:17
21	B*58:02	51	DQB1*03:19	81	DRB1*14:05
22	B*59:01	52	DQB1*03:23	82	DRB1*14:23
23	C*04:01	53	DQB1*03:25	83	DRB1*14:27
24	C*07:04	54	DQB1*04:01	84	DRB1*14:44
25	C*07:19	55	DQB1*04:02	85	DRB1*14:68
26	C*18:01	56	DQB1*04:03	-	-
27	DPB1*04:02	57	DQB1*05:01	-	-
28	DPB1*05:01	58	DQB1*05:02	-	-
29	DPB1*09:01	59	DQB1*05:03	-	-
30	DPB1*10:01	60	DQB1*05:06	-	-

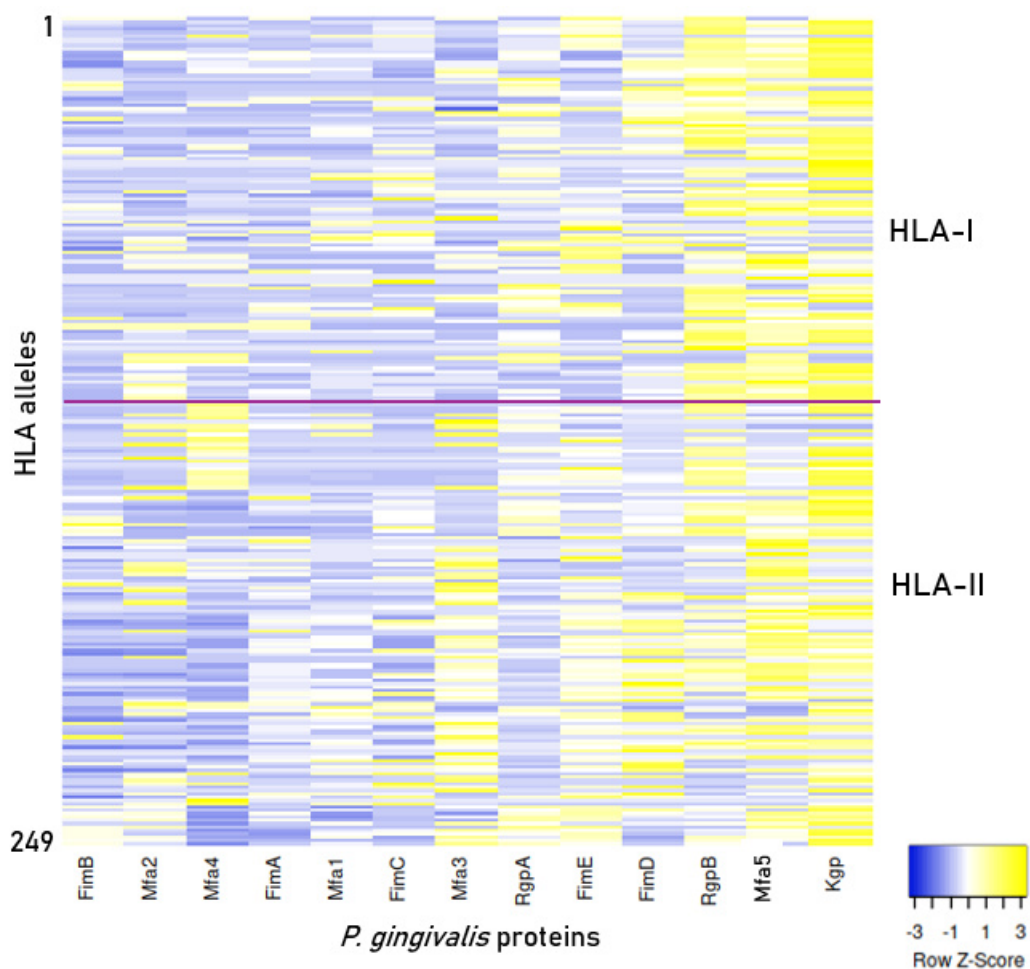


Figure 2. Normalized heatmap to illustrate the data in Table 2. The scale represents Z-scores across rows (protein), from low (blue) to high (yellow). HLA: human leukocyte antigen.

P. gingivalis proteins

The frequency distribution of hits per protein is shown in Figure 3. It can be seen that number of hits per protein varied substantially, reflecting the higher chance for hits in proteins with longer AA sequences (Table 1). Indeed, there was a high correlation between the number of hits and the number of AAs (Figure 4 Pearson $r = 0.931$, $P < 0.001$, $N = 13$ proteins).

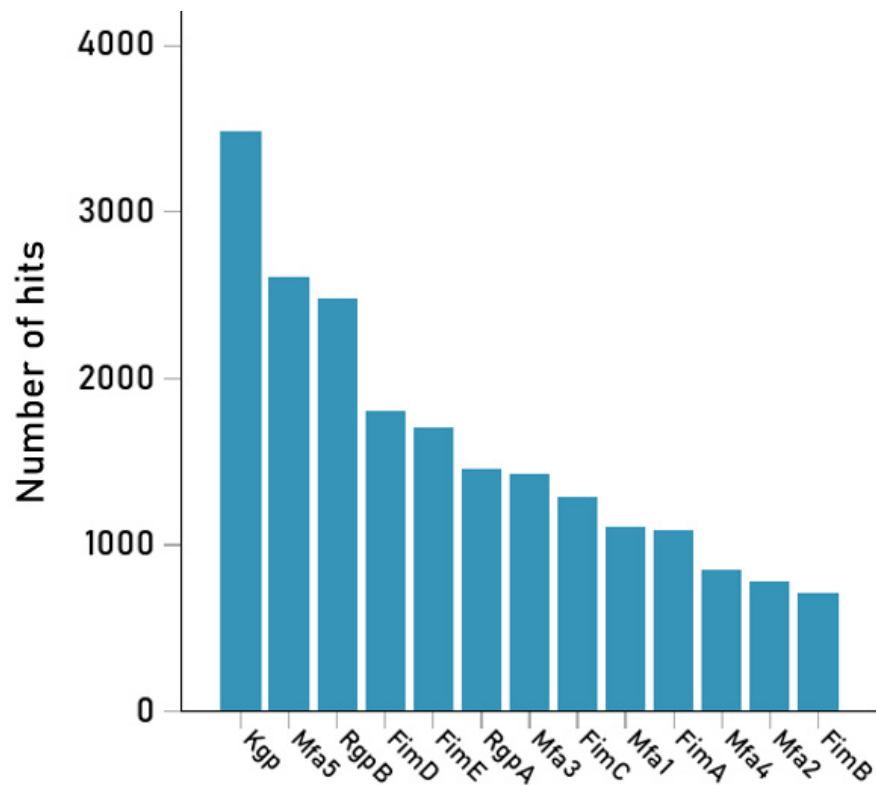


Figure 3. Frequency distribution of hits (predicted best $IC_{50} < 50$ nM) for the 13 *P. gingivalis* proteins tested with 249 human leukocyte antigen (HLA)-I/II alleles that showed at least one hit. Plotted data are from the bottom row (in bold) in Table 2.

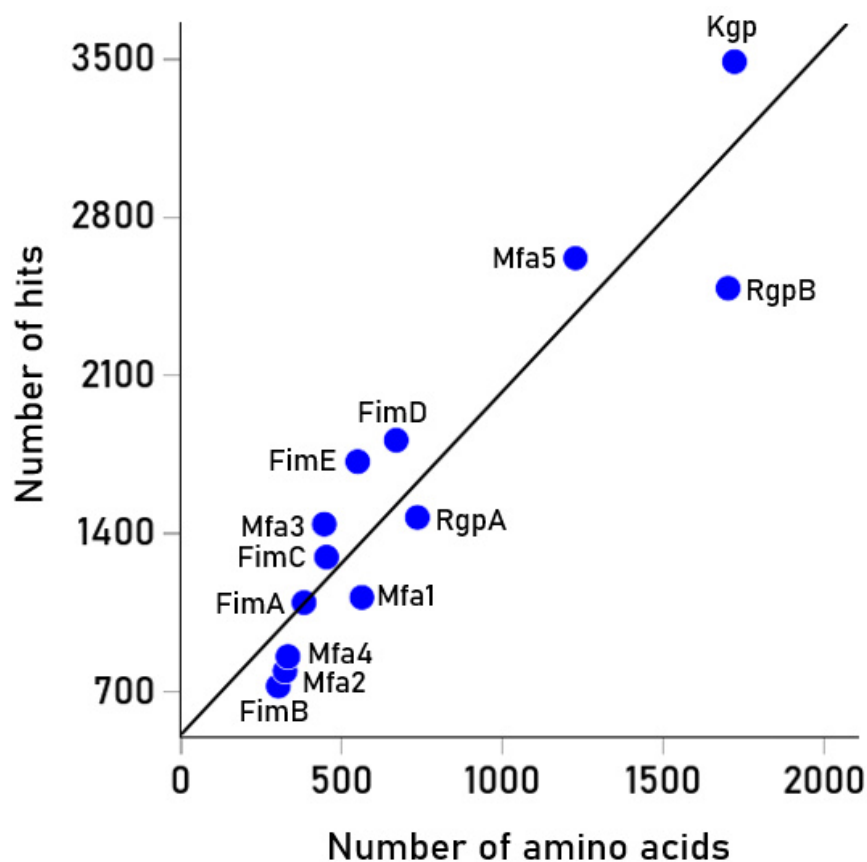


Figure 4. Scatterplot of number of hits vs. length of amino acid sequence of the 13 *P. gingivalis* proteins to illustrate the linear dependence of the former on the latter.

The 13 columns of hits per allele across the 249 alleles in Table 2 constitute the “immunogenetic profiles” of the 13 *P. gingivalis* proteins. We computed and evaluated all possible pairwise Pearson correlations ($N = \frac{13 \times 12}{2} = 78$) between the immunogenetic profiles of the 13 proteins. Remarkably, all profiles were positively and highly significantly intercorrelated, as shown in Table 4 and illustrated in Figure 5. Very similar results were obtained for nonparametric Spearman correlations.

Table 4. Pearson correlations between immunogenetic profiles of 13 *P. gingivalis* proteins (N = 249 alleles).

Protein	FimB	FimA	FimC	FimD	FimE	Mfa1	Mfa2	Mfa3	Mfa4	Mfa5	RgpA	Kgp	RgpB
FimB													
FimA	0.788												
FimC	0.773	0.880											
FimD	0.699	0.912	0.904										
FimE	0.814	0.924	0.878	0.902									
Mfa1	0.818	0.944	0.866	0.888	0.933								
Mfa2	0.832	0.875	0.778	0.758	0.841	0.869							
Mfa3	0.728	0.893	0.757	0.864	0.869	0.882	0.816						
Mfa4	0.43	0.579	0.588	0.631	0.677	0.574	0.53	0.479					
Mfa5	0.875	0.949	0.857	0.898	0.929	0.937	0.886	0.912	0.568				
RgpA	0.890	0.887	0.876	0.846	0.893	0.886	0.863	0.76	0.657	0.905			
Kgp	0.899	0.849	0.787	0.772	0.869	0.876	0.867	0.746	0.665	0.899	0.938		
RgpB	0.882	0.872	0.802	0.811	0.899	0.896	0.845	0.772	0.676	0.921	0.939	0.962	

All *P*-values were highly statistically significant, ranging from 1.65×10^{-141} to 1.31×10^{-12} . These values Bonferroni-corrected for 78 multiple comparisons, ranged from 1.28×10^{-139} to 1.01×10^{-10} .

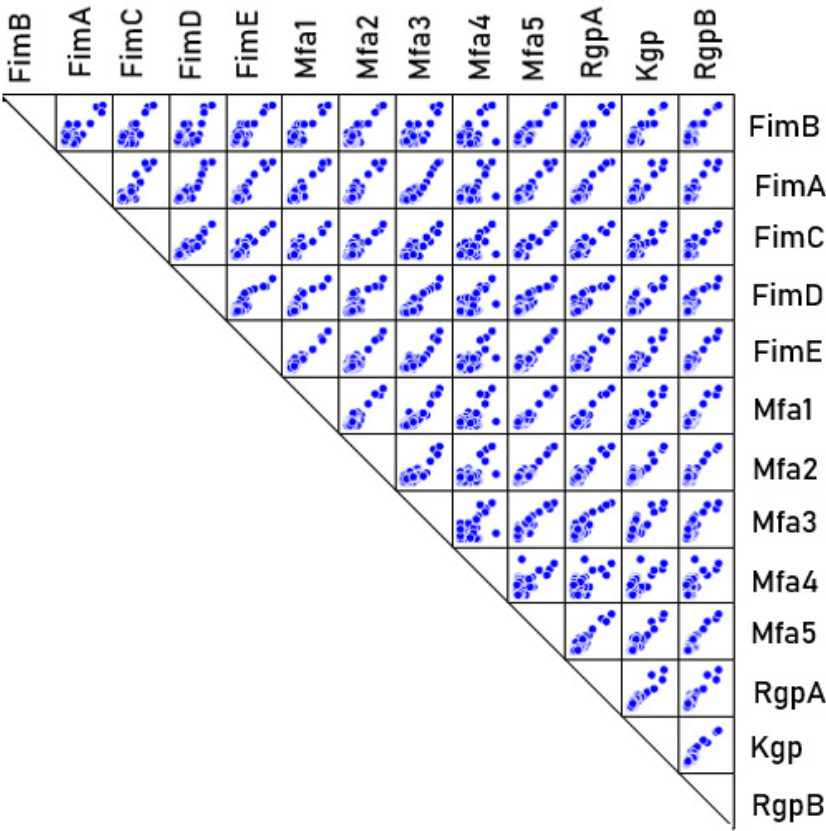


Figure 5. Scatterplots of pairs of immunogenetic profiles between all 78 pairs of *P. gingivalis* proteins. The correlation for each pair is given in Table 4. See text for details.

HLA alleles

The number of hits per HLA Class and gene is given in Table 5. It can be seen that alleles of all HLA-I genes had high percentages of hits ($A > C > B$), for an overall hit percentage of 81.7%. By contrast, HLA-II alleles had an overall hit percentage of 69.3%, with DRB1 gene leading (92.2%), DPB1 gene following (63.4%), and DQB1 gene totally absent. The frequency distribution of hits per HLA allele is shown in Figure 6. It can be seen that the distribution tends to exponential, with a few alleles having a lot of hits; for example, DRB1*01:18, DRB1*01:01, DRB1*01:20 and DRB1*10:01 have more than 600 hits. Alleles with zero hits were also observed in other genes, with lowest occurrence in gene A of HLA-I (4.9%) and gene DRB1 of HLA-II (7.8%). The promiscuity of HLA-II alleles (candidates for vaccine development) are given in Table S4.

Table 5. Number of hits per gene and human leukocyte antigen (HLA) class.

Class	Gene	N alleles tested	N alleles with hits	N alleles without hits
HLA-I	A	41	39 (95.1%)	2 (4.9%)
	B	72	52 (72.2%)	20 (27.8%)
	C	29	25 (86.2%)	4 (13.8%)
	Total	142	116 (81.7%)	26 (18.3%)
HLA-II	DPB1	41	26 (63.4%)	15 (36.6%)
	DQB1	35	0 (0.0%)	35 (100%)
	DRB1	116	107 (92.2%)	9 (7.8%)
	Total	192	133 (69.3%)	59 (30.7%)

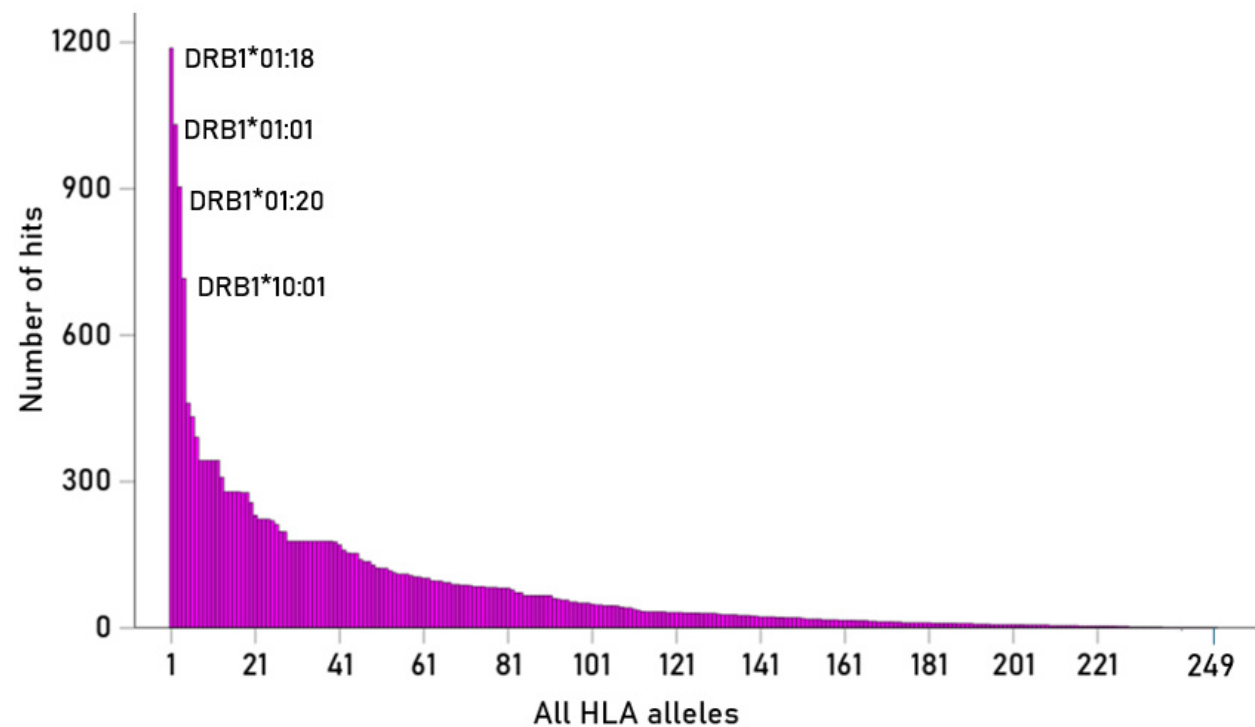


Figure 6. The number of hits for each human leukocyte antigen (HLA)-I/II allele is plotted, ranked from high to low. The 4 alleles names had the highest number of hits.

The 249 rows of hits per protein across the 13 proteins in Table 2 constitute the “protein profiles” of a given allele. We computed and evaluated all possible pairwise Pearson correlations ($N = \frac{249 \times 248}{2} = 30,876$) among these protein profiles. We found the following: of the total 30,876 correlations, (a) 69 (0.223%) were practically zero; (b) 9,554 (30.943%) were negative (range: -0.0001 to -0.776) comprising 121 statistically significant correlations at the nominal (uncorrected) level of $P < 0.05$ (P -value

range: 0.0018 to 0.0495) but nonsignificant when Bonferroni-corrected for 30,876 multiple comparisons ($P < 0.05$); and (c) 21,253 (68.833%) correlations were positive (range: 0.999 to 0.008), comprising 9,024 statistically significant at the nominal (uncorrected) $P < 0.05$ level (P -value range: $P < 0.00001$ to $P = 0.0499$), including 244 correlations with significant Bonferroni-corrected P -values ($P < 0.05$).

Peptides

We further investigated the association between 15-mer peptides and HLA-II alleles to identify peptides suitable for development of vaccines against *P. gingivalis*. Indeed, we identified 798 unique 15-mer peptides (Table S5) that bound with predicted high-affinity binding to 133 HLA-II molecules in 6,343 pHLA-II combinations (Table S6) where it can be seen that there were frequently multiple hits for the same protein-allele combinations. It should be noted that 770/798 (96.5%) of these peptides were associated with alleles of the DRB1 gene (Table S5) which, unlike the DPB1 and DQB1 genes, possesses the same alpha chain. The frequency distribution of unique 15-mer, strongly binding peptides is illustrated in Figure 7A, and their association with specific HLA-II alleles is illustrated in Figure 7B.

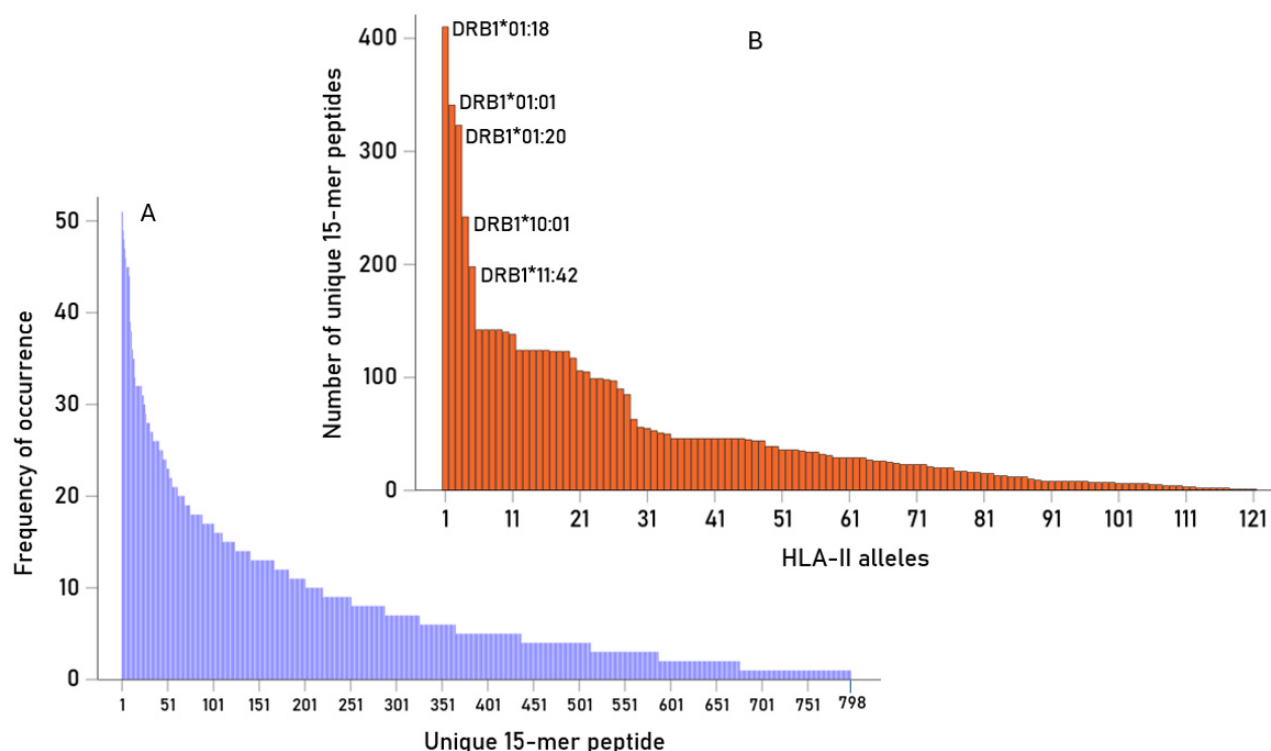


Figure 7. Unique 15-mer peptides. (A) Frequency of occurrence of the 798 unique peptides, ranked from high to low. (B) Number of unique peptides per human leukocyte antigen (HLA)-II allele strongly binding to them. See text for details.

Overlap with other human proteins

We tested for possible overlap of the 798 unique 15-mer peptides with other human proteins by comparing them against the human proteome dataset version 24.1, provided by The Human Protein Atlas (The Human Protein Atlas. Accessed on October 22, 2025. https://www.proteinatlas.org/about/download#protein_atlas_data), comprising a total of 83,607 human proteins. We did not find any matches. This suggests that potential vaccines based on those peptides are not likely to cause autoimmune adverse effects.

Discussion

P. gingivalis is a key pathogen implicated in periodontal disease, a common condition in adults that not only affects oral health but also contributes to systemic diseases [6, 7]. As with other pathogens, the human immune system targets *P. gingivalis* and other invading organisms via interacting innate and adaptive

immune system responses. Local inflammatory responses initiated by the innate immune system are aimed at preventing the bacteria from further invasion. If successful, the infection is resolved, and homeostasis of the microbial biofilm and periodontal health is maintained. In parallel, the adaptive immune system is activated as a second line of defense, for which HLA, the focus of the present paper, is critical. The HLA system plays a central role in immune system responses to various invaders, including bacteria, viruses, and cancer, with both Class I and II contributing to highly specific adaptive immune system responses aimed at pathogen neutralization, if not elimination. Successful resolution of infection via HLA hinges on binding affinity between an HLA molecule and *P. gingivalis* peptides as an initial step that permits presentation of the HLA-peptide complex to lymphocytes to facilitate immune responses against antigenic peptides. In contrast, insufficient binding affinity hinders clearance of the infection, the result of which includes dysbiosis of the biofilm, tissue damage, and chronic inflammation that may extend beyond local periodontal effects to impact distant organs [19]. Thus, prevention of *P. gingivalis* propagation and dissemination is important, and HLA plays a major role in natural defenses against it.

HLA-peptide binding affinity is at the very core of the adaptive immune system response targeting *P. gingivalis*. Here we found that of the ~3 million HLA-*P. gingivalis* peptide combinations tested across the 13 proteins, 20,926 were associated with high-affinity binding “hits”. Those hits spanned both HLA classes and all of the HLA genes with the exception of DQB1, possibly due to its testing paired with only one alpha chain (DQA*01:01). Similarly, the hits for DPB1 alleles could be underestimated, given that only one alpha chain was used for pairing (DPA*01:03). Approximately 75% of the alleles tested had at least one high-affinity hit for *P. gingivalis* peptides; some alleles (i.e., DRB1*01:18, DRB1*01:01) had over 1,000 hits across the 13 *P. gingivalis* proteins tested. Alleles with higher frequency hits have more opportunities to initiate adaptive immune system responses targeting *P. gingivalis* compared to alleles with few hits; individuals possessing alleles with higher frequency hits are presumably less likely to have periodontitis related to *P. gingivalis* due to enhanced ability to neutralize or eliminate the bacteria. This stands in marked contrast to the 85 alleles that did not have any high-affinity binding hits with any of the *P. gingivalis* proteins. Since each individual possesses 12 HLA alleles (two for each gene) that code for HLA glycoproteins that bind and present peptides to T cells, the lack of protection against *P. gingivalis* by those alleles with no high-affinity hits may be offset by other alleles an individual possesses, depending on the individual’s HLA composition. To our knowledge, this is the first study to evaluate high resolution in silico HLA binding affinity en masse with *P. gingivalis* proteins. Several prior studies that have evaluated HLA with regard to periodontitis have documented both protective and susceptibility HLA alleles [49, 50, 74]; however, periodontitis is linked to several bacterial species [75] and HLA-periodontitis associations are not necessarily attributable to *P. gingivalis*. Indeed, a recent study found that antibody levels against two bacteria associated with periodontitis, *Aggregatibacter actinomycetemcomitans* and *P. gingivalis*, were associated with different HLA alleles [76], leading the authors to emphasize the genetic variation in the immune system response to pathogens associated with periodontitis. Here we show that the genetic variation in immune system response extends to different proteins of the same pathogen.

With respect to the 13 proteins tested, all 13 proteins were characterized by high-affinity hits although there was considerable variation in the total number of high-affinity binding hits for each protein. For instance, Kgp had ~5x as many high-affinity hits across alleles as FimB (Kgp: 3,490 vs. FimB: 725). Proteins associated with a greater number of high-affinity hits across alleles are more likely to bind with a variety of HLA proteins to stimulate adaptive immune responses. Here, gingipains Kgp, RgpB, and minor fimbriae Mfa5, the longest proteins, had the most hits. Gingipains, the primary virulence factors of *P. gingivalis*, play a major role in every aspect of infection, including attachment and colonization, tissue invasion, and evasion of innate immune defenses [17]. Thus, HLA that bind and neutralize gingipains are likely to reduce their potential virulence. Similarly, HLA binding with Mfa5, one of the minor fimbriae proteins involved in adhesion to host cells, is likely to disrupt attachment and invasion via adaptive immune system responses targeting the Mfa5 protein. Relative to other Mfa proteins, Mfa5, an ancillary tip protein, is structurally distinct [77]. It is unclear to what extent those structural differences influence differences in HLA binding; however, it has been recognized that Mfa5 antibodies (which are produced as a result of high-affinity HLA-

II binding) may hinder establishment and proliferation of *P. gingivalis*, thereby preventing colonization and chronic inflammation that has been associated with periodontitis as well as systemic diseases [77].

P. gingivalis has been implicated in numerous systemic diseases, including Alzheimer's disease (AD), rheumatoid arthritis, and heart disease, among others [78]. Both direct bacterial invasion and indirect mechanisms tied to inflammatory responses contribute to systemic effects associated with *P. gingivalis*. Notably, *P. gingivalis* also interacts synergistically with several common viruses that are implicated in AD and other systemic diseases [79]. *P. gingivalis* can survive unbound in the cytoplasm and spread to neighboring cells, pass to and infect oral epithelial cells and endothelial cells of blood vessels, and translocate and disseminate to other organs via the bloodstream and other pathways [5, 10, 80–82]. Indeed, *P. gingivalis* is among the most abundant species found in coronary and femoral artery tissues from patients with atherosclerosis [83] and serum and synovial fluid of patients with rheumatoid arthritis [84]. Moreover, *P. gingivalis* DNA and gingipain antigens have been identified in the brain and cerebrospinal fluid of individuals with AD and shown to correspond with AD pathology [11]. Substantial additional evidence implicates *P. gingivalis* in AD and other neurodegenerative conditions, including Parkinson's disease and multiple sclerosis via neuroinflammation and oxidative stress [10, 82]. The extensive research linking *P. gingivalis* to systemic diseases highlights the importance of prevention and/or intervention for oral health as well as systemic health.

Conventional therapies to combat *P. gingivalis* include antimicrobial antiseptics (e.g., chlorhexidine) and antibiotics; however, limitations of these approaches, including concern about antibiotic resistance [85, 86], have given way to alternative strategies. Several novel therapeutic approaches targeting *P. gingivalis*, discussed elsewhere [82], have shown promise in pre-clinical studies, including various nano-medicine based approaches, gingipain inhibitors, and peptide-based strategies targeting gingipain and other *P. gingivalis* peptides. Development of vaccines represents another promising avenue for preventing *P. gingivalis*-related disease with considerable recent and ongoing *P. gingivalis* vaccine development research underway, particularly targeting FimA, gingipains, and outer membrane proteins [87–89]. The selection of immunogenic antigens is of paramount importance for vaccine development. An important consideration with regard to selection of immunogenic antigens for vaccines is individual HLA-II composition since binding affinity of HLA-II molecules varies across antigens. Production of antibodies, whether from natural immunity or vaccination, depends on HLA Class II-antigen binding as an initial step. That is, the adaptive immune response depends on the interaction between host HLA and *P. gingivalis* protein peptides. Here we identified immunogenic 15-mer peptide sequences and provided the corresponding HLA to which they bound with high-affinity. Several 15-mer sequences were characterized by high binding affinity for multiple HLA alleles, potentially reflecting promising candidates for future vaccine development, an avenue for future study. Since the peptides did not overlap with any of the human proteome, the risk of autoimmunity is expected to be reduced. It is worth noting that similar immunoinformatic approaches have been used as the in recent multi-epitope *P. gingivalis* vaccine design efforts, albeit limited to identification of epitopes that bind with DRB1*0101 [90]. Identification of candidate epitopes in silico is a promising initial step in *P. gingivalis* vaccine development that narrows the scope of antigens to those predicted to bind with high-affinity and elicit an immune response [91, 92], setting the stage for in vitro and in vivo studies evaluating the safety and efficacy of peptide-based vaccines.

The key innovation of our study lies in the exhaustive testing of all possible linear epitopes of the standard 15-AA length for HLA-II presentation, thus screening for the most promising peptides to be evaluated further by in vitro, ex vivo, and in vivo methods for vaccine development. And the key discovery is the identification of 798 15-mer peptides that are exclusively non-self, since they were not found in proteins of the human connectome, making them safe against autoimmune untoward effects. Notably, 770 of those peptides were associated with HLA-II DRB1 gene, the alleles of which all possess a constant alpha chain and hence are the same in all individuals. Naturally, more steps would be required to use those peptides in development of vaccines against *P. gingivalis*. Such steps would include, but not be limited to: (1) determining/confirming in vitro their binding affinities [91, 92] to the associated DRB1 alleles, (2) evaluating the capacity of specific pHLA-II complexes to elicit adequate CD4+ engagement and proliferation,

(3) possible pairing the peptide with a suitable adjuvant, (4) assessing for adequate production of neutralizing antibodies against *P. gingivalis*, (5) evaluating protection against *P. gingivalis* infection in vaccinated animals, and (6) assessing in those animals the occurrence of adverse effects before considering running clinical trials in humans.

Finally, it should be emphasized that the use of such vaccines would be for prophylactic purposes, not for a therapeutic effect, given the various known mechanisms of immune evasion by *P. gingivalis* [48, 58, 93] which would be expected to appreciably reduce a robust antibody production.

Limitations

The hits for DPB1 and DQB1 genes are possibly underestimated, given that only one alpha chain was used for pairing, namely DPA*01:03 and DQA*01:01, respectively. Although both of these specific alpha chains are very frequent, DP and DQ alpha chains can vary substantially, especially among different ethnicities and among different alpha-beta chain combinations, making practically infeasible the exhaustive testing of all possible DPA/DPB and DQA/DQB combinations.

Abbreviations

AA: amino acid

APCs: antigen-presenting cells

HLAs: human leukocyte antigens

pHLA: peptide-human leukocyte antigen

TCR: T-cell receptor

Supplementary materials

The supplementary tables for this article are available at: https://www.explorationpub.com/uploads/Article/file/1003271_sup_1.pdf.

Declarations

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Author contributions

LMJ: Conceptualization, Investigation, Funding acquisition, Writing—original draft, Writing—review & editing. MS: Data curation, Software, Writing—review & editing. APG: Data curation, Formal analysis, Visualization, Funding acquisition, Writing—original draft, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

Apostolos P. Georgopoulos, who is the Editorial Board Member and Guest Editor of Exploration of Immunology, and Lisa M. James, who is the Guest Editor of Exploration of Immunology, had no involvement in the decision-making or the review process of this manuscript. Matthew Sanders declares no conflicts of interest.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

All data used were retrieved from freely accessible websites and, as such, are publicly and freely available (<http://tools.iedb.org/mhci/>). Other datasets that support the findings of this study are available from the corresponding author upon reasonable request.

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