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Bioinformatics-Based Predictions of Peptide Binding to Disease-Associated HLA Proteins Suggest Explanation for Shared Autoimmunity

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Abstract:

Aim: This study was designed to examine the immunogenetic basis for shared autoimmunity, resulting in autoantigen presentation that leads to the production of two or more disease-specific autoantibodies.

Methods: A bioinformatics approach based on peptide binding predictions to disease-associated HLA determinants has been developed and tested here using 11 disease associations between autoimmune systemic and mucocutaneous blistering disorders. Various HLAs associated with antigens within a given "disease model" (set of HLA class II and protein sequences known to be associated with a specific autoimmune disease) were tested and ranked against the antigenic proteins, first with proteins they are known to associate with and then with proteins known to be implicated in a second disease model. In every case binding predictions were compared for different proteins binding to the same HLA. Subsequently, disease-related autoantigens have been tested for their binding affinity against each disease-specific HLA class II protein.

Results: For a single HLA haplotype, several binders have been generated from a related autoantigen with the variable binding score. In most cases, the binding score corresponding to the interactions between the autoantigen-derived epitope and the HLA associated with one disease was similar or lower than the interactions between the epitope from proteins associated with the second disease and the same HLA. Notably, there was no compelling promiscuity in peptide binding to each of the HLA molecules, in spite of the promiscuous nature of HLA class II binding.

Conclusions: The data suggest that, in susceptible individuals, shared autoimmunity might be initiated by two types of HLA/peptide interaction; first between an autoantigen-derived epitope and its disease-associated HLA molecules, and second, between a different peptide of the same autoantigen and HLA proteins specific for the second disease.

Keywords: autoantigenic epitopes, autoimmune blistering diseases, HLA determinants, peptide binding, Rankpep tool

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Introduction

Autoimmune mucocutaneous blistering diseases (AMBD) such as pemphigus vulgaris (PV), pemphigus foliaceus (PF), bullous pemphigoid (BP), ocular cicatricial pemphigoid (OCP), dermatitis herpetiformis (DH) and mucous membrane pemphigoid (MMP), are a group of rare organ-specific diseases that affect skin and multiple mucous membranes.¹⁻⁵ PV is a potentially fatal disease characterized by the loss of intercellular adhesion of keratinocytes, resulting in acantholysis.⁶⁻⁸ In the serum of PV patients, high titers of circulating autoantibodies targeting the epidermal adhesion molecule desmoglein 3 (Dsg3)-keratinocyte transmembrane proteins localized in the desmosome, essential for maintaining the integrity of the epidermis-are believed to cause clinical disease by direct binding to and disruption of desmoglein proteins.^{1,9} The association of HLA class II antigens with susceptibility to PV has been demonstrated in numerous studies.¹⁰⁻¹⁴ In Ashkenazi Jews, PV appears tightly linked to the rare haplotype HLA-DR4 (DRB1*0402): DQB1*0302, while in non-Jewish patients, it is linked to the haplotype DRB1*404X: DQB1*0503.15

MMP affects mucous membranes of the body and is characterized by the presence of autoantibodies to human $\beta4$ integrin,^{16,17} while BP which predominantly affects the skin and is associated with bullous pemphigoid antigen 1 (BPAg1) and 2 (BPAg2).¹⁸ Both BP and MMP have been shown to have a strong linkage to DQB1*0301.^{18,19} It has been demonstrated that the same patient may have antibodies against more than one autoantigen within the skin and mucous membrane, resulting in more than one autoimmune mucocutaneous disease. For example, patients with PF may develop BP,^{20,21} patients with MMP may have PV (22), and some patients are affected with both PV and OCP.²³

OCP is a systemic autoimmune pemphigoid disorder that has both ocular and non-ocular manifestations. OCP can cause bullous lesions of the skin and mucous membranes that result in scarring of the affected skin, conjunctiva (inner lining of the eye), and other mucous membranes.^{24,25} Different epithelial membrane zone components have been recognized by antibodies in patients with OCP, ie, BPAg1 and BPAg2, laminin 5, laminin 6, type VII collagen, β 4 integrin subunit, and antigens with unknown



identities (a 45-kd protein, uncein, a 168-kd epithelial protein, and a 120-kd epithelial protein).^{26,27} Among white patients in the United States, OCP is associated with the DQB1*0301 allele.

DH is an autoimmune blistering disorder associated with a gluten-sensitive enteropathy. It is characterized by grouped excoriations, erythematous, urticarial plaques, and papules with vesicles. DH is caused by the deposition of IgA in the papillary dermis, which triggers an immunologic cascade, resulting in neutrophil recruitment and complement activation.^{28,29} DH is associated with an increased expression of HLA-A1, HLA-B8, HLA-DR3, and HLA-DQ2 haplotypes.^{30,31} Evidence is mounting that epidermal transglutaminase 3 (TGM3), a cytosolic enzyme involved in cell envelope formation during keratinocyte differentiation, is the autoantigen of DH. Theoretically, DH is caused by dermal deposition of circulating immune complexes containing both IgA and TGM3.32,33

In contrast to these organ-specific diseases, connective tissue disorders, or systemic diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and systemic sclerosis (SSc), involve multiple tissues and organs.34-36 Mixed connective tissue disease (MCTD) is also a systemic autoimmune syndrome that is characterized by the presence of high titers of serum antibodies against small nuclear ribonuclear proteins (U-snRNPs),^{37,38} in particular against U1 small nuclear RNP polypeptide (U1 snRNP). It has been suggested that MCTD represents a distinct clinical entity, based on clinical manifestations that separate MCTD from other connective tissue diseases.³⁹ Various associations of HLA class II antigens with MCTD have been reported, including HLA-B7 and HLA-Dw1.40 In another study, HLA-DR4 was found to be significantly increased in MCTD,⁴¹ whereas others reported an association between HLA-DQw3 and anti-RNP antibodies in patients with MCTD.⁴² Interestingly, MCTD patients with increased IgG autoantibodies against U1-70 kD polypeptide have an increased prevalence of HLA-DR4 compared with controls.⁴³ Furthermore, molecular biology studies have shown that most MCTD patients carrying HLA-DR4 or HLA-DR2 alleles share a region of homology consisting of seven amino acids in the HLA-DRB1 gene.44 This "shared epitope" of HLA-DR molecules, in different alleles



and in different patients with MCTD, may be important for the modulation of the autoimmune response to the U1-70 kD antigen.⁴⁵

Based on the accumulated evidence of shared autoimmunity, it has been intriguing to investigate the relationship between the genetic and immunological mechanisms for the simultaneous production of two or more autoantibodies in patients exhibiting more than one autoimmune disease. A hypothesis, which in part may explain some of the increased susceptibility to both autoimmune blistering and systemic connective tissue diseases, has recently been proposed.⁴⁶ This hypothesis is based on the unequivocal evidence that CD4⁺ T cells play a critical role in autoantibody production, implying that existence of HLA class IIrestricted T cell epitopes might trigger autoimmunity. Three possible scenarios for the immunopathogenic mechanisms leading to breakage of tolerance and induction of two distinct autoimmune diseases in the same individual have been discussed: 1) T cell epitopes of the two different autoantigens associate with each of the susceptible HLA molecules, resulting in dual autoimmunity; 2) a single epitope of an autoantigen binds to both HLA specificities, leading to the induction of both diseases by cross- reactivity; and 3) two distinct epitopes of the same autoantigen are able to bind two different HLA molecules that are associated with the two diseases, implying that both T cell epitopes originating from one autoantigen will activate immunopatogenic mechanisms by binding to two HLA molecules specific for two diseases. In order to test each of these hypotheses, bioinformatics-based predictions of peptide binding to disease-associated HLA determinants have been generated using multi-HLA II peptide binding analysis. This communication explores the nature of autoantigen-derived epitopes and their binding characteristics to HLA proteins in the context of shared autoimmunity.

Methods

Protein sequences

The protein sequences of autoantigens were collected from the Consensus Coding Sequence Database (CCDS), a collaborative effort between the NCBI and several other organizations which contains consistently annotated protein coding regions of human and mouse genes.⁴⁷ Only human sequences were used in this project, and alternate exons were included in the sequences. The autoantigens tested in this study are listed in Table 1, and in most cases consist of the entire protein sequence from which specific autoantigens (such as BP180 and BP230) are derived.

Peptide-HLA II binding predictions

The analysis of peptide binding to HLA II molecules known to be involved in autoimmune mucocutaneous blistering diseases was based on the use of the same methodology applied by the Rankpep web server.⁴⁸ Rankpep predicts peptide binding using position specific motif matrices—also known as motif profiles—that are derived from known peptide binders.^{49,98} A program was written, cross-HLA II-binding analyzer, to perform multiple rankings of predicted binding potentials and classify the binding predictions into sets: predictions for protein-HLA II sets known to be involved in disease genesis. Results were organized by disease model—sets of HLA II and proteins known to be involved in the genesis of specific autoimmune diseases were used.

The cross-HLA II-binding analyzer performs three types of sorting based on the three scenarios proposed in this paper: 1) Single HLA II recognition, 2) Dual HLA II recognition with a single epitope, and 3) Dual HLA II recognition with dual epitopes. The analysis was designed to group the components of each disease model, the HLA IIs and proteins involved in known disease interactions—for example, HLA-DQB1*0301 with alpha 1 type XVII collagen (BP180) and dystonin (BP230) in the BP model—and sort results by within-model and cross-model HLA II-peptide binding pairings. Some details of the cited scenarios are as follows:

Scenario 1—Single HLA recognition: This scenario is assumed to be the standard case, since each disease model exists independently. The cross-HLA II-binding analyzer generates a series of ranked results within the known disease models described above (sets of HLA II and proteins known to contain antigenic sequences), showing all predicted binders for each HLA II-protein pairing—peptides scored above the binding threshold for that pairing. Because these interactions are within known disease models, they are used as reference values.

Scenario 2—Dual HLA II recognition with a single epitope: the cross-HLA II-binding analyzer has an intersection analysis function, which is used



Disease	HLA II	Autoantigen	CCDS ID	Reference
Pemphigus vulgaris	HLA-DR4 (DRB1*0402) DQwB1*0302 HLA-DR4 (DRB1*0404) DQ5 (DQB1*0503)	Desmoglein 3	11898.1	10–15
Mucous membrane pemphigoid	HLA-DQ7 (DQB1*0301)	β4 integrin	11727.1	16,17
Bullous pemphigoid	HLA-DQ7 (DQB1*0301)	Alpha 1 type XVII collagen (BP180)	7554.1	18,19
		Dystonin (BP230)	4959.1	
Ocular cicatricial	HLA-DQ7 (DQB1*0301)	Alpha 1 type XVII collagen (BP180)	7554.1	26,27
pemphigoid	HLA-DR4 (DRB1*0401)	β4 integrin	11727.1	
Mixed connective tissue disease	HLA-B7, HLA-Dw1 HLA-DQw3	U1 sn-RNP polypeptide	12756.1	38,39 41–43
Dermatitis herpetiformis	HLA-DQ8 (DQA1*0301/ DQB1*0302)	Transglutaminase 3	33435.1	28–33
	HLA-DQ2 (DQA1*0501/ DQB1*0201)			52,53
Pemphigus foliaceus	HLA-DRB1 (DRB1*0404, DRB1*1402, DRB1*1406, DRB1*1401, DRB1*0102)	Desmoglein 1	11896.1	20,21, 57

Table 1. Autoantigens and HLA associations in autoimmune blistering and systemic diseases.

Abbreviation: CCDS, consensus coding sequence project.⁴⁷ (http://www.ncbi.nlm.nih.gov/projects/CCDS/).

to find promiscuous peptides in a series of two HLA II-peptide binding predictions. To identify promiscuous peptide-binding peptides, the analysis was limited to the set of the top 5% of peptides in each group of results. This analysis identifies promiscuous peptide binders across known disease models. When a common peptide was found in more than one autoantigen, it was included in an intersection analysis report, detailing the binding score of the common peptide for each matrix.

Scenario 3—Dual HLA recognition with dual epitopes: the cross-HLA II-binding analyzer produces results for cross-model pairings of HLA IIs and proteins. To evaluate the potential for the pairings to produce immunogenic reactions, binding predictions (binding affinity, number of predicted binders) across models are compared to the top predicted binding scores for known immunogenic reactions within known disease models (Scenario 1).

Results

Based on the published observations of shared autoimmunity and on theoretical predictions exploring the probability of its occurrence, the following disease associations have been tested: PV/MMP, PF/BP, PV/OCP, PV/BP, PV/MCTD, PF/MCTD, BP/MCTD, DH/MCTD, OCP/MCTD, MMP/MCTD and BP/DH. The list of autoantigens and HLA associations in autoimmune blistering and systemic diseases is presented in Table 1. For most diseases in this study, eg, PV, MMP, DH, PF and MCTD, a single autoantigen has been reported, with the exception of BP and OCP that are characterized by the presence of the same two autoantigens, BPAg1 (BP180), derived from alpha 1 type XVII collagen and BPAg2 (also known as BP230), part of the dystonin protein. It is noteworthy that MMP, BP and OCP are all associated with the prevalent HLA-DQB1*0301 allele, while PV, DH, PF and MCTD each carry distinct HLA haplotypes.

Three hypothetical models of peptide-HLA II interactions proposed by Fridkis-Hareli⁴⁶ were tested using HLA-specific binding matrices and autoantigen sequences listed in Table 1. For each HLA specificity, the autoantigen of interest was examined for the presence of potential binding epitopes and scored based on



peptide binding affinity. The results arranged by disease model are shown in Supplemental Tables 1–11. All potential epitopes (sequences predicted to bind above the binding threshold for the HLA matrix were retrieved from each analysis (raw data not shown). It is important to note that comparisons were made between HLA-peptide binding analyses against the same HLA molecule—all binding scores and values were relative to that specific HLA class II. It should also be noted that not all the HLA specificities known to associate with a particular disease were available from the database and thus were not included in the present report.

PV/MMP

Autoantigenic proteins associated with each of these diseases were tested for binding to the HLA haplotypes as described below:

PV Model: the HLA II-peptide biding analysis for desmoglein 3 preproprotein generated 991 sequences in total (Supplemental Table 1). Four Dsg3-derived peptides were predicted to bind to HLA-DQ8 (DQA1*0301/DQB1*0302) above the binding threshold, with a predicted range of 36.91%–25.22% (from high to low optimal binding). In contrast, binding of the same autoantigen to HLA-DR4 (DRB1*0402) determinants resulted in 11 predicted binders with a range of 40.33%–25.80% of the optimal score. Similarly, five predicted binders of Dsg3 to HLA-DR4 (DRB1*0404) were identified with a range of 53.46%–32.23% of the optimal score (Supplemental Table 1A). The sequences of Dsg3-derived binding epitopes are presented in Supplemental Table 1B.

MMP Model: Table 2 shows that the analysis for HLA-DQ7 (DQB1*0301) and β 4 integrin generated 1814 sequences. Fourteen peptides were predicted to bind, at 44.19%–25.90% of the optimal binding score. For peptide sequences refer to Supplemental Table 1B.

PV/MMP: The cross-model analysis matches HLA-DQ7 (DQB1*0301) (from the MMP model) with Dsg3, the antigen-producing protein from the PV model. Four sequences from Dsg3 are predicted to bind, with scores between 37.32% and 29.70% of the optimal score for HLA-DQ7 (DQB1*0301). These sequences are within the range of binders predicted for the in-model interactions, but four of the predicted in-model binders have higher scores than the best cross-model prediction (Supplemental Table 1A).

Table 2. Predicted binding epitopes derived from autoan-tigensspecific for blistering and systemic diseasecombinations.

HLA II/Protein	PV	MMP	PF	BP	OCP	DH	MCTD
PV	20	4		4	47		18
MMP	47	14					73
PF			27	6			22
BP	69		104	26		21	96
OCP	65				188		73
DH				6		3	18
MCTD	7	3	4	3	9	4	5

Notes: The number of predicted binders resulting from all MHC associated with a disease model (x-axis) and all protein sequences associated with another disease model (y-axis). Cells in bold are in-model results (predicted binders when testing all HLAs from one disease model against all protein sequences from the same disease model). Example: The total number of binding sequences predicted when analyzing all HLAs from the PV disease model against all protein sequences in the BP disease model is 69 (column one, row four).

Conversely, the cross-model analysis matches $\beta4$ integrin (MMP model) with HLA-DQ8 (DQA1*0301/ DQB1*0302) (14 predicted binders), HLA-DR4 (DRB1*0402) (16 predicted binders) and HLA-DR4 (DRB1*0404) (17 predicted binders) from the PV model. Interestingly, the two highest scoring peptides from the HLA-DQ8 (DQA1*0301/DQB1*0302)— $\beta4$ integrin (DERCHLDTT and ANRCKKAPV), scored higher than all the predicted binders from the PV inmodel analysis. In contrast, the binding of $\beta4$ integrin to HLA-DR4 (DRB1*0402) and HLA-DR4 (DRB1*0404) was within the binding range of Dsg3 to these molecules (Supplemental Table 1B).

PF/BP

In this case, three autoantigens, ie, Dsg1 for PF, alpha 1 type XVII collagen (BP180) and dystonin (BP230) for BP have been analyzed for their binding to several disease-associated HLA haplotypes, as shown in Supplemental Table 2. Analysis of Dsg1 binding to PF-associated molecules revealed 1041 sequences in total, whereas alpha 1 type XVII collagen (BP180) generated 1489 sequences and dystonin (BP230) generated 2641 sequences derived from their binding to BPassociated MHC molecules (Supplemental Table 2A).

PF Model: Peptide binding analysis for desmoglein 1 (Dsg1) to HLA-DR1 (DRB1*0101) showed 22 results with 53%–16% predicted optimal binding. In addition, analysis of Dsg1 and HLA-DR4 (DRB1*0404) identified five binders in the range of 48%–32% of predicted optimal values. In contrast, analysis for Dsg1 binding to HLA-DR4 (DRB1*0406) and HLA-DR1 (DRB1*0102) showed no binding epitopes above the binding threshold (Supplemental Table 2A). Peptide sequences are shown in Supplemental Table 2B.

BP Model: HLAII-peptide binding results for alpha 1 type XVII collagen peptides binding to HLADQ7 (DQB1*0301) showed 14 peptide sequences ranging between 43%–26% optimal binding (Supplemental Table 2A). Binding of dystonin to the same molecules resulted in 12 predicted binders with 31%–26% of optimal binding (Supplemental Table 2A).

PF/BP: Analysis of Dsg1 binding to BP-associated HLA-DQ7 (DQB1*0301) molecules resulted in six peptides with 39%-28% optimal binding (Supplemental Table 2A). Notably, these values were lower than the binding of Dsg1 to PF-associated MHC molecules. Predictions for alpha 1 type XVII collagen peptides binding to PF-associated HLA-DR1 (DRB1*0101) resulted in 30 binders with 40%-17% optimal binding (Supplemental Table 2A). In contrast, analysis of alpha 1 type XVII collagen/HLA-DR1 (DRB1*0102) interactions showed no detectable binding. On the other hand, the binding of alpha 1 type XVII collagen to HLA-DR4 (DRB1*0404) showed higher range of optimal binding (52%-35%) for six predicted epitopes (Supplemental Table 2A). Interestingly, predictions of alpha 1 type XVII collagen binding to HLA-DR4 (DRB1*0406) resulted in one peptide epitope with the binding score of 36.062 and optimal binding of 49.23% (Supplemental Table 2A). Peptide sequences are listed in Supplemental Table 2B.

Binding of dystonin to PF-associated HLA-DR1 (DRB1*0101), HLA-DR1 (DRB1*0102), HLA-DR4 (DRB1*0404), HLA-DR4 (DRB1*0406) was tested similarly to alpha 1 type XVII collagen. For HLA-DR1 (DRB1*0101) molecules, 56 predicted binders with 44%–16% optimal binding have been identified, and for HLA-DR4 (DRB1*0404), 11 dystonin-derived binders with 54%–32% optimal binding have been detected (Supplemental Table 2A). Of note is that these values are higher than the ones found for dystonin binding to BP-associated molecules. Interestingly, no predicted epitopes were found either for HLA-DR1 (DRB1*0102) or for HLA-DR4 (DRB1*0406) interactions with dystonin. In summary, these results suggest that here, as in the case of



PV/MMP, epitopes derived from one disease-specific autoantigenic protein may bind both disease-specific HLA molecules.

PV/OCP

Analysis of Dsg-3-derived peptides to PV-associated HLA-DQ8 (DQA1*0301/DQB1*0302), HLA-DR4 (DRB1*0402) and HLA-DR4 (DRB1*0404) molecules has been described in *PV* section (Supplemental Table 1). Likewise, due to the fact that OCP shares the same autoantigens and HLA specificities with BP and MMP, ie, alpha 1 type XVII collagen, β 4 integrin and HLA-DQ7 (DQB1*0301), the corresponding data have been provided in *BP* and *MMP* sections (Supplemental Tables 1 and 2). Analysis of β 4 integrin binding to OCP-associated MHC molecules generated 1814 peptide sequences, whereas alpha 1 type XVII collagen generated 1489 sequences (Supplemental Table 3A).

PV/OCP: PV-specific desmoglein 3 preproprotein peptide binders examined for the OCP-associated HLA-DQ7 (DQB1*0301) revealed four binders with 37%–29% predicted optimal binding, as described for PV/MMP model (Supplemental Table 1A). The binding of Dsg3 to HLA-DR4 (DRB1*0401) resulted in 43 binders with 46%–11% predicted optimal values (Supplemental Table 3A). In the case of OCP-related autoantigen association with PV-specific MHC, eight binders derived from alpha 1 type XVII collagen (BP180) exhibited 36%-25% optimal predicted binding to HLA-DQ8 (DQA1*0301/DQB1*0302). The binding to HLA-DR4 (DRB1*0402) was between 38%–28% optimal values for four predicted binders, while the binding to HLA-DR4 (DRB1*0404) was even higher (52%-34% optimal binding). Another potential OCP-associated autoantigen, β4 integrin, bound to PV-specific HLA molecules with differential predicted scores as shown in Supplemental Table 3A. For HLA-DQ8 (DQA1*0301/DQB1*0302), 14 binders with 42%-25% optimal binding have been identified, whereas 16 binders were detected for HLA-DR4 (DRB1*0402) (37% optimal binding), and 17 peptides for HLA-DR4 (DRB1*0404) with 51%-34% optimal binding (Supplemental Table 3A). Interestingly, the binding of β4 integrin to PV-associated HLA-DR4 (DRB1*0404) was higher than to OCP-associated molecules (51% vs. 44%, respectively). Peptide sequences are shown in Supplemental Table 3B.



PV/BP

For this disease combination, individual parts of PV/ Dsg3 and BP/alpha 1 type XVII collagen/dystonin analysis have been described in *PV* and *BP* sections, respectively (Supplemental Tables 1 and 2).

PV/BP: Analysis of the binding of Dsg3 to BPassociated HLA-DQ7 (DQB1*0301) resulted in four binders with 37%-29% optimal binding (Supplemental Table 4A). In the opposite direction, the binding of alpha 1 type XVII collagen to PV-associated HLA-DR4 (DRB1*0402), HLA-DR4 (DRB1*0404), and HLA-DQ8 (DQA1*0301/DQB1*0302) showed four binders (38%–28% optimal binding), six binders (52%-34% optimal binding) and eight binders (36%–25% optimal binding), respectively. For dystonin-derived peptides, 28 predicted binders were found with DRB1*0402 (37%–28% optimal binding), 11 peptides bound to DRB1*0404 (54%-32% optimal binding), and 12 predicted binders (47%-25% optimal binding) were detected for HLA-DQ8 molecules (Supplemental Table 4A). Of note is that the binding score for dystonin-derived peptides bound to PV-associated HLA-DQ8 molecules was higher than the one for dystonin binding to BP-associated HLA-DQ7 molecules (Supplemental Table 4A). Peptide sequences are presented in Supplemental Table 4B.

PV/MCTD

PV-related Dsg3 association with its HLA-DQ8 (DQA1*0301/DQB1*0302) receptors was already described in this report (Supplemental Tables 1, 3 and 4). Peptide binding analysis of MCTD-specific autoantigen UI-snRNP C [Homo sapiens] resulted in 429 sequences in total (Supplemental Table 5). Binding of UI-snRNP-derived peptides to HLA-DR1 (DRB1*0101) revealed three predicted epitopes with 37%–25% optimal binding, while interaction with the 9mer HLA-B07 resulted in two peptides with 63%–62% optimal binding (Supplemental Table 5A). PV-related Dsg3 association with its HLA-DQ8 (DQA1*0301/DQB1*0302) receptors was already described in this report (Supplemental Tables 1, 3 and 4).

PV/MCTD: The combination of PV and MCTD was tested using autoantigens UI-snRNP and Dsg-3, and HLA molecules associated with both diseases, ie, HLA-DR1 (DRB1*0101), HLA-DR4 (DRB1*0402), HLA-DR4 (DRB1*0404), HLA-DR4 (DRB1*0406),

HLA-DQ8 (DQA1*0301/DQB1*0302) and HLA-B07 alleles. The binding of PV-specific Dsg3 to MCTD-associated HLA-DR1 (DRB1*0101) showed 18 binders with 44%-17% optimal binding, while analysis of Dsg3/9mer-HLA-B07 interactions showed no predicted binding epitopes (Supplemental Table 5A). Similarly, there was no binding of UI-snRNP to PV-associated HLA-DR4 (DRB1*0404), but three peptides (55%-26% optimal binding) were found to bind HLA-DR4 (DRB1*0402), and four peptides (40%-27% optimal binding) were detected for HLA-DQ8 (DQA1*0301/DQB1*0302) molecules (Supplemental Table 5A). Importantly, the optimal binding of UI-snRNP-derived peptides to PV-associated HLA-DR4 (DRB1*0402) was higher than its binding to MCTD-related HLA-DR1 (DRB1*0101) but lower than binding to the second susceptible MCTD allele, HLA-B07 (Supplemental Table 5). Peptide sequences are shown in Supplemental Table 5B.

PF/MCTD

Binding analysis of PF- and MCTD-related peptides to their disease-specific HLA molecules was described in the earlier sections of this report (Supplemental Tables 2 and 5). The largest number of Dsg1-derived epitopes was found to bind to HLA-DR1 (DRB1*0101) as compared to other PF-specific alleles (Supplemental Table 6). This disease combination is unusual since both diseases share the presence of HLA-DR1 (DRB1*0101), suggesting that PF- and MCTD-derived peptides might bind to the same molecule and thus trigger initiation of the second disease.

PF/MCTD: Binding analysis of Dsg1-derived peptides to MCTD-associated HLA-DR1 (DRB1*0101) molecules showed 22 epitopes (53%–16% optimal binding), while no binders were found for the 9mer-HLA-B07 (Supplemental Table 6A). Predictions for UI-snRNP-derived peptides bound to HLA-DR1 (DRB1*0101), HLA-DR1 (DRB1*0102), HLA-DR4 (DRB1*0404) and HLA-DR4 (DRB1*0406) molecules showed three (38%–25% optimal binding), zero, zero, and one binders (35% optimal binding), respectively (Supplemental Table 6A). Interestingly, the binding of Dsg1-derived peptides to HLA-DR1 (DRB1*0101) was higher than that of the UI-snRNP-derived peptides as expressed by the optimal binding values. Peptide sequences are shown in Supplemental Table 6B.

BP/MCTD

Binding of alpha 1 type XVII collagen and dystonin to BP-associated HLA-DQ7 (DQB1*0301) molecules, as well as the binding of UI-snRNP to MCTD-associated HLA-DR1 (DRB1*0101) and the 9mer-HLA-B07 has been described in the previous sections of this study and is shown in Supplemental Tables 2, 4, 5 and 6.

BP/MCTD: Binding analysis of alpha 1 type XVII collagen peptides to MCTD-specific HLA-DR1 (DRB1*0101) resulted in 30 predicted peptides (40%–17% optimal binding), while the binding to the HLA-B07 molecules showed nine binders (59%-45% optimal binding) (Table 7). Moreover, the binding of dystonin-derived peptides to HLA-DR1 (DRB1*0101) showed 56 peptides (44%-17% optimal binding), and only one peptide (53% optimal binding) for the 9mer-HLA-B07 molecules (Supplemental Table 7A). Interestingly, three UI-snRNP-derived peptides were shown to bind to BP-associated HLA-DQ7 (DOB1*0301) molecules (33%-26% optimal binding). Here, the binding of BP- and MCTD-associated autoantigens to their disease molecules was similar to the cross-disease combination. Peptide sequences are presented in Supplemental Table 7B.

DH/MCTD

Analysis of DH-specific TGM3 transglutaminase 3 peptide binders resulted in 685 peptide sequences (Supplemental Table 8). Binding predictions for TGM3-derived peptides to HLA-DQ8 (DQA1*0301/ DQB1*0302) showed three binders (30%–28.5% optimal binding), whereas no binders were found for HLA-DQ2 (DQA1*0501/DQB1*0201) (Supplemental Table 8A). Studies of UI-snRNP/HLA-DR1 (DRB1*0101)/9mer-HLA-B07 have been described in the previous sections (Supplemental Tables 5–7).

DH/MCTD: Binding analysis of TGM3 to HLA-DR1 (DRB1*0101) alleles resulted in 17 binders (41%–17% optimal binding), but only one binder was found for the 9mer-HLA-B07 molecules (optimal binding 47.5%). In the opposite direction, the binding of UI-snRNP to HLA-DQ2 (DQA1*0501/ DQB1*0201) showed four peptides (40%–27% optimal binding) and no binding to HLA-DQ8 (DQA1*0301/DQB1*0302) molecules (Supplemental Table 8A). Peptide sequences are shown in Supplemental Table 8B.

OCP/MCTD

For a single disease model, analysis of OCP- and MCTD-specific peptides bound to their associated HLA molecules has been shown earlier (Supplemental Tables 3, 5–8).

OCP/MCTD: Several UI-snRNP-derived peptide epitopes were shown to bind to OCP-associated HLA-DQ7 (DQB1*0301) and HLA-DR4 (DRB1*0401) molecules. Thus, three peptides bound to HLA-DQ7 (33%–26% optimal binding), and six epitopes bound to HLA-DR4 molecules (29%–15% optimal binding) (Supplemental Table 9A, B). On the other hand, 30 OCP-derived alpha 1 type XVII collagen peptides bound to MCTD-associated HLA-DR1 (DRB1*0101) (40%-17% optimal binding) and nine alpha 1 type XVII collagen peptides bound to the 9mer-HLA-B07 (59%–45% optimal binding). In the case of β 4 integrin, 29 binders were detected for MCTD-associated HLA-DR1 (DRB1*0101) (37%-17% optimal binding) and five peptides were predicted to bind to the 9mer-HLA-B07 (62%-46% optimal binding). Peptide sequences are shown in Supplemental Table 9B.

MMP/MCTD

Analysis of MMP-specific β 4 integrin binding to MMP-associated HLA-DQ7 (DQB1*0301) molecules, as well as the binding of MCTD-related UI-snRNP peptides to MCTD-specific HLA-DR1 (DRB1*0101) and the 9mer-HLA-B07 has been described in the previous sections of this report (Supplemental Tables 1, 5–9).

MMP/MCTD: In the dual disease model, the binding of β 4 integrin to HLA-DR1 (DRB1*0101) resulted in 29 predicted epitopes (37%–17% optimal binding), while only five β 4 integrin-derived peptides were found to bind to the 9mer-HLA-B07 (62%–46% optimal binding), as shown in Supplemental Table 10A. On the other hand, three UI-snRNP-derived peptides bound to HLA-DQ7 (DQB1*0301) molecules (33%–26% optimal binding). For peptide sequences refer to Supplemental Table 10B. Thus, based on similar values for peptide binding in these two disease models, it is possible that autoantigen-derived epitopes from one disease interact with the HLA alleles of the second disease.

BP/DH

Analysis of BP-specific autoantigens alpha 1 type XVII collagen and dystonin, as well as of DH-related





TGM3 binding to HLA molecules known to be associated with BP (within a known disease model) has been performed and described in the previous sections of this study (Supplemental Tables 2, 4, 7 and 8).

BP/DH: Binding of type XVII collagen-derived peptides to DH-associated HLA-DQ8 (DQA1*0301/DQB1*0302) resulted in eight top binders (36%–25% optimal binding), and in one binder for HLA-DQ2 (DQA1*0501/DQB1*0201) molecules (optimal binding 45.89%) (Table 11A). For dystonin-related peptides, 12 were found to bind HLA-DQ8 (DQA1*0301/DQB1*0302) (47%–25% optimal binding) but none to HLA-DQ2 (DQA1*0501/DQB1*0201) molecules (Supplemental Table 11A). In the opposite direction, six TGM3-derived peptides were predicted to bind BP-associated HLA-DQ7 (DQB1*0301) molecules (45%–26% optimal binding). Peptide sequences are shown in Supplemental Table 11B.

Based on the predicted optimal binding data, these results suggest that epitopes derived from the autoantigenic proteins specific for one disease may bind to one or more HLA alleles associated with the second disease with various affinities. Most importantly, these observations show that while one peptide is capable of binding to its disease-associated HLA, a different peptide of the same autoantigen may bind to the HLA related to the second disease. This phenomenon may produce T cell recognition with different signaling outcomes, leading to the production of several autoantibody specificities characteristic for each of the induced disease conditions.

Discussion

It has been well documented that autoimmune diseases may coexist in the same patient, either sequentially or concurrently.^{50–64} PV, DH, BP, and SLE have all been reported in association with other autoimmune diseases as well as with each other. In particular, observations of dual autoimmunity in some patients who concurrently develop organ-specific and systemic disease have been reported.^{52,54,55,58,60,62,63} Multiple factors, including those of immunological, genetic, endocrine and environmental origin, contribute to the above condition. The immunogenetic mechanisms of this phenomenon present an intriguing unresolved problem of autoimmune predisposition, calling for development of prospective approaches of prediction and ultimately prevention of the disease. As a matter of fact, the involvement of T cells in immunopathogenesis of MCTD, PV and MMP has been well established. In MCTD, the role of anti-RNP-reactive T cells in autoantibody production has been demonstrated.^{65,66} In PV, it has been shown that B cells function as antigen-presenting cells stimulating Dsg3-specific CD4⁺ T helper (Th) cells to secrete cytokines such as interleukin (IL)-4, IL-6 and IL-10 which are required for proliferation of memory B cells and differentiation into antibody-producing plasma cells.^{67–69} Thus, the interplay between B and T cells seems to be critical, which is further supported by the finding that depletion of CD4⁺ T cells prevents antibody production.⁶⁹ Moreover, a clinical study showed that the mean frequency of Th2 CD4⁺ T cells was significantly elevated in PV patients with active disease, while no responses were detected for patients with disease in remission or controls.⁷¹ Characterization of autoreactive T-cells has led to identification of immunodominant T-cell epitopes and the repertoire of Dsg3- or Dsg1-specific T-cells at the clonal level.^{72,73} Lastly, the potential role for antigen-specific autoreactive T cells in the pathogenesis of MMP has also been addressed.^{74,75} Collectively, these observations suggest that T cell epitopes of the respective autoantigens may bind to their HLA molecules and trigger the activation of autoreactive T cells, which in turn would induce production of pathogenic autoantibodies.

In the present study, a bioinformatics-based search for potential epitopes restricted by HLA molecules associated with autoimmune mucocutaneous blistering diseases and systemic diseases has been undertaken in order to address the immunogenetics of the phenomenon of shared autoimmunity. The data across different disease combinations obtained in this report suggest that coexistence of two autoimmune diseases in the same patient might be triggered by the following mechanisms: 1) binding of each of the autoantigenic peptides related to a specific disease, to its specific HLA-associated molecules, or 2) binding of two epitopes derived from the same autoantigen to two HLA class II molecules, each associated with one disease. This binding may potentially result in differential signaling leading to the generation of disease-specific antibodies which contribute to the pathogenesis of both disease conditions. The data on the number of predicted peptide binding epitopes for each disease combination described in this study is



presented in Table 2. The highest number of binders was found for OCP while the lowest was in the case of DH, BP/MCTD and MMP/MCTD. Figure 1 shows disease models arranged by the number of predicted binders from other diseases. In each case, the point of reference is the HLA class II molecule. An analysis of in-model binding between HLA II molecules and associated protein within a given disease model is compared to the binding predictions for those same HLA II molecules against the set of proteins associated with the second disease model (cross-model analysis).

It should be noted that there are certain limitations to the methodology employed in this study. The binding matrices used are based on motifs developed from sequences known to bind to the MHC for which the matrix is developed. There are inherent problems which limit the suitability of the matrices for prediction of novel binding sequences, particularly the variable number of known binding sequences available for the development of binding matrices, in some cases quite small. Another limitation is that laboratory confirmation of binding predictions has yet to be completed. However, a recent publication has identified a peptide epitope derived from BP180 associated with IgA dermatosis that was shown to interact with monoclonal antibodies⁷⁶. Parts of BP180 mapped sequences SMDRIEKDRL and QEELWMFVRKKL in this publication were predicted by our Rankpep tool as follows: the WMFVRKKLM epitope (overlapping sequence underlined) is a predicted binder to HLA-DR1 (DRB1*0101) in the top 2% of ranked peptides.



Disease models and peptides bound from other models

Figure 1. Disease models and peptides bound from other models.



The same epitope is also in the top 2% of ranked peptides for HLA-DR4 (DRB1*0402), where potential binders should be concentrated.^{48,49} This makes <u>WMFVRKKLM</u> a potentially antigenic sequence for MCTD, PV and PF. The epitope <u>IEKDRLQGM</u>, although not predicted above the binding threshold, was also within the top 2% of predicted binders to HLA-DR4 (DRB1*0402).

Following pioneering biochemical studies which led to elucidation of peptide motifs associated with class I and class II MHC receptors,77-80 numerous analyses on the nature of the peptide/MHC interactions in the context of autoimmune/inflammatory diseases have been performed showing promiscuity of peptide binding to class II MHC molecules.^{81,82} In the present study, each autoantigen of interest was subjected to the cross-HLA II-binding analyzer tool resulting in multiple peptides which were ranked based on the probability of their binding to the respective HLA molecule. It is of interest that, in spite of the large number of sequences generated for each autoantigen (varying from 429 for UI-snRNP to 2641 for dystonin) the number of the actual binders above the threshold was specific for each peptide/HLA combination and resulted in either none, very few or multiple binders, as shown in Supplemental Tables 1-11. This is likely due to the polymorphism in the HLA pocket residues allowing specific peptide motifs to bind based on the size and hydrophobicity of the pockets, so that only the matching amino acids of the peptide would fit in.

Sequences of autoantigenic immunodominant epitopes for a number of blistering diseases have been previously reported.⁸³⁻⁹³ In the most studied model, PV, extensive analysis of peptide motifs bound to the susceptible alleles showed sequence specificities and variability in the HLA binding pockets.84-86 For example, at least nine previously identified stimulatory Dsg3 peptide sequences corresponding to the amino acid residues 96-112 (PFGIFVVDKNTGDINIT), 191-205 (NSKIAFKIVSQEPAG), 206-220 (TPM-FLLSRNTGEVRT), 252-266 (ECNIKVKDVNDN-FPM), 342-356 (SVKLSIAVKNKAEFH), 380-394 (GIAFRPASKTFTVQK), 763-777 (SGTMRTRH-STGGTNK), 810-824 (NDCLLIYDNEGADAT) and 963-977 (ERVICPISSVPGNLA) were shown to bind to PV-associated HLA-DR4 (DRB1*0402) and DQ5 (DQB1*0503) with a sliding window of up to three amino acids for the core residues.⁸⁴ In the present study, our binding analysis of Dsg3 epitope binding to DRB1*0402 revealed several sequences that were identical to the reported core and flanking residues within the peptide Dsg3 (flanking residues spaced, core underlined): NSK <u>IAFKIVSQE</u> PAG—191-205 (NSK<u>IAFKIVSQE</u>PAG); SGT <u>MRTRHSTGG</u> TNK-763-777 (SGT<u>MRTRHSTGG</u>TNK); and NDC <u>LLIYDNEGA</u> DAT—810-824 (NDC<u>LLIYDNEGA-</u> DAT) (ref. 82 and Supplemental Table 1B).

It is of interest to note that, according to Mouquet et al,⁸⁷ human Dsg1 was found to contain a T cell epitope capable of binding to PF-associated HLA Class II DRB1*0102 molecules. In contrast, no predicted binders derived from Dsg1 were detected for HLA-DR1 (DRB1*0102) in the present study (Supplemental Table 2). Also of interest, a recent study showed that the HLA-DR3 (DRB1*0301) molecule is linked to endemic PF in Tunisian patients.⁹² It would be of interest to analyze the peptide binding predictions on Dsg1 to this PF-associated HLA molecule in order to identify potential epitopes.

Importantly, no similar sequences were found in two different autoantigens specific for the two diseases, suggesting that promiscuous binding of the same epitope to the two HLA alleles associated with these diseases is unlikely to be the cause of shared autoimmunity. Rather, the data presented in this study demonstrates the possibility that an additional epitope derived from the same autoantigen binds to the HLA specific for the second disease. To our knowledge, this is the first study suggesting the potential mechanism of the induction of dual autoimmunity mediated by epitopes derived from a single autoantigen. In support of this mechanism, it is noteworthy that the affinity of the binding between the autoantigenic peptide epitope, the susceptible HLA and the TCR play an important role in T cell activation. Due to certain degree of promiscuity and specificity in peptide recognition by the HLA receptors, not a single binding affinity, but rather a range of affinities would account for the productive interaction between the peptide epitopes, HLA and the TCR, leading to T cell-mediated B cell activation and antibody secretion. Modeling of the bound conformation of PV-associated peptides revealed the role of DRB1*0402 in the selection of specific self-epitopes.⁸⁴ Several studies suggest that autoantigenic peptides do not necessarily bind to disease-associated HLA molecules with high affinity,

but rather within the intermediate range, thus allowing for the rescue of autoreactive T cells by virtue of weaker HLA/peptide/TCR interactions. In contrast, protective HLA proteins are more efficient binders of self-antigens, which results in elimination of autoreactive T cells.⁸⁵

It should be noted that peptide binding to HLA is facilitated by the interactions between the amino acid residues lining the groove of HLA molecules and the side chains of the bound peptide. The binding pockets of HLA class II, defined by the polymorphic β chain and the more conservative α chain of the $\alpha\beta$ heterodimer, share homology between some alleles but may also differ from other alleles as defined by size, charge and hydrophobicity.83 Thus, autoantigens may not share sequence homology, but still may encompass peptides able to bind different HLA due to the presence of certain amino acids which would fit to the binding pockets of the HLA molecules. In spite of this fact, the two peptides may share common binding motifs, dictated by structural requirements of the HLA pockets accommodating the peptides. Due to the degenerate nature of the HLA binding and TCR recognition, an observation which has been widely accepted for the past decade,⁹⁴ common binding motifs would be sufficient to allow peptide binding to different HLA molecules. However, in this case, it is possible that the recognition of the HLA/peptide complex by T cells will differ depending on the orientation of the TCR interacting with the amino acids facing away from the binding groove, and thus will result in differential activation by T cells.

Molecular and cellular mechanisms governing the concurrent or sequential presence of autoimmune blistering and systemic diseases in patients remain to be elucidated. Investigation of these mechanisms has been significantly delayed due to the lack of animal models in which both the systemic and organspecific autoimmune diseases can be induced. To this end, only a small number of experimental models of susceptibility to a single disease have been developed with limited success.^{91,95-97} Development of such animal models allowing investigation of the effects of the triggering factors on shared autoimmunity would require genetic manipulations enabling the introduction of elements of susceptibility, ie, human HLA and/ or autoantigen-specific TCR/BCR. Thus, a transgenic mouse model expressing two disease-associated



HLA and two TCR/BCR specific for each of the autoantigenic peptides would be most suitable for this purpose. In these mice, the experimental approach would include the administration of disease-inducing peptides, separately or concomitantly, and monitoring the animals for manifestations of each disease. In parallel, ex-vivo functional analysis including antigen-specific proliferation, cytokine secretion and antibody phenotyping, has to be performed. The in vitro binding studies employing purified HLA proteins and synthetic peptides, and the cellular assays with antigen-presenting cells and patient's lymphocytes would also be instrumental.

To our knowledge, this is the first study reporting extensive analysis of peptide binding predictions to a number of HLA alleles associated with autoimmune blistering and systemic diseases. Further studies of these patients, and especially of T and B lymphocytes administered into HLA-transgenic mice, will provide valuable information on cellular and molecular mechanisms critical for immunoregulation and production of pathogenic autoantibodies. Such studies have significant clinical ramifications and implications for the development of novel immune therapies targeting both autoimmune diseases. The elucidation of HLArestricted immune recognition mechanisms prompting the production of two or more disease-specific autoantibodies holds significant clinical ramifications and implications for the development of more effective treatment protocols. Currently, blistering and systemic diseases are treated by a number of protocols, including administration of IV Ig regiments, bone marrow transplantation, steroids (prednisone, prednisolone, dapsone, clobetasol), adjuvant drugs (azathioprine, mycophenolate mofetil, cyclosporine, rituximab) and emerging treatments by gene therapy or stem cell transplantation. These treatments are aimed at suppression or replacement of affected proteins and cells, with no specificity of targeting individual components.

Our findings provide important information on the identity of potential epitopes implicated in pathogenesis of blistering and systemic diseases, and specifically, on autoantibody reactivity in these patients. Potential therapies for these conditions could include targeted strategies to eliminate these autoantibodies and/or combination therapy with agents directed against several such specificities.

Abbreviations

AMBD, autoimmune mucocutaneous blistering diseases; APC, antigen-presenting cells; BP, bullous pemphigoid; DH, dermatitis herpetiformis; Dsg, desmoglein; HLA, human leukocyte antigens; IL, interleukin; MCTD, mixed connective tissue disease; MMP, mucous membrane pemphigoid; OCP, ocular cicatricial pemphigoid; PF, pemphigus foliaceus; PV, pemphigus vulgaris; RNP, ribonucleoprotein antigen; TCR, T cell receptor; Th, T helper cells.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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Supplementary Material

Table S1A. Rankpep analysis of PV- and MMP-derived autoantigens predicted to bind their HLA-associated alleles in a one- and two-disease model.

Disease 1	МНС	Performance*	Disease 2	Protein	Total sequences
PV	HLA-DQ8 (DQA1*0301/DQB1*0302)	0.72 ± 0.06	PV	desmoglein 3 preproprotein	991
	HLA-DR4 (DRB1*0402)	0.72 ± 0.04		desmoglein 3 preproprotein	991
	HLA-DR4 (DRB1*0404)	0.61 ± 0.05		desmoglein 3 preproprotein	991
	HLA-DQ8 (DQA1*0301/DQB1*0302)	0.72 ± 0.06	MMP	β4 integrin	1814
	HLA-DR4 (DRB1*0402)	0.72 ± 0.04		β4 integrin	1814
	HLA-DR4 (DRB1*0404)	0.61 ± 0.05		β4 integrin	1814
MMP	HLA-DQ7 (DQB1*0301)	na	MMP	β4 integrin	1814
	HLA-DQ7 (DQB1*0301)	na	PV	desmoglein 3 preproprotein	991



Total predicted binders	Threshold	High binding score	Low binding score	% optimal high	% optimal low
4	12.635	18.963	12.956	36.91	25.22
11	11.444	17.99	11.507	40.33	25.8
5	12.059	20.331	12.258	53.46	32.23
14	12.635	21.785	13.172	42.4	25.64
16	11.444	16.62	_	37.04	_
17	12.059	19.434	12.808	51.1	33.68
14	11.701	20.182	11.829	44.19	25.9
4	11.701	17.045	13.563	37.32	29.7

Notes: *Development and performance of matrices is described in detail in ref. 48; For other details refer to Methods section of this report.

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Disease	MHC	Threshold	Autoantigen	Total predicted binders	Top binders	Score	% optimal
PV-PV	HLA-DQ8 (DQA1*0301/	12.632	desmoglein 3	4	NNRCEMPRS	18.963 15.007	36.91
			highiopiorelli		WGIEGAHPE	13.2	25.69
					WVKFAKPCR	12.956	25.22
	HLA-DR4 (DRB1*0402)	11.444	desmoglein 3	11	TRYGRPHSG	17.99	40.33
			preproprotein		MRTRHSTGG	17.387	38.98
					IAFKIVSQE	15.149	33.96
					IKFVKNMNR	15.046	33.73
					VKYVMGRND	14.554	32.63
					ITYRISGVG	13.746	30.82
					LLIYDNEGA	12.572	28.19
					IAKITSDYQ	12.438	27.89
					ISRYRVQST	11.643	26.1
					VYFFTSGNE	11.59	25.98
					VRTLTNSLD	11,507	25.8
	HLA-DR4 (DRB1*0404)	12.059	desmoglein 3	5	ILVHGELRI	20.331	53.46
			preproprotein		FPMFRDSQY	16.921	44.49
					KNMNRDSTF	14.837	39.01
					IAFRPASKT	13.182	34.66
					INVREGIAF	12.258	32.23
PV-MMP	HLA-DQ8 (DQA1*0301/	12.632	β4 integrin	14	DERCHLDTT	21,785	42.4
	DQB1*0302)				ANRCKKAPV	20,134	39.19
					KEDHYMLRE	18,019	35.07
					WERPRRPNG	17,709	34.47
					DKPCSGRGE	17,191	33.46
					LRRSQMSPQ	16,831	32.76
					DRRCNTQAE	16,281	31.69
					QYRTQDYPS	14,323	27.88
					DLYILMDFS	14,223	27.68
					NAKAAGSRK	13,872	27.0
					WARLLLAAL	13,739	26.74
					NFKVKMVDE	13,515	26.31
					FHDLKVAPG	13,357	26.0
					LAKHNIIPI	13,172	25.64
		12.632	alpha 1 type XVII	œ	PGRPGIKGE	18,587	36.18
			collagen (BP180)		PAGPAGLPG	17,805	34.66
			- -		NADSGLKAE	16,228	31.59
					DRGPAGPPG	15,018	29.23
					WGPAPAWCP	14,162	27.56
					PKGDRGFPG	13,865	26.99
					DRLQGMAPA	13,846	26.95
					GAKGAMGPA	13.11	25.52
	HLA-DR4 (DRB1*0402)	11.444	β4 integrin	12	ICNGRGHCE	20,417	45.77





38.97 38.75 33.97 31.78 31.78 31.54 31.18 30.62 30.29	38.04 38.14 32.17 28.45	51.1 51.1 39.49 38.47 38.47 34.48 33.76 33.76 33.76 33.76 33.76	33.68 51.77 45.37 38.4 35.81 35.81 35.49	
17,384 17,283 15,15 14,177 14,176 14,068 13,509 13,509 13,509	16,967 15,227 14,347 12,689	12,007 15,006 15,007 15,005 13,151 13,151 12,033 12	12,808 19,689 17,255 13,619 13,497	20, 13, 20, 182 19.047 18.434 16.829 14.888 14.888
ILMDFSNSM VGFKEDHYM VRWKVTNNM VVRWKVTNN VKYWIQGDS LAGIMSRND IITIESQDG VCYGEGRYE LRTEVTSKM VRLLAKHNI VRRFHVQLS	ILSYGSSGG IRVRLQSAS IRVRLQSAS	RTGSFHIRR FRVDGDSPE KVCAYGAQG ILMDFSNSM LVFSTESAF YTMEGDGAP RRPNGDIVG INYSAIHPG IPVEGELLF IPIIPDIPI PVFRVRAQS FHYEADGAN YMLRENLMA PRCERPLQG LTADQDARG QRAFHDLKV	RLAFNVVSS RLLSTDASH YAGNGGLLG YLTSPDVRS RRAHSPAST KQSLTHGSS	LPPSGKPMG YRYTVKARN NYSAIHPGL APRSAKPAL YCACCKACL DVPAGTATL IRRVLDGGK
	4	17	ω	4
	alpha 1 type XVII collagen (BP180)	β4 integrin	alpha 1 type XVII collagen (BP180)	β4 integrin
	11.444	12.059	12.059	31.451
		HLA-DR4 (DRB1*0404)		HLA-DQ7 (DQB1*0301)
				MMP-MMM

Disease	MHC	Threshold	Autoantigen	Total predicted binders	Top binders	Score	% optimal
					FRQQPNAGK	14.639	32.05
					IYQVQLRAL	14.228	31.15
					YSDDVLRSP	13.589	29.75
					RAQSQEGWG	13,035	28.54
					SCVQCQAWG	12,643	27.68
					ADQDARGMV	12,108	26.51
					VIRRVLDGG	11,829	25.9
	HLA-DQ7 (DQB1*0301)	31.451	alpha 1 type XVII	14	IRRSILPYG	19.68	43.09
			collagen (BP180)		FDYSELASH	19.381	42.44
					STDASHSRG	16.697	36.56
					ILDANLPSH	16.398	35.9
					AGPAGLPGH	16.234	35.55
					VWSSTLPAG	15.634	34.23
					SLGAGGAFG	13.849	30.32
					IRGPPGPSG	13.625	29.83
					SSQSVSGTY	13.531	29.63
					NTNAYSAGS	13.391	29.32
					YRRAHSPAS	12,928	28.31
					LSSYLHTAG	12,403	27.16
					DIHSYGSSG	12,396	27.14
					APGPAGPAG	11,938	26.14
MMP-PV	HLA-DQ7 (DQB1*0301)	31.451	desmoglein 3	4	ATESGGAAG	17.045	37.32
			preproprotein		LVDYILGTY	15.092	33.05
					ITSDYQATQ	14.73	32.25
					YRLVVSGAD	13.563	29.7

Glutting et al



Table S1B. (Continued)

Disease 1	MHC	Performance	Disease 2	Protein	Total sequences	Total predicted binders	Threshold	High binding score	Low binding score	% optimal high	% optimal low
ЬF	HLA-DR1	0.75 ± 0.04	ЬF	desmoglein 1	1041	22	8.009	25.889	8.032	53.66	16.65
		0.72 ± 0.04		desmoglein 1	1041	0	33.00	I	I	Ι	I
	HLA-DR4	0.61 ± 0.05		desmoglein 1	1041	5	12.059	18.417	12.178	48.42	32.02
	(URB1 0404) HLA-DR4 (NDB1*0106)	na		desmoglein 1	1041	0	25.605	Ι	Ι	Ι	I
	(DRB1*0101) (DRB1*0101)	0.75 ± 0.04	ВР	alpha 1 type XVII collagen	1489	30	8.009	19.267	8.273	39.93	17.15
	HLA-DR1	0.75 ± 0.04		dystonin	2641	56	8.009	21,334	8,064	44.22	16.71
	(DRB1*0102) HLA-DR1 (DRB1*0102)	0.72 ± 0.04		alpha 1 type XVII collagen	1489	0	33.00	I	I	I	I
	HLA-DR1	0.72 ± 0.04		(BP180) dystonin (PD220)	2641	0	33.00	I	I	I	I
	(DRB1*0404) HLA-DR4 (DRB1*0404)	0.61 ± 0.05		alpha 1 type XVII collagen	1489	Q	12.059	19.689	13.157	51.77	34.59
	HLA-DR4	0.61 ± 0.05		(BP180) dystonin	2641	11	12.059	20,577	12,103	54.1	31.82
	(DRB1 0404) HLA-DR4 (DRB1*0406)	na		(BF230) alpha 1 type XVII collagen	1489	-	25.605	36.062	I	43.23	I
	HLA-DR4	na		(BP180) dystonin	2641	0	25.605	I	I	I	I
ВР	(DKB1-0400) HLA-DQ7 (DQB1*0301)	вп	ВР	(BF230) alpha 1 type XVII collagen	1489	4	11.701	19.68	11.938	43.09	26.14
	HLA-DQ7 (DOB1*0301)	na		(BF 100) dystonin (BP230)	2641	12	11.701	16,983	12,013	37.19	26.3
	HLA-DQ7 (DQB1*0301)	na	ЪF	desmoglein 1	1041	9	11.701	18.207	12.73	39.87	27.87

Peptide binding predictions of shared autoimmunity

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Table S2B.	Peptide sequences of PF- ¿	and BP-derived a	autoantigens predicte	d to bind their HLA-associated	d alleles in a one- ar	nd two-disea	ase model.
Disease	MHC	Threshold	Autoantigen	Total predicted binders	Top binders	Score	% optimal
РЕ-РЕ	HLA-DR1 (DRB1*0101)	8.009	desmoglein 1	22 (top ten seguences shown)	YEAMQSLQL YFCQKAYAY	25.889 18.86	53.66 39.09
					IKFAACRE	18.451	38.24
					IRTMNNFLD	16.935	35.1
					VFSMATFAG	16.001	33.16
					VFSMATFAG	16.001	33.16
					YKLKASAIS	14.479	30.01
					ICQEYSGTL	13.778	28.56
					WMAVIFFIS	11.917	24.7
					YCRALNSMG	11.759	24.37
	HLA-DR1 (DRB1*0102)	33	desmoglein 1	0			
	HLA-DR4 (DRB1*0404)	12.059	desmoglein 1	5	RVVSGAGVT	18.417	48.42
)		KPLDYEAMQ	13.233	34.79
					MAVIFFISG	12.663	33.29
					TASIGHMRS	12.326	32.41
					GAGSGALSG	12.178	32.02
	HLA-DR4 (DRB1*0406)	25.605	desmoglein 1	0			
PF-BP	HLA-DR1 (DRB1*0101)	8.009	alpha 1 type XVII	30 (top ten	LTGMPGIRG	19,267	39.93
	~		collagen (BP180)	sequences shown)	YRRAHSPAS	17,904	37.11
)		FTASPASIA	16,536	34.27
					YAELSSRIL	15.97	33.1
					MRGLPGAVG	15,095	31.29
					YGAIQGPPG	14.75	30.57
					LQGMAPAAG	14.65	30.36
					IKGEPGAPG	14,646	30.36
					LKAEANGDL	14,629	30.32
					WKWLLGLLL	12,638	26.19
		8.009	dystonin (BP230)	56 (top ten	FQAMENRML	21,334	44.22
				sequences shown)	YTALVTLMT	18,836	39.04
					IKQMEKDLA	17,855	37.01
					WHKEKADQL	17,566	36.41
					LAFLEAQAA	17,355	35.97
					YRAMVDSQQ	17,008	35.25
					IDKMVALAF	16,637	34.48
					RAAMQTQWS	16,464	34.12
					YIKFAGDSL	16,398	33.99
					YKSTIANLM	15,891	32.94
	HLA-DR1 (DRB1*0102)	33	alpha 1 type XVII	0			
		33	dvetonin (BP 100)	C			
	HI A-DR4 (DRB1*0404)	12 050	alnha 1 tvne XVII	۵ س	RISTRASH	19 689	51 77
		600.4	collagen (BP180)	D	VAGNGGLLG	17,255	45.37
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88. 56.4 57.2 57.4 57.5 57.5 57.5 57.5 57.5 57.5 57.5	9.23	3.09 2.44	6.56 5.9	5.55	4.23	0.32	9.83	9.03 0.20	8.31	7.16	7.14	6.14	7.19	4.04 2.45	2.42	1.5	1.43	8.46	7.53	7.36	7.16	6.41	ontinued)
13,606 13,619 13,619 13,619 13,497 13,497 14,606 15,619 17,561 17,561 17,561 17,561 17,561 17,561 17,561 12,983 12,993 12,993 12,993 12,993 12,909 12,103 33 33 12,103 33 34,07 35,09 36,09 37,09 38,09 39,09 30,09 31,2,99 32,09 33,09 33,09 33,09 33,09 34,09 35,09 36,09 37,09 38,09 39,09 30,09 31,09 32,09 33,09 33,09 <td< td=""><td>13,157 4</td><td>19.68 4 19.381 4</td><td>16.697 3 16.398 3</td><td>16.234 3</td><td>15.634 3</td><td>13.849 3</td><td>13.625 2</td><td>13.331 Z</td><td>12,928 2</td><td>12,403 2</td><td>12,396 2</td><td>11,938 2</td><td>16,983 3 4 E 04 2 2</td><td>13.913 3 14.818 3</td><td>14,805 3</td><td>14,386 3</td><td>14,356 3</td><td>12,997 2</td><td>12,573 2</td><td>12,495 2</td><td>12,406 2</td><td>12.06 2 12.013 2</td><td></td></td<>	13,157 4	19.68 4 19.381 4	16.697 3 16.398 3	16.234 3	15.634 3	13.849 3	13.625 2	13.331 Z	12,928 2	12,403 2	12,396 2	11,938 2	16,983 3 4 E 04 2 2	13.913 3 14.818 3	14,805 3	14,386 3	14,356 3	12,997 2	12,573 2	12,495 2	12,406 2	12.06 2 12.013 2	
YLTSPDVRS RRAHSPAST KQSLTHGSS IALAEEVRK KQMEKDLAF MVLFQEESG FEFFNDAKE MALRNECSS IRASNVASI RQVFHALED FNINEAIEQ YDMHTEVTT VITENDISG ILAGNALQS RQIRTPLER	AAYNADSGL	IRRSILPYG FDYSELASH	STDASHSRG ILDANLPSH	AGPAGLPGH	VWSSTLPAG	SLGAGGAFG	UKGPPGPSG	NTNAVSG17	YRRAHSPAS	LSSYLHTAG	DIHSYGSSG	APGPAGPAG	FESYGHSSH MEDCHLACS	YRDTYHPLD	LTPSVTPAY	IEPQVHSRL	FAQTLHPSL	ITQSLNSGF	LLQRQKATV	LRHTVTARQ	ADFDFHTGL	ISPTGNEAM	
7	- C	4											12										
dystonin (BP230)	alpha 1 type XVII collagen (BP180) dvstonin (BP230)	apticating (EV 200) alpha 1 type XVII collagen (BP180))										dystonin (BP230)										
12.059	25.605	11.701																					
	HLA-DR4 (DRB1*0406)	HLA-DQ7 (DQB1*0301)																					
		BP-BP																					

Table S2B	1. (Continued)						
Disease	MHC	Threshold	Autoantigen	Total predicted binders	Top binders	Score	% optimal
BP-PF	HLA-DQ7 (DQB1*0301)	11.701	desmoglein 1	6	YCRALNSMG	18,207	39.87
					SDGAIHSWA	17,857	39.1
					IEGVGSPAG	16,299	35.69
					YALAVRGSD	14,801	32.41
					LTEGVKTSG	12,806	28.04
					ISGGIGSSG	12.73	27.87



Table S3A	 Rankpep anal 	lysis of PV- and (OCP-derived	autoantigens p	predicted to bin	nd their HLA	-associated	alleles in a	a one- anc	d two-diseas	e model.
Disease 1	MHC	Performance	Disease 2	Protein	Total sequences	Total predicted binders	Threshold	High binding score	Low binding score	% optimal high	% optimal low
PV	HLA-DQ8 (DQA1*0301/ DQB1*0302)	0.72 ± 0.06	PV	desmoglein 3 preproprotein	991	4	12.635	18.963	12.956	36.91	25.22
	HLA-DR4 (DRB1*0402)	0.72 ± 0.04		desmoglein 3 preproprotein	991	11	11.444	17.99	11.507	40.33	25.8
	HLA-DR4 (DRB1*0404)	0.61 ± 0.05		desmoglein 3 preproprotein	991	ប	12.059	20.331	12.258	53.46	32.23
	HLA-DQ8 (DQA1*0301/ DQB1*0302)	0.72 ± 0.06	OCP	alpha 1 type XVII collagen (BP180)	1489	ω	12.632	18.587	13.11	36.18	25.52
	HLA-DQ8 (DQA1*0301/ DQB1*0302)	0.72 ± 0.06		β4 integrin	1814	14	12.632	21.785	13.172	42.4	25.64
	HLA-DR4 (DRB1*0402)	0.72 ± 0.04		alpha 1 type XVII collagen (BP180)	1489	4	11.444	16.967	12.689	38.04	28.45
	HLA-DR4 (DRB1*0402)	0.72 ± 0.04		β4 integrin	1814	16	11.444	16.62	I	37.04	I
	HLA-DR4 (DRB1*0404)	0.61 ± 0.05		alpha 1 type XVII collagen (BP180)	1489	Q	12.059	19.698	13.157	51.77	34.59
	HLA-DR4 (DRB1*0404)	0.61 ± 0.05		β4 integrin	1814	17	12.059	19.434	12.808	51.1	33.68
OCP	HLA-DQ7 (DQB1*0301)	ла	OCP	alpha 1 type XVII collagen (BP180)	1489	14	11.701	19.68	11.938	43.09	26.14
	HLA-DQ7 (DOR1*0301)	na		β4 integrin	1814	14	11.701	20.182	11.829	44.19	25.9
	HLA-DR4 (DRB1*0401)	0.68 ± 0.01		alpha 1 type XVII collagen (BP180)	1489	76	4.853	18.832	4.855	42.71	11.01
	HLA-DR4 (DRB1*0401)	0.68 ± 0.01		β4 integrin	1814	84	4.853	19.344	4.867	43.87	11.04
	HLA-DQ7 (DQB1*0301)	na	PV	desmoglein 3 preproprotein	991	4	11.701	17.045	13.563	37.32	29.7
	HLA-DR4 (DRB1*0401)	0.68 ± 0.01		desmoglein 3 preproprotein	991	43	4.853	20.296	4.991	46.03	11.32

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Disease	MHC	Threshold	Autoantigen	Total predicted binders	Top binders	Score	% optimal
PV-PV	HLA-DQ8 (DQA1*0301/	12.632	desmoglein 3	4	NNRCEMPRS	18.963	36.91
	DQB1°0302)		preproprotein			15.007	29.21 25.60
						12 956	25.03 25.22
	HI A-DR4 (DRB1*0402)	11 444	desmodlein 3	5	TRYGRPHSG	17.99	40.33
		-	prenronrotein	Ξ	MRTRHSTGG	17,387	38.98
					IAFKIVSOF	15 149	33.96
						15 046	23.73
							01.00 02.00
							52.03 20.03
						13.740	30.82
					LLIYDNEGA	12.572	28.19
					IAKITSDYQ	12.438	27.89
					ISRYRVQST	11.643	26.1
					VYFFTSGNE	11.59	25.98
					VRTLTNSLD	11,507	25.8
	HLA-DR4 (DRB1*0404)	12.059	desmoglein 3	5	ILVHGELRI	20.331	53.46
			preproprotein		FPMFRDSQY	16.921	44.49
			-		KNMNRDSTF	14.837	39.01
					IAFRPASKT	13.182	34.66
					INVREGIAF	12.258	32.23
PV-OCP	HLA-DQ8 (DQA1*0301/	12.632	alpha 1 type XVII	8	PGRPGIKGE	18.587	36.18
	DOB1*0302)		collagen (BP180)	1	PAGPAGL PG	17,805	34,66
					NADSGI KAF	16 228	31.59
					DRGPAGPPG	15,018	29.23
					WGPAPAWCP	14 162	27.56
						13,000	26.00
						10,000	20.03
						-0,040	Z0.90
					CANGAMGPA	10.11	70.07
		12.632	34 Integrin	14	DERCHLUI	21,785	42.4
					ANRCKKAPV	20,134	39.19
					KEDHYMLRE	18,019	35.07
					WERPRRPNG	17,709	34.47
					DKPCSGRGE	17,191	33.46
					LRRSQMSPQ	16,831	32.76
					DRRCNTQAE	16,281	31.69
					QYRTQDYPS	14,323	27.88
					DLYILMDFS	14,223	27.68
					NAKAAGSRK	13,872	27.0
					WARLIAAL	13 739	26.74
						13,515	26.31
						13,357	26.0
						13 172	25.64
		11 ЛЛЛ	Inha 1 two XVII	~		16 067	20.04
			מואים איש איש collagen (BP180)	4	LLTWLLLLG	10,301 15.227	34.14





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28.45 28.45 28.45 33.075 33.075 33.075 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 33.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.05 35.0535.0535.05 35.0535.0	25.94 51.77 45.37 38.4 35.81 35.81	511.0 51	43.09 43.09 42.44 (Conti
14,347 12,639 12,639 17,384 17,384 14,177 14,177 13,659 13,659 13,659 13,659 13,659 13,659 13,659 13,659 11,872 11,872 11,872 11,7388 11,7388 11,7388 11,7388 11,7388 11,7388 11,7388 11,7388 1	11,572 19,689 17,255 13,619 13,497	19,407 19,407 19,407 19,407 13,032 13,031 13,031 13,033 1,	19.68 19.381
IRVRLQSAS IHSYGSSGG ICNGRGHCE ILMDFSNSM VRWKVTNN VRWKVTNN VRWKVTNN VRWWQGDS LAGIMSRND IITIESQDG VCYGEGRYE LAGIMSRND IITIESQDG VCYGEGRYE LAGIMSRND IITIESQDG VCYGEGRYE LAGIMSRND IITIESQDG VCYGEGRYE LAGIMSRND IITIESQDG VCYGEGRYE LAGIMSRND IITIESQDG VCYGEGRYE LAGIMSRND IITIESQDG VCYGEGRYE LAGIMSRND IITIESQDG VCYGEGRYE LAGIMSRND IITIESQDG VCNMESSFQ LCNDRGRCS IVVMESSFQ LCNDRGRVLSN	LVRLLAKHN RLLSTDASH YAGNGGLLG YLTSPDVRS RRAHSPAST KQSLTHGSS	RTGSFHIRR FRVDGDSPE KVCAYGAQG ILMDFSNSM LVFSTESAF YTMEGDQGAP RRPNGDIVG INYSAIHPG IPVEGELLF IPIIPDIPI YVFRVRAQS FHYEADGAN YMLRENLMA PRCERPLQG LTADQDARG QRAFHDLKV	FDYSELASH
6	Q	15	1
β4 integrin	alpha 1 type XVII collagen (BP180)	β4 integrin	alpha 1 type XVII collagen (BP180)
11 . 444.	12.059	12.059	11.701
	HLA-DR4 (DRB1*0404)		HLA-DQ7 (DQB1*0301)
			OCP-OCP

Disease	МНС	Threshold	Autoantigen	Total predicted binders	Top binders	Score	% optimal
					STDASHSRG	16.697 16.308	36.56 35.0
					AGPAGI PGH	16 234	35.55 35.55
					VWSSTLPAG	15.634	34.23
					SLGAGGAFG	13.849	30.32
					IRGPPGPSG	13.625	29.83
					SSQSVSGTY	13.531	29.63
					NTNAYSAGS	13.391	29.32
					YRRAHSPAS	12,928	28.31
					LSSYLHTAG	12,403	27.16
					DIHSYGSSG	12,396	27.14
				•		11,938	26.14
			34 Integrin	<u>+1</u>		20.182	44.19
					YKY I VKAKN NYSAIHPGI	19.166 19.047	41.97 41.7
					APRSAKPAL	18,434	40.36
					YCACCKACL	16.829	36.85
					DVPAGTATL	15.922	34.86
					IRRVLDGGK	14.888	32.6
					FRQQPNAGK	14.639	32.05
					IYQVQLRAL	14.228	31.15
					YSDDVLRSP	13.589	29.75
					RAQSQEGWG	13,035	28.54
					SCVQCQAWG	12,643	27.68
					ADQDARGMV	12,108	26.51
					VIRRVLDGG	11,829	25.9
	HLA-DR4 (DRB1*0401)	4,853	alpha 1 type XVII	76 (top ten	YHNNMTTQS	18,832	42.71
			collagen (BP180)	sequences shown)	YRRAHSPAS	17.57	39.85
					YAGNGGLLG	16,995	38.55
					YGAIQGPPG	16,763	38.02
					HVWSSTLPA	16,655	37.78
					FRGIVGPPG	15,877	36.01
					YAKTASLGG	14,274	32.37
					WWKWLLGLL	14,086	31.95
					YAAENSDSF	13,332	30.24
					LRGEVGLPG	13,088	29.68
			B4 integrin	84 (top ten	YRTQDGTAQ	19.344	43.87
)	sequences shown)	YWIQGDSES	19.108	43.34
					FWWLIPLLL	14.965	33.94
					WWLIPLLLL	14.619	33.16
					KVQARTTEG	13.835	31.38
					LHRMTTTSA	13.518	30.66
					YMLRENLMA	13.312	30.19

Table S3B. (Continued).



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2.611 28.6	2.471 28.29	2.112 27.47	.537 26.17	7,045 37.32	5,092 33.05	1.73 32.25	3,563 29.7),296 46.03	5,321 34.75	1,638 33.2	3,127 29.77	3,066 29.63	2,754 28.93	2,398 28.12	2,309 27.92	.28 25.58).616 24.08
GWSGQTCNC 12	WRPDSTHLL 12	RRSQMSPQG 12	KMFQKTRTG 11	ATESGGAAG 17	LVDYILGTY 15	ITSDYQATQ 14	YRLWSGAD 13	WFEIQTDPR 20	FVKCQTLSG 15	LRFQVTDLD 14	WVKFAKPCR 13	YFSQKAFAC 13	YRVQSTPVT 12	AVWSITTLN 12	YLVTETYSA 12	FVKNMNRDS 11	YSASGSLVQ 10
				4				43 (top ten	sequences shown)								
				desmoglein 3	preproprotein			desmoglein 3	preproprotein								
				11.701				4,853									
				HLA-DQ7 (DQB1*0301)				HLA-DR4 (DRB1*0401)									
				OCP-PV													



Table S4A. Rankpep analysis of PV- and BP-derived autoantigens predicted to bind their HLA-associated alleles in a oneand two-disease model.

Disease 1	МНС	Performance	Disease 2	Protein	Total sequences
PV	HLA-DQ8 (DQA1*0301/DQB1*0302)	0.72 ± 0.06	PV	desmoglein 3 preproprotein	991
	HLA-DR4 (DRB1*0402)	0.72 ± 0.04		desmoglein 3 preproprotein	991
	HLA-DR4 (DRB1*0404)	0.61 ± 0.05		desmoglein 3 preproprotein	991
	HLA-DQ8 (DQA1*0301/DQB1*0302)	0.72 ± 0.06	BP	alpha 1 type XVII collagen (BP180)	1489
	HLA-DQ8 (DQA1*0301/DQB1*0302)	0.72 ± 0.06		dystonin (BP230)	2641
	HLA-DR4 (DRB1*0402)	0.72 ± 0.04		alpha 1 type XVII collagen (BP180)	1489
	HLA-DR4 (DRB1*0402)	0.72 ± 0.04		dystonin (BP230)	2641
	HLA-DR4 (DRB1*0404)	0.61 ± 0.05		alpha 1 type XVIÍ collagen (BP180)	1489
	HLA-DR4 (DRB1*0404)	0.61 ± 0.05		dystonin (BP230)	2641
BP	HLA-DQ7 (DQB1*0301)	na	BP	BP180 alpha 1 type XVII collagen	1489
	HLA-DQ7 (DQB1*0301)	na		dystonin (BP230)	2641
	HLA-DQ7 (DQB1*0301)	na	PV	desmoglein 3 preproprotein	991



Total predicted binders	Threshold	High binding score	Low binding score	% optimal high	% optimal low
4	12.635	18.963	12.956	36.91	25.22
11	11.444	17.99	11.507	40.33	25.8
5	12.059	20.331	12.258	53.46	32.23
8	12.632	18.587	13.11	36.18	25.52
12	12.632	24,137	13,043	46.98	25.39
4	11.444	16.967	12.689	38.04	28.45
28 6	11.444 12.059	16,557 19.698	12,753 13.157	37.12 51.77	28.59 34.59
11 14	12.059 11.701	20,577 19.68	12,103 11.938	54.1 43.09	31.82 26.14
12 4	11.701 11.701	16,983 17.045	12,013 13.563	37.19 37.32	26.3 29.7

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Table S4B. Peptide sequences of PV- and BP-derived autoantigens pr	

Disease	MHC	Threshold	Autoantigen	Total predicted binders	Top binders	Score	% optimal
Nd-Nd	HLA-DQ8 (DQA1*0301/ DQB1*0302)	12.632	desmoglein 3 preproprotein	4	NNRCEMPRS DAVCSSSPS WGIEGAHPE	18.963 15.007 13.2	36.91 29.21 25.69
	HLA-DR4 (DRB1*0402)	11.444	desmoglein 3 preproprotein	5	WVKFAKPCK TRYGRPHSG MRTRHSTGG IAFKIVSQE IKYVMGRND ITYRISGVG LLIYDNEGA IAKITSDYQ ISRYRVQST VYFFTSGNE VRTITNSLD	12.956 17.99 15.149 13.746 13.746 12.572 11.643 11.59 11.50	25.22 38.98 33.96 33.73 33.73 33.73 33.73 26.1 26.1 26.1 26.1 26.1
	HLA-DR4 (DRB1*0404)	12.059	desmoglein 3 preproprotein	Ω	ILVHGELRI FPMFRDSQY KNMNRDSTF IAFRPASKT INVRFGIAF	20.331 16.921 14.837 13.182	2005 53.46 39.01 39.01 39.01 30.01
PV-BP	HLA-DQ8 (DQA1*0301/ DQB1*0302)	12.632	alpha 1 type XVII collagen (BP180)	ω	PGRPGIKGE PAGPGIKGE NADSGLKAE DRGPAGPPG WGPAPAWCP PKGDRGFPG DRLQGMAPA GAKGAMGPA	15,587 17,805 15,018 13,865 13,865 13,846	26.99 26.99 26.99 26.99 26.95 26.95 26.95 26.95 26.95
		12.632	dystonin (BP230)	72	ITRAHAVAE IKRCKETSE PAYTPGFPS VSWHYLINE VQRVAKLRD AYRAAMQTQ DEIMALRNE VRGIRVPPE IVREKEAAE	24,137 26,169 15,507 15,481 15,481 15,481 15,471 15,033 15,033 15,033 15,033	46.98 335.14 30.13 30.13 27.26 27.
	HLA-DR4 (DRB1*0402)	11.444	alpha 1 type XVII collagen (BP180)	4	VLKGVVDPE ILSYMSSSG LLTWLLLLG IRVRLQSAS IHSYGSSGG	13,926 16,967 15,227 14,347 12,689	27.11 38.04 32.17 28.45





(Continued)							
31.43	14,356	FAQILHPSL					
31.5	14,386						
32.42	14,805	LTPSVTPAY					
32.45	14,818	YRDTYHPLD					
34.84	15.913	NFDGDHACS					
37.19	16,983	FESYGHSSH	12	dystonin (BP230)			
26.14	11,938	APGPAGPAG					
27.14	12,396	DIHSYGSSG					
27.16	12,403	LSSYLHTAG					
28.31	12,928	YRRAHSPAS					
29.32	13.391	NTNAYSAGS					
29.63	13.531	SSQSVSGTY					
29.83	13.625	IRGPPGPSG					
30.32	13.849	SLGAGGAFG					
34.23	15.634	VWSSTLPAG					
35.55	16.234	AGPAGLPGH					
35.9	16.398	ILDANLPSH					
36.56	16.697	STDASHSRG					
42.44	19.381	FDYSELASH		collagen (BP180)			
43.09	19.68	IRRSII PYG	14	alnha 1 tvne XVII	11 701	HI A-DO7 (DOR1*0301)	RP-RP
32.36	12,309	VII ENDISG					
34.02	12.94	YDMHTEVTT					
34.16	12,993	FNINEAIEQ					
36.41	13,846	RQVFHALED					
37.64	14,316	IRASNVASI					
41.66	15,845	MALRNECSS					
46.15	17,551	FEFFNDAKE					
47.28	17,983	MVLFQEESG					
54.1	20,577	KQMEKDLAF	11	dystonin (BP230)	12.059		
34.59	13,157	IALAEEVRK					
35.49	13,497	KQSLTHGSS					
35.81	13,619	REAHSPAST					
38.4	14,606	YI TSPDVRS					
11.10	19,089		٥	alpha 1 type XVII	RCU.21	HLA-UK4 (UKB1°0404)	
32.11	14,323	IARKKDYHA					
32.38	14,444	LLNFRNQLE					
32.94	14,692	LRRKRDNEE					
33.55	14,966	IIQLKPRNS					
33.86	15,105	FRKKMEKLM					
34.21	15.26	VRNIRLRLE					
35.38	15,783	LLRWTQEPQ	(
36.32	16.202	LSNLOSRFE	shown)				
36.95	16,481	IANRVORDS	sequences		-		
37.12	16.557	LLNWVDEMO	28 (top ten	dvstonin (BP230)	11,444		

Table S4B	ł. (Continued)						
Disease	МНС	Threshold	Autoantigen	Total predicted binders	Top binders	Score	% optimal
					ITQSLNSGF	12,997	28.46
					LLQRQKATV	12,573	27.53
					LRHTVTARQ	12,495	27.36
					ADFDFHTGL	12,406	27.16
					ISPTGNEAM	12.06	26.41
					IIDVLIATK	12,013	26.3
BP-PV	HLA-DQ7 (DQB1*0301)	11.701	desmoglein 3	4	ATESGGAAG	17,045	37.32
			preproprotein		LVDYILGTY	15,092	33.05
					ITSDYQATQ	14.73	32.25
					YRLVVSGAD	13,563	29.7



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Disease 1	МНС	Performance	Disease 2	Protein	Total sequences	Total predicted binders	Threshold	High binding score	Low binding score	% optimal high	% optimal low
PV	HLA-DQ8 (DQA1*0301/ DQB1*0302)	0.72 ± 0.06	PV	desmoglein 3 preproprotein	991	4	12.635	18.963	12.956	36.91	25.22
	HLA-DR4 (DRB1*0402)	0.72 ± 0.04		desmoglein 3 preproprotein	991	11	11.444	17.99	11.507	40.33	25.8
	HLA-DR4 (DRB1*0404)	0.61 ± 0.05		desmoglein 3 preproprotein	991	ى ک	12.059	20.331	12.258	53.46	32.23
	HLA-DQ8 (DQA1*0301/ DQB1*0302)	0.72 ± 0.06	MCTD	U1-snRNP	429	4	12.635	20.599	13.862	40.09	26.98
	HLA-DR4 (DRB1*0402)	0.72 ± 0.04		U1-snRNP	429	б	11.444	24.837	11.702	55.68	26.24
	HLA-DR4 (DRB1*0404)	0.61 ± 0.05		U1-snRNP	429	0	12.059	I	I	I	I
MCTD	HLA-DR1 (DRB1*0101)	0.75 ± 0.04	MCTD	U1-snRNP	429	ო	8.009	18.186	12.243	37.69	25.38
	9mer-HLA-B07	na		U1-snRNP	429	2	19.18	28.526	27.961	63.48	62.22
	HLA-DR1 /DDB1*0101)	0.75 ± 0.04	PV	desmoglein 3	991	18	8.009	21.359	8.202	44.27	17.00
	9mer-HLA-B07	na		desmoglein 3	991	0	19.18	I	I	I	I
				preproprotein							

Table S5A. Rankpep analysis of PV- and MCTD-derived autoantigens predicted to bind their HLA-associated alleles in a one- and two-disease model.



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Disease	MHC	Threshold	Autoantigen	Total predicted binders	Top binders	Score	% optimal
Vd-Vd	HLA-DQ8 (DQA1*0301/ DQB1*0302)	12.632	desmoglein 3 preproprotein	4	NNRCEMPRS DAVCSSSPS WGIEGAHPE	18.963 15.007 13.2 12 956	36.91 29.21 25.69 25.22
	HLA-DR4 (DRB1*0402)	11.444	desmoglein 3 preproprotein	£	TRYGRPHSG MRTRHSTGG IAFKIVSQE IKFVKNMNR VKYVMGRND ITYRISGVG LLIYDNEGA IAKITSDYQ ISRYRVQST	12.53 17.387 15.046 14.554 13.746 12.572 12.438 11.643	20.32 28.98 33.73 32.63 32.63 32.63 30.82 28.19 27.89 26.1
	HLA-DR4 (DRB1*0404)	12.059	desmoglein 3 preproprotein	Q	VYFFTSGNE VRTLTNSLD ILVHGELRI FPMFRDSQY KNMNRDSTF IAFRPASKT	11.59 11.507 20.331 16.921 14.837 13.182	25.98 25.8 53.46 39.01 34.66
PV-MCTD	HLA-DQ8 (DQA1*0301/ DQB1*0302)	12.632	U1-snRNP	4	INVREGIAF IKRIHMVYS RERARRERE FEDPRDAPP	12.258 20,599 16,863 16,611	32.23 40.09 32.82 32.33
	HLA-DR4 (DRB1*0402)	11.444	U1-snRNP	ю	PSEAGDAPP LKMWDPHND IEYEHERDM	13,862 24,837 13,188	26.98 55.68 29.57
MCTD-MCTD	HLA-DR4 (DRB1*0404) HLA-DR1 (DRB1*0101)	12.059 8.009	U1-snRNP U1-snRNP	0 %	VKGWKPKKL YKHADGKKI YCGIAPYIR	11,702 18.186 13.599	26.24 37.69 28.19
	9mer-HLA-B07	19.18	U1-snRNP	2	FVARVNYDT RPRRLGGGL	12.243 28.526 27.064	25.38 63.48
MCTD-PV	HLA-DR1 (DRB1*0101)	8.009	desmoglein 3 preproprotein	18	YFSQKAFAC YEQLQSVKL CRALNAQGL	21,359 21,359 20,238 18,448	02.22 44.27 41.95 38.24
					YRLVVSGAD FKKLAEISL YDNEGADAT IAFRPASKT	18,426 16,908 13,857 12,468	38.19 35.04 28.72 25.84
					YQATQKITY YTGPYTFAL YLMIDSKTA	12,421 12.22 11.791	25.74 25.33 24.44

P



23.68 23.68 23.08 21.7 20.5 19.48 19.48	17.0
11,427 11,135 10,792 9,889 9,397 9,214	8,202
CCSFIADDL LLLLLAPLL WLAVYFFTS WLAVYFFTS YVMGRNDGG ISSVPGNLA ITTLNATSA LRFQVTDLD	YQAIDEDTN
	0
	desmoglein 3 preproprotein
	9.18
	19
	9mer-HLA-B07





Table S6A. Rankpep analysis of PF- and MCTD-derived autoantigens predicted to bind their HLA-associated alleles in a one- and two-disease model.

Disease 1	МНС	Performance	Disease 2	Protein	Total sequences
PF	HLA-DR1 (DRB1*0101)	0.75 ± 0.04	PF	desmoglein 1	1041
	HLA-DR1 (DRB1*0102)	0.72 ± 0.04		desmoglein 1	1041
	HLA-DR4 (DRB1*0404)	0.61 ± 0.05		desmoglein 1	1041
	HLA-DR4 (DRB1*0406)	na		desmoglein 1	1041
	HLA-DR1 (DRB1*0101)	0.75 ± 0.04	MCTD	U1-snRNP	429
	HLA-DR1 (DRB1*0102)	0.72 ± 0.04		U1-snRNP	429
	HLA-DR4 (DRB1*0404)	0.61 ± 0.05		U1-snRNP	429
	HLA-DR4 (DRB1*0406)	na		U1-snRNP	429
MCTD	HLA-DR1 (DRB1*0101)	0.75 ± 0.04	MCTD	U1-snRNP	429
	9mer-HLA-B07	na		U1-snRNP	429
	HLA-DR1 (DRB1*0101)	0.75 ± 0.04	PF	desmoglein 1	1041
	9mer-HLA-B07	na		desmoglein 1	1041



Total predicted	Threshold	High binding	Low binding	% optimal high	% optimal low
22	8 009	25.889	8.032	53.66	16.65
0	33	_	-	_	-
5	12.059	18.417	12.178	48.42	32.02
0	25.605	_	-	_	-
3	8.009	18.186	12.243	37.69	25.38
0	33	_	_	_	_
0	12.059	_	_	_	_
1	25.605	25.891	_	35.35	_
3	8.009	18.186	12.243	37.69	25.38
2	19.18	28.526	27.961	63.48	62.22
22	8.009	25.889	16.001	53.66	33.16
0	19.18	-	-	-	-

Disease MHC Threshold Autoantigen Total predicted binders Score % optimal FF-FF HLA-DR1 (DR811'010) 8.009 desmoglein 2.0(10) ten sequences YEAMOSCAL 55.88 33.6 FF-FF HLA-DR1 (DR811'010) 8.009 desmoglein 2.0(10) ten sequences YEAMOSCAL 55.88 33.6 FF-FF HLA-DR1 (DR811'010) 8.009 desmoglein 2.0(10) ten sequences YEAMOSCAL 55.88 33.6 FHA-DR1 (DR811'0102) 33 desmoglein 0 YEAMOSCAS 14779 33.0 FHA-DR1 (DR811'0102) 33 desmoglein 5 YEAMOSCAS 14779 33.73 FHA-DR1 (DR811'010) 8.009 desmoglein 5 YEAMOSCAS 14779 33.73 FHA-DR1 (DR811'010) 8.009 U1'snRNP 0 YEAMOSCAS 14779 33.73 FHA-DR1 (DR81'0101) 8.009 U1'snRNP 3 YEAMOSCAS 14749 32.63 MCD-MCDB HLA-DR1 (DR81'0101) 8.009 U1'snRNP								
FFF HubBr1 (DRB110101) 8.009 desmoglein 1 2.1 (top ten sequences vEMCIQL 5.689 5.691 5.691 5.691 5.691 5.691 5.691 5.691 5.691 5.691 5.691 5.691 5.611 6.611 5.712 2.437 2.	Disease	MHC	Threshold	Autoantigen	Total predicted binders	Top binders	Score	% optimal
FI-UA-DFI TFU-LOR TFU-LOR 13,15 33,16 FI-MACTD HLA-DFI (DRB1*0404) 2.059 33,16 VFSMATFAG 14,373 33,36 FI-MACTD HLA-DFI (DRB1*0404) 12,059 desmoglein1 0 VFSMATFAG 14,373 33,36 FI-MACTD HLA-DFI<(DRB1*0404)	PF-PF	HLA-DR1 (DRB1*0101)	8.009	desmoglein 1	22 (top ten sequences	YEAMQSLQL	25.889	53.66
Frankure Basel					snown)	YFUUKAYAY	18.80	39.09
FH-MCTD IETIMINED 15 335 351 FMATEA 6001 336 VFSIMTFAG 6001 336 FMATEA 6001 3778 265 351 7778 265 FMATEA 6001 376 VFSIMTFAG 61001 336 FMADR1 CREVSGIL 13778 265 8565 45778 265 FMADR1 55 605 desmogleIn1 0 75 75 277 263 FMADR1 12.059 desmogleIn1 0 75 76 233 247 MAUFFFS 12.059 desmogleIn1 0 75 233 247 MCD-MCTD HLA-DR1 (DRB170101) 8.009 U1-snRNP 3 75 247 247 MCTD-MCTD HLA-DR1 (DRB170101) 8.009 U1-snRNP 3 756 247 3241 MCTD-MCTD HLA-DR1 (DRB170101) 8.009 U1-snRNP 3 756 247 247 MCTD-MCTD <td></td> <td></td> <td></td> <td></td> <td></td> <td>IKFAAACRE</td> <td>18.451</td> <td>38.24</td>						IKFAAACRE	18.451	38.24
PF-MCTD HLA-DR1 (DRB1*0102) 33 desmoglein 1 0 VFSMATFAG 6.001 33.6 VFSMATFAG 6.001 33.6 9.75						IRTMNNFLD	16.935	35.1
Fraction Constrained Constrained <thconstrained< th=""> <thconstrained< th=""> <t< td=""><td></td><td></td><td></td><td></td><td></td><td>VFSMATFAG</td><td>16.001</td><td>33.16</td></t<></thconstrained<></thconstrained<>						VFSMATFAG	16.001	33.16
F-MCTD HLA-DR1 (DR81'0102) 33 desmoglein 1 0 CCQENSGN 13,775 3265 HLA-DR1 (DR81'0102) 33 desmoglein 1 5 VCMALNSMG 11,759 24,37 FM-DR4 (DR81'0404) 12.059 desmoglein 1 5 VCMALNSMG 11,759 24,37 FM-DR4 (DR81'0404) 12.059 desmoglein 1 5 VCMALNSMG 11,759 24,37 FM-DR4 (DR81'0102) 33 U1-sinRNP 5 VCMALDSKM 12,759 23,33 MCD-MCTD HLA-DR1 (DR81'0102) 8,009 U1-sinRNP 3 VCMADGKK 18,166 37,69 MCD-MCTD HLA-DR1 (DR81'0101) 8,009 U1-sinRNP 1 VCMADGKKK 13,539 25,38 MCD-MCTD HLA-DR1 (DR81'01010) 8,009 U1-sinRNP 1 12,335 32,339 MCD-MCTD HLA-DR1 (DR81'01010) 8,009 U1-sinRNP 1 12,335 32,339 32,339 MCD-MCTD HLA-DR1 (DR81'01010) 8,009 U1-sinRNP 1 <t< td=""><td></td><td></td><td></td><td></td><td></td><td>VFSMATFAG</td><td>16.001</td><td>33.16</td></t<>						VFSMATFAG	16.001	33.16
Flux-DF1 (DRB1*0102) 33 besmoglein 1 6esmoglein 1 5 brown/ brown/ brown/ COCEVSGTI 13778 brown/ brown/ brown/ 23778 brown/ brown/ brown/ 23778 brown/ brown/ brown/ 23778 brown/ brown/ brown/ 23778 brown/ brown/ brown/ 23778 brown/ brown/ brown/ 23778 brown/ brown/ brown/ 23778 brown/ brown/ brown/ 23778 brown/ brown/ brown/ 23778 brown/ brown/ brown/ 23778 brown/ brown/ 23778 brown/ brown/ 23778 brown/ brown/ 23778 brown/ brown/ 23778 brown/ brown/ 23778 brown/ 23788 brown/ 23788 brown/ 23788 brown/ 23788 brown/ 23788 brown/ 23788 brown/ 23788 brown/ 23788 brown/ 23788 brown/ 23778 brown/ 23788 brown/ 23788 brown/ 23788 brown/ 23788 brown/ 23788 brown/ 23788 brorown/ 23788 brorowrowrown/						YKLKASAIS	14.479	30.01
HLA-DR1 (DRB1*0102) 33 HLA-DR4 (DRB1*0404) 12.059 12.059 desmoglein 1 desmoglein 1 5 5 KMANIFFIS KPUSCAGVT 11.759 34.73 24.37 24.32 PF-MCTD HLA-DR1 (DRB1*0404) 12.059 desmoglein 1 5 KPUSCAGVT 13.233 32.32 PF-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 VKHMDGKKI 12.359 23.37 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 VKHMDGKKI 13.239 22.03 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 0 VKHMDGKKI 13.599 28.19 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 0 VKHMDGKKI 13.599 28.19 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 0 VKHADGKKI 13.599 28.19 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 0 VKHADGKKI 12.439 25.36 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 1 27.69 28.19						ICQEYSGTL	13.778	28.56
HLA-DR1 (DRB1*0102) 33 HLA-DR4 (DRB1*0102) 33 desmoglein 1 0 5 VCRALINSIG 11.750 24.37 FH-DR4 (DRB1*0102) 12.059 desmoglein 1 5 RVVSGAGVT 18.417 48.42 FH-DR4 (DRB1*0101) 12.059 desmoglein 1 5 RVVSGAGVT 18.417 48.42 FH-DR4 (DRB1*0101) 8.009 U1-sinRNP 0 VKHADGKKI 18.18 32.02 HLA-DR4 (DRB1*0101) 8.009 U1-sinRNP 0 VKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0102) 33 U1-sinRNP 0 VKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-sinRNP 0 VKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-sinRNP 0 VKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DR1*0101) 8.009 U1-sinRNP 0 VKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DR1*010101) 8.009 U1-sinRNP<						WMAVIFFIS	11.917	24.7
HLA-DR1 (DRB1*10404) 33 12059 desmoglein 1 desmoglein 1 0 5 RVVSGAGY 18.417 48.42 FF-MCTD HLA-DR4 (DRB1*0404) 12.059 desmoglein 1 5 KPLDYEAM0 12.235 32.32 FF-MCTD HLA-DR4 (DRB1*0404) 25.605 desmoglein 1 0 KYVSGAGY 13.233 32.47 FF-MCTD HLA-DR1 (DRB1*0101) 8.009 U1:snRNP 3 VKHADGKKI 18.186 32.63 MCTD-MCTD HLA-DR1 (DRB1*0102) 33 U1:snRNP 3 VKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0102) 33 U1:snRNP 0 YKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1:snRNP 1 2 YKHADGKKI 13.599 26.36 MCTD-MCTD HLA-DR4 (DRB1*0101) 8.009 U1:snRNP 1 2 2 2 MCTD-MCTD HLA-DR4 (DRB1*0404) 12.059 2 2 2 2 2 2 2 2 2 2 2 2 2						YCRALNSMG	11.759	24.37
PF-MCTD HLA-DR4 (DRB1*0404) 12.059 desmoglein 1 5 RVSGGGVT 18.417 48.2 PF-MCTD HLA-DR4 (DRB1*0406) 25.605 desmoglein 1 0 263GSALSG 12.633 33.29 PF-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-sinRNP 3 U1-sinRNP 12.635 33.24 MAVIFFISG CCGASALSG 12.617 3.75 YKHADGKKI 13.759 28.19 MCTD-MCTD HLA-DR1 (DRB1*0102) 33 U1-sinRNP 0 YKHADGKKI 13.559 28.19 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.003 U1-sinRNP 0 YKHADGKKI 13.599 28.16 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.003 U1-sinRNP 0 YKHADGKKI 13.599 28.16 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.003 U1-sinRNP 1 YKHADGKKI 13.599 28.16 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.003 U1-sinRNP 1 YKHADGKKI 13.599 28.13 MCTD-FF		HLA-DR1 (DRB1*0102)	33	desmoglein 1	0			
PF-INCTD HLA-DR4 (DRB1*0406) 25.605 desmoglein 1 0 YKHADGKKI 18.186 37.233 34.79 PF-MCTD HLA-DR4 (DRB1*0101) 8.009 U1*sinRNP 3 VKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0102) 33 U1*sinRNP 3 VKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0102) 33 U1*sinRNP 0 YKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1*sinRNP 0 YKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1*sinRNP 1 YKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1*sinRNP 1 YKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1*sinRNP 2 YKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1*sinRNP 2 YKHADGKKI 18.186 37.69		HLA-DR4 (DRB1*0404)	12.059	desmoglein 1	5	RVVSGAGVT	18.417	48.42
PF-MCTD HLA-DR4 (DR81*0406) 25.605 desmoglein 1 0 MAVIFFISG 12.653 33.216 PF-MCTD HLA-DR1 (DR81*0101) 8.009 U1-snRNP 0 YKHADGKI 12.178 2.263 MCTD-MCTD HLA-DR1 (DR81*0101) 8.009 U1-snRNP 0 YKHADGKI 12.178 2.235 MCTD-MCTD HLA-DR1 (DR81*0102) 3.33 U1-snRNP 0 YKHADGKI 12.178 2.536 MCTD-MCTD HLA-DR1 (DR81*0102) 3.33 U1-snRNP 0 YKHADGKI 12.243 2.538 MCTD-MCTD HLA-DR1 (DR81*0101) 8.009 U1-snRNP 0 YKHADGKI 12.433 2.535 MCTD-MCTD HLA-DR1 (DR81*0101) 8.009 U1-snRNP 0 YKHADGKI 12.435 2.538 MCTD-PF HLA-DR1 (DR81*0101) 8.009 U1-snRNP 2 YKHADGKI 18.63 3.63 MCTD-PF HLA-DR1 (DR81*0101) 8.009 U1-snRNP 2 YKHADGKI 1.245 2.633 2.633 2.635 <td></td> <td></td> <td></td> <td></td> <td></td> <td>KPLDYEAMQ</td> <td>13.233</td> <td>34.79</td>						KPLDYEAMQ	13.233	34.79
Fr-MCTD HLA-DR4 (DRB110406) 25.605 desmoglein 1 0 TASIGHMRS 12.326 32.41 PF-MCTD HLA-DR1 (DRB110101) 8.009 U1*snRNP 3 VKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB110102) 33 U1*snRNP 0 YKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB110102) 33 U1*snRNP 0 YKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB110101) 8.009 U1*snRNP 0 YKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB110101) 8.009 U1*snRNP 0 YKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB110101) 8.009 U1*snRNP 0 YKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB110101) 8.009 U1*snRNP 0 YKHADGKKI 18.186 37.69 MCTD-MC HLA-DR1 (DRB110101) 8.009 U1*snRNP 2 YKHADGKKI 18.186 37.69 MCTD-						MAVIFFISG	12.663	33.29
PF-MCTD HLA-DR4 (DRB1*0406) 25.605 desmoglein 1 0 CGAGSGALSG 12.178 32.02 PF-MCTD HLA-DR1 (DRB1*0101) 8.009 U1*snRNP 3 U1*snRNP 3 YKHADGKKI 18.166 37.69 28.19 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1*snRNP 0 YKHADGKKI 18.166 37.69 28.19 MCTD-MCTD HLA-DR4 (DRB1*0406) 25.605 U1*snRNP 0 YKHADGKKI 18.166 37.69 28.19 MCTD-MCTD HLA-DR4 (DRB1*0406) 25.605 U1*snRNP 0 YKHADGKKI 13.268 33.48 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1*snRNP 1 YKHADGKIR 13.268 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1*snRNP 1 YKHADGKIR 13.268 37.69 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 U1*snRNP 2 YKHADGKIR 12.695 33.61 MCTD-FF HLA-DR1 (DRB1*0101) 8.009 U1*snRNP						TASIGHMRS	12.326	32.41
PF-MCTD HLA-DR4 (DRB1*0101) 3.009 U1:snRNP 0 YKHADGKK 18,186 37.69 33.15 33.15 33.15 33.15 33.15 33.15 33.15 33.15 33.15 33.15 33.15 33.16 33.16 37.69 33.16 32.16 37.69 33.16 32.16 32.16 32.16 32.16 32.16 32.16 32.16 32.16 32.16 32.16 32.16 32.16 32.16 32.						GAGSGALSG	12.178	32.02
PF-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 YKHADGKKI 18,186 37.69 HLA-DR1 (DRB1*0102) 33 U1-snRNP 0 YKHADGKKI 18,186 37.69 HLA-DR4 (DRB1*0404) 12.059 U1-snRNP 0 YKHADGKKI 18,186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0406) 25.605 U1-snRNP 0 YKHADGKKI 18,186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0406) 25.605 U1-snRNP 1 YKHADGKKI 18,186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 1 YKHADGKKI 18,186 37.69 MCTD-FF HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 YKHADGKKI 13.599 28.19 MCTD-FF HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 YKHADGKKI 28.66 28.38 MCTD-FF HLA-DR1 (DRB1*0101) 8.009 Gesmoglein 1 22 (top ten sequences YKLAAGKE 28.66 28.33 MCTD-FF HLA-DR1 (DRB1*		HLA-DR4 (DRB1*0406)	25.605	desmoglein 1	0			
McTD-MCTD HLA-DR1 (DRB1*0102) 33 U1-snRNP 0 YCGIAPYIR 13,599 28:19 23:38 23:	PF-MCTD	HLA-DR1 (DRB1*0101)	8.009	U1-snRNP	0	YKHADGKKI	18,186	37.69
HLA-DR1 (DRB1*0102) 33 HLA-DR4 (DRB1*0102) 33 HLA-DR4 (DRB1*0102) 13 2.0.590 U1-snRNP 0 U1-snRNP FVARWYDT 12.243 25.38 33.35 25.38 35.35 25.605 11-snRNP 0 U1-snRNP 1 20.01 35.35 20.15 20.01 35.35 20.15 20.01 35.35 20.36 21.505 20.15 20.01 <						YCGIAPYIR	13,599	28.19
HLA-DR1 (DRB1*0102) 33 HLA-DR4 (DRB1*0101) 0 12.059 U1-snRNP 0 0 SRYDERPGP 25,891 35.35 HLA-DR4 (DRB1*0101) 8.009 U1-snRNP 1 0 SRYDERPGP 25,891 35.35 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 1 1 3 YKHADGKKI 18.186 37.69 28.19 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 YKHADGKKI 18.186 37.69 28.19 35.35 MCTD-FF HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 RPRLGGGL 28.589 55.366 53.48 MCTD-FF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences YEAMQSLOL 27.961 52.36 MCTD-FF HLA-DR1 (DRB1*0101) 8.009 MCFMANNT 12.243 25.68 55.1 MCTD-FF HLA-DR1 (DRB1*011) 2.009 MEFAMANTELD 12.273 27.961 52.361 MCTD-FF HLA-DR1 (DRB1*011) 2.009 MEFAMANTELD <						FVARVNYDT	12,243	25.38
HLA-DR4 (DRB1*0404) 12.059 U1-snRNP 0 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 1 55.891 35.35 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 1 55.801 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 1 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 761 25.38 26.19 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 761 22.23 23.66 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences 7FCQKAYNY 12.543 53.66 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences 7FCQKANN 12.413 33.16 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences 7FCQKANN 13.473 33.16 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequ		HLA-DR1 (DRB1*0102)	33	U1-snRNP	0			
HLA-DR4 (DRB1*0406) 25.605 U1-snRNP 1 SRYDERPGP 25,831 35.35 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 VKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 PKHADGKKI 18.186 37.69 Mer-HLA-B07 19.18 U1-snRNP 2 PRRUNYDT 12.243 25.38 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 PRRUGGGI 28.53.66 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences YEAMOSLOL 25,889 53.66 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences YEAMOSLOL 25,889 53.66 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 YEAMOSLOL 25,889 53.66 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 YEAMOSLOL 25,889 53.66 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 YEAMOSLOL 25,839 <t< td=""><td></td><td>HLA-DR4 (DRB1*0404)</td><td>12.059</td><td>U1-snRNP</td><td>0</td><td></td><td></td><td></td></t<>		HLA-DR4 (DRB1*0404)	12.059	U1-snRNP	0			
MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 YKHADGKKI 18.186 37.69 28.19 9mer-HLA-B07 19.18 U1-snRNP 2 PVCGIAPYIR 13.599 28.19 25.38 9mer-HLA-B07 19.18 U1-snRNP 2 RPRR_GGCL 28.526 63.48 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences YEAMORCL 27.961 62.22 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences YEAMORCL 25.68 33.09 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences YEAMORCL 27.961 62.22 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences YEAMORCL 18,451 38.24 IRTMNNFLD KFAAACRE 18,451 38.24 18,451 38.24 33.16 Meu-HLA-B07 19.18 desmoglein 1 27 (top ten sequences YEALASAIS 14,479 30.01		HLA-DR4 (DRB1*0406)	25.605	U1-snRNP	-	SRYDERPGP	25,891	35.35
McTD-PF HLA-B07 19.18 U1-snRNP 2 YCGIAPYIR 13.599 28.19 McTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences APRDPIPYL 27.961 62.22 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences YEAMOSLQL 25,889 53.66 MortD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences YEAMOSLQL 25,889 53.66 MortD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences YEAMOSLQL 25,889 53.66 MortD-PF HLA-DR1 (DRB1*0101) 8.009 16,001 33.16 YFCQKAYNY 18.451 38.24 MortHLA YEAMOSCOL 26,001 33.16 YFCMAYSAIS 14,479 30.01 MortHLA-B07 19.18 desmoglein 1 0 YFCMAYSAIS 14,479 32.65 MortHLA-B07 19.18 desmoglein 1 0 YFCMAYSAIS 11,477 23.37 MortHLA-B07 19.18 desmoglein 1 0 YFCMAYSAIS 11,477 23	MCTD-MCTD	HLA-DR1 (DRB1*0101)	8.009	U1-snRNP	ო	YKHADGKKI	18.186	37.69
9mer-HLA-B07 19.18 U1-snRNP 2 FVARVNYDT 12.243 25.38 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences PEAMOSLOL 27.961 62.22 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences PEAMOSLOL 25,889 53.66 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences PEAMOSLOL 25,889 53.66 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences PEAMOSLOL 25,889 53.66 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences PEAMOSLOL 23.66 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 H451 33.16 Pier-HLA-B07 19.18 desmoglein 1 0 11,477 24.37 9mer-HLA-B07 19.18 desmoglein 1 0 24.37 24.37						YCGIAPYIR	13.599	28.19
9mer-HLA-B07 19.18 U1-snRNP 2 RPRRLGGL 28.526 63.48 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences FAMOSLQL 25,889 53.66 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences YEAMOSLQL 25,889 53.66 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences YEAMOSLQL 25,889 53.66 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences YEAMOSLQL 25,889 53.66 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 iff and						FVARVNYDT	12.243	25.38
MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences APRDPIPYL 27.961 62.22 MCTD-PF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences YEAMOSLQL 25,889 53.66 YFCQKAYAY 18.86 39.09 IKFAAACRE 18,451 38.24 YKLKASAIS YKLKASAIS 14,479 30.01 33.16 YKLKASAIS YKLKASAIS 14,479 30.01 33.16 YMAVIFFIS YKLKASAIS 14,479 30.01 24.7 Omer-HLA-B07 19.18 desmoglein 1 0 24.37		9mer-HLA-B07	19.18	U1-snRNP	2	RPRRLGGGL	28.526	63.48
MCTD-FF HLA-DR1 (DRB1*0101) 8.009 desmoglein 1 22 (top ten sequences reamoning in the second reamoning in the sequences reamoning in the second reamoning						APRDPIPYL	27.961	62.22
Shown) Shown) YFCQKAYN 18.86 39.09 IRTMNNFLD 16,935 35.1 18,451 38.24 IRTMNNFLD 16,935 35.1 16,001 33.16 YKLKASAIS 14,779 30.01 16,001 33.16 YKLKASAIS 14,479 30.01 10,017 24.7 YKLKASAIS 11,917 24.7 YMAVIFFIS 11,759 24.37 9mer-HLA-B07 19.18 desmoglein 1 0 11,497 23.83	MCTD-PF	HLA-DR1 (DRB1*0101)	8.009	desmoglein 1	22 (top ten sequences	YEAMQSLQL	25,889	53.66
IKFAACRE 18,451 38.24 IRTMNNFLD 16,935 35.1 VFSMATFAG 16,001 33.16 YKLKASAIS 14,479 30.01 ICQEYSGTL 13,778 28.56 WMAVIFFIS 11,917 24.7 YVMGNNPAD 11,759 24.37 9mer-HLA-B07 19.18 desmoglein 1 0					shown)	YFCQKAYAY	18.86	39.09
IRTMNNFLD 16,935 35.1 VFSMATFAG 16,001 33.16 YKLKASAIS 14,479 30.01 ICQEYSGTL 13,778 28.56 WMAVIFFIS 11,917 24.7 YCRALNSMG 11,759 24.37 YVMGNNPAD 11,497 23.83						IKFAACRE	18,451	38.24
WESMATFAG 16,001 33.16 YKLKASAIS 14,479 30.01 YKLKASAIS 14,479 30.01 ICQEYSGTL 13,778 28.56 WMAVIFFIS 11,917 24.7 YCRALNSMG 11,759 24.37 9mer-HLA-B07 19.18 desmoglein 1 0						IRTMNNFLD	16,935	35.1
YKLKASAIS 14,479 30.01 ICQEYSGTL 13,778 28.56 WMAVIFFIS 11,917 24.7 YCRALNSMG 11,759 24.37 YVMGNNPAD 11,497 23.83 9mer-HLA-B07 19.18 desmoglein 1 0						VFSMATFAG	16,001	33.16
ICQEYSGTL 13,778 28.56 WMAVIFFIS 11,917 24.7 YCRALNSMG 11,759 24.37 YVMGNNPAD 11,497 23.83 9mer-HLA-B07 19.18 desmoglein 1 0						YKLKASAIS	14,479	30.01
WMAVIFFIS 11,917 24.7 YCRALNSMG 11,759 24.37 YVMGNNPAD 11,497 23.83 9mer-HLA-B07 19.18 desmoglein 1 0						ICQEYSGTL	13,778	28.56
YCRALNSMG 11,759 24.37 YVMGNNPAD 11,497 23.83 9mer-HLA-B07 19.18 desmoglein 1 0						WMAVIFFIS	11,917	24.7
YVMGNNPAD 11,497 23.83 9mer-HLA-B07 19.18 desmoglein 1 0						YCRALNSMG	11,759	24.37
9mer-HLA-B07 19.18 desmoglein 1 0						YVMGNNPAD	11,497	23.83
		9mer-HLA-B07	19.18	desmoglein 1	0			



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Table S7A.	. Rankpep analysi	is of BP- and MC	CTD-derived	autoantigens	predicted to bi	nd their HLA	-associated a	alleles in a	one- and t	wo-diseas	e model.
Disease 1	MHC	Performance	Disease 2	Protein	Total sequences	Total predicted binders	Threshold	High binding score	Low binding score	% optimal high	% optimal low
ВР	HLA-DQ7 (DQB1*0301)	в	ВР	alpha 1 type XVII collagen (BP180)	1489	14	11.701	19.68	11.938	43.09	26.14
	HLA-DQ7 (DQB1*0301)	na		dystonin (BP230)	2641	12	11.701	16,983	12,013	37.19	26.3
	ĤLA-DQ7 (DQB1*0301)	na	MCTD	ÙI-snRŇP	429	с	11.701	15.071	11.87	33	25.99
MCTD	HLA-DR1 (DRB1*0101)	0.75 ± 0.04	MCTD	U1-snRNP	429	с	8.009	18.186	12.243	37.69	25.38
	9mer-HLA-B07	na		U1-snRNP	429	2	19.18	28.526	27.961	63.48	62.22
	HLA-DR1 (DRB1*0101)	0.75 ± 0.04	ВР	alpha 1 tvne XVII	1489	30	8.009	19.267	8.273	39.93	17.15
				collagen (BP180)							
	HLA-DR1 (DRB1*0101)	0.75 ± 0.04		dystonin (BP230)	2641	56	8.009	21,334	8,064	44.22	16.71
	9mer-HLA-B07	na		àlpha 1 type XVII	1489	G	19.18	26.397	20.217	58.74	44.99
				collagen (BP180)							
	9mer-HLA-B07	na		dystonin (BP230)	2641		19.18	23.701	I	52.74	I

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Disease MHC Trvshold Autoantigen Total prodicted Top binders Soore % optimal B ⁻ B ^P HLADO7 (DGB110301) 11.701 aphra 1 type XVII 14 ETYSLEASH 19381 42.44 B ⁻ B ^P HLADO7 (DGB110301) 11.701 aphra 1 type XVII 14 ETYSLEASH 19381 42.44 BP-BP HLADO7 (DGB110301) 11.701 oilagen (BP180) 14 ETYSLEASH 19381 42.44 BP-BP HLADO7 (DGB110301) 11.701 oilagen (BP180) 14 ETYSLEASH 19381 42.53 BP-MCTD HLADO7 (DGB110301) 11.701 LIDALINESH 10.83 22.43 BP-MCTD HLADO7 (DGB110301) 11.701 U1-smRNP 12.33 22.43 22.43 22.43 22.43 22.43 22.43 22.43 22.43 22.43 22.43 22.44 22.44 22.44 22.44 22.44 22.44 22.44 22.44 22.44 22.44 22.44 22.44 22.44 22.44 22.44								
BP-BP HA-DG7 (DGB1'0301) 11.701 alpha 1 (pe K) 14 FD75LASH 1008 4204 PA PA <td< th=""><th>Disease</th><th>MHC</th><th>Threshold</th><th>Autoantigen</th><th>Total predicted binders</th><th>Top binders</th><th>Score</th><th>% optimal</th></td<>	Disease	MHC	Threshold	Autoantigen	Total predicted binders	Top binders	Score	% optimal
Production EDYSELSH 19.381 24.44 Collagen (BP180) FDYSELSH 19.381 55.5 CALL CLAULPSH 6.53 55.5 55.5 CALL CALL CALLSH 13.33 20.5 CALL CALL CALL 55.5	BP-BP	HLA-DQ7 (DQB1*0301)	11.701	alpha 1 type XVII	14	IRRSILPYG	19.68	43.09
Physical Standard Standard				collagen (BP180)		FDYSELASH	19.381	42.44
Income Income<						STDASHSRG	16.697	36.56
BP-MCTD HLA-DG7 (DGB11'0301) 11.701 U1-sinRN 25.33 2						ILDANLPSH	16.398	35.9
Product Process State						AGPAGLPGH	16.234	35.55
BP-MCTD HLA-DO7 (DOB110301) 11.701 U1-snRNP 32.55 32.65 BP-MCTD HLA-DO7 (DOB110301) 11.701 U1-snRNP 32.65 32.65 BP-MCTD HLA-DO7 (DOB110301) 11.701 U1-snRNP 32.65 32.65 BP-MCTD HLA-DO7 (DOB110301) 11.701 U1-snRNP 32.755 14.83 32.465 BP-MCTD HLA-DO7 (DOB110301) 11.701 U1-snRNP 32.755 14.816 32.455 MCTD-MCTD HLA-DO7 (DOB110301) 11.701 U1-snRNP 3 NFDGDHACS 16.983 32.455 MCTD-MCTD HLA-DO7 (DOB110301) 11.701 U1-snRNP 3 NFDGDHACS 16.983 32.455 MCTD-MCTD HLA-DO7 (DOB11031) 11.701 U1-snRNP 3 NFDGLAPACS 14.916 32.655 MCTD-MCTD HLA-DO7 (DOB11031) 11.701 U1-snRNP 3 NFDGLAPACS 14.916 37.655 MCTD-MCTD HLA-DO7 (DCB11031) 8.009 U1-snRNP 3 NFDRLAPACS 16.917						VWSSTLPAG	15.634	34.23
Procredent Socs/Socry 3325 2063 NTANYSAGS Socs/Socry 3331 2063 NTANYSAGS NTAPULOR 1000 2403 2413 NTAPULOR HUA-DOT U1-SIRNP 3 1100RUNSGF 2403 NCTD-MCTD HLA-DR1 (DRB11010) 8.009 U1-SIRNP 2405 2405 MCTD-MCTD HLA-DR1 (DRB11010) 8.009 U1-SIRNP 2405 2405 MCTD-MCTD HLA-DR1 (DRB1100) 8.009 U1-SIRNP 2405 2405 MCTD-MCTD HLA-DR1 (DRB11010) 8.009 U1-SIRNP 2405 <td< td=""><td></td><td></td><td></td><td></td><td></td><td>SLGAGGAFG</td><td>13.849</td><td>30.32</td></td<>						SLGAGGAFG	13.849	30.32
Premention Presson 2353 2053 Premention Premention Premention 2333 2331 2333 2333 2333 2333 2333 2333 2333 2333 2333 2333 2333 2331 2333 2333 2333 2333 2343 2343 2343 2343 2344 2345 2343 2344 2343 2344 2345 2343 2344 2345 2346 <						IRGPPGPSG	13.625	29.83
Price MinWrSocs 3331 2932 Price University 2403 2716 Price University 2203 2716 Price Price 1987 2203 2716 Price Price Price 2403 2736 Price Price Price 2573 2446 Price Price Price 2573 246 Price Price Price 2573 2736 Price Price Price 2406 2716 Price Price Price 2406 2736						SSQSVSGTY	13.531	29.63
PENCTD HLA-DG7 (DQB1*0301) 11.701 U1-snRN 12.557 ESYCHASSA 12.338 26.14 PE-MCTD HLA-DG7 (DQB1*0301) 11.701 U1-snRN 12.95 ESYCHASSA 12.338 26.41 PE-MCTD HLA-DG7 (DQB1*0301) 11.701 U1-snRN 12.95 EAGTHHPSL 12.365 22.395 27.14 PP-MCTD HLA-DG7 (DQB1*0301) 11.701 U1-snRN 12.96 EAGTHHPSL 12.365 22.365 PMCTD-MCTD HLA-DG7 (DQB1*0301) 11.701 U1-snRN 3 WRPARLGGG 27.75 27.75 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRN 3 WRPARLGGG 27.75 27.75 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRN 3 YRHALGGG 27.76 27.76 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRN 3 YRHALGGG 27.76 27.76 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRN 3 YRHALGGGG 27.76 27.79						NTNAYSAGS	13.391	29.32
BP-MCTD HLA-DG7 (D0B1'0301) 11.701 U1-snRNP 27.16 D1HSYGSSG 2.403 27.19 BP-MCTD HLA-DG7 (D0B1'0301) 11.701 U1-snRNP 1.4818 32.45 BP-MCTD HLA-DG7 (D0B1'0301) 11.701 U1-snRNP 1.4818 32.45 BP-MCTD HLA-DG7 (D0B1'0301) 11.701 U1-snRNP 1.4818 32.45 BP-MCTD HLA-DG7 (D0B1'0301) 11.701 U1-snRNP 3.55 EPOVINERL 1.4365 31.5 BP-MCTD HLA-DG7 (D0B1'0301) 11.701 U1-snRNP 3 SRFSGKPRG 1.2997 27.65 MCTD-MCTD HLA-DR1 (DRB1'0101) 8.009 U1-snRNP 3 SRFSGKPRG 1.8765 27.65 MCTD-MCTD HLA-DR1 (DRB1'0101) 8.009 U1-snRNP 3 SRFSGKPRG 1.8765 27.65 MCTD-MCTD HLA-DR1 (DRB1'0101) 8.009 U1-snRNP 3 SRFSGKPRG 1.8765 27.69 27.65 MCTD-BP HLA-DR1 (DRB1'0101) 8.009 U1-snRNP 3 SRFSGKPRG 1.8765 27.69 27.65 27.65 27.65						YRRAHSPAS	12,928	28.31
BP-MCTD HLA-DQ7 (DQB1*0301) 12 DHSYCSSG 12336 27.14 PEPCPAGFAG 1938 27.14 PEPCPAGFAG 1938 27.14 PEPCPAGFAG 1938 27.14 PEPCPAGFAG 16983 37.19 PEPCPAGFAG 27.14 PEPCPAGFAG 27.14 PEPCPAGFAG 27.15 27.24 PEPCPAGFAG 27.16 27.45 27.75 27.55 27.95 27.96 27.16 27.46 27.75 27.75 27.75 27.75 27.75 27.75 27.75 27.92 27.76 27.76 27.76 27.76 27.76 27.76 27.75 27.92 27.76 27.75 27.92 27.76 27.76 27.76 27.76 27.76 27.76 27.76 27.76 27.76 27.76 27.76 27.76 27.76						LSSYLHTAG	12,403	27.16
Proprint dystonin (BP230) 12 RFGPMCPAG 1,398 26,14 April RESYCHSSH 6,883 37,19 37,19 RESYCHSSH RESYCHSSH 1,805 32,45 RESYCHSSH 1,805 32,45 RESYCHSSH 1,805 32,45 RESYCHSRSH 1,305 31,5 RESYCHSR 1,701 U1-snRvP 3 RCTD-MCTD HLA-DG7 (DGB1*0301) 11,701 U1-snRvP 3,05 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRvP 3,05 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRvP 3 5,071 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRvP 3 5,071 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRvP 3 7,064 MCTD-MD HLA-DR1 (DRB1*0101) 8.009 U1-snRvP 3 7,064 MCTD-MD HLA-DR1 (DRB1*0101) 8.009 U1-snRvP 3 7,064 MCTD-MD HLA-DR1 (DRB1*0101) 8.009<						DIHSYGSSG	12,396	27.14
dystorin (BP230) 12 FESVGHSH 16.83 37.19 MFEGDHACS 14318 34.44 YRDTHPLD 14318 34.44 YRDTHPLD 14318 34.44 YRDTHPLD 14368 32.45 EP-MCTD HLA-DG7 (D2B1'0301) 11.701 U1-snRNP 3 BP-MCTD HLA-DG7 (D2B1'0301) 11.701 U1-snRNP 3 MCTD-MCTD HLA-DG7 (D2B1'0301) 11.701 U1-snRNP 3 MCTD-MCTD HLA-DG7 (D2B1'0301) 11.701 U1-snRNP 3 MCTD-MCTD HLA-DR1 (DRB1'0101) 8.009 U1-snRNP 3 WRTBRLIGGG 12.71 330 MCTD-MCTD HLA-DR1 (DRB1'0101) 8.009 U1-snRNP 3 MCTD-MCTD HLA-DR1 (DRB1'0101) 8.009 U1-snRNP 3 MCTD-MCTD HLA-DR1 (DRB1'0101) 8.009 U1-snRNP 3 MCTD-BP HLA-DR1 (DRB1'0101) 8.009 U1-snRNP 3 MCTD-BP HLA-DR1 (DRB1'0101) 8.009 U1-snRNP 2 MCTD-BP HLA-DR1 (DRB1'0101) 8.009 J10-snRN'ND1 12.223 MCTD-BP HLA-DR1 (DRB1'0101) 8.009 J10-snRN'ND1 12.836 <t< td=""><td></td><td></td><td></td><td></td><td></td><td>APGPAGPAG</td><td>11,938</td><td>26.14</td></t<>						APGPAGPAG	11,938	26.14
MCTD-BPL S15 S164 BP-MCTD HLA-DQ7 (DQB1'0301) 11.701 U1-snRN 14.818 32.45 BP-MCTD HLA-DQ7 (DQB1'0301) 11.701 U1-snRN 14.818 32.45 BP-MCTD HLA-DQ7 (DQB1'0301) 11.701 U1-snRN 3 SKRSISKPG 12.997 27.53 BP-MCTD HLA-DQ7 (DQB1'0301) 11.701 U1-snRNP 3 SKRSISKPG 12.406 27.75 MCTD-MCTD HLA-DD7 (DQB1'0301) 11.701 U1-snRNP 3 SKRSISKPG 12.406 27.75 MCTD-MCTD HLA-DR1 (DRB1'0101) 8.009 U1-snRNP 3 SKRSISKPG 12.406 27.75 MCTD-BP HLA-DR1 (DRB1'0101) 8.009 U1-snRNP 3 SKRSISKPG 12.406 27.75 MCTD-BP HLA-DR1 (DRB1'0101) 8.009 U1-snRNP 3 SKRSISKPG 12.406 27.79 MCTD-BP HLA-DR1 (DRB1'0101) 8.009 U1-snRNP 3 SKRSISKPG 13.76 27.92 MCTD-BP				dystonin (BP230)	12	FESYGHSSH	16,983	37.19
RPDTVHPL 14,818 32.45 FPOTHPRL 14,818 32.45 FPOTHPRL 14,386 31.5 FADTHPRL 12,307 28.46 ILOROKATIV 2.573 27.53 LIADAT U1-SIRNE 2.64 NCTD-MCTD HLA-DR1 (DR81*0101) 8.009 U1-SIRNE 2.64 MCTD-MCTD HLA-DR1 (DR81*0101) 8.009 U1-SIRNE 2.63 2.75 MCTD-MCTD HLA-DR1 (DR81*0101) 8.009 U1-SIRNE 1.87 2.69 2.819 MCTD-MCTD HLA-DR1 (DR81*0101) 8.009 U1-SIRNE 1.87 2.69 2.819 MCTD-MCTD HLA-DR1 (DR81*0101) 8.009 U1-SIRNE 1.87 2.69 2.819 MCTD-MCTD HLA-DR1 (DR81*0101) 8.009 U1-SIRNE 2.88 2.816 2.76 2.819 2.819						NFDGDHACS	15.913	34.84
BP-MCTD HLA-DQ7 (DQB1*0301) 11.701 U1-snRNP 14,805 32,42 BP-MCTD HLA-DQ7 (DQB1*0301) 11.701 U1-snRNP 3 14,356 31,43 BP-MCTD HLA-DQ7 (DQB1*0301) 11.701 U1-snRNP 3 SKR95(HTGL 12,406 27.16 MCTD-MCTD HLA-DQ7 (DQB1*0301) 11.701 U1-snRNP 3 SKR95(HTGL 12,406 27.16 MCTD-MCTD HLA-DQ7 (DQB1*0101) 8.009 U1-snRNP 3 SKR95(HTGL 12,406 27.16 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 SKR95(HTGL 12,406 27.16 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 SKR95(HTGL 12,406 27.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 SKR95(HTGL 12,406 27.69 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 27.69 26.99 28.19 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 RPRNVND1 12.296 27.96 26.99						YRDTYHPLD	14,818	32.45
BP-MCTD HLA-DQ7 (DQB1*0301) 11.701 U1-snRuP 31.5 FAOLHPSL 14.366 31.5 FAOTUHPSL TGSLNSGF 12.997 28.46 11.307 27.53 27.53 BP-MCTD HLA-DQ7 (DQB1*0301) 11.701 U1-snRuP 3 12.495 27.36 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRuP 3 SKRSGKPRG 15.071 26.3 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRuP 3 SKRSGKPRG 15.071 33.0 WCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRuP 3 SKRSGKPRG 15.071 26.3 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRuP 3 SKRSGKPRG 12.875 27.92 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 U1-snRuP 3 YCHADGKW 12.82 27.92 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 U1-snRuP 3 YCHADGKW 12.82 27.92 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 U1-snRuP 2 YCHADGKW 12.63 37.11						LTPSVTPAY	14,805	32.42
BP-MCTD HLA-DG7 (DQB1*0301) 11.701 U1-snRNP 14,356 31,43 BP-MCTD HLA-DG7 (DQB1*0301) 11.701 U1-snRNP 3 SPTGNEART 12,495 27.36 BP-MCTD HLA-DG7 (DQB1*0301) 11.701 U1-snRNP 3 SPTGNEAR 12,495 27.36 BP-MCTD HLA-DG7 (DQB1*0301) 11.701 U1-snRNP 3 SPTGNEAR 12,495 27.36 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 SPTGNEARG 12,775 25.99 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 SPTGNEARG 12,755 27.32 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 SPTGNEARG 12,755 27.32 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 SPTGNPPYL 12,961 62.23 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 PCIAPYIR 12,275 27.39 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 12,275 13,276 13,11<						IEPQVHSRL	14,386	31.5
BP-MCTD HLA-DQ7 (DQB1*0301) 11.701 U1-snRNP 3 LLQRQKATV 12.997 28.46 MCTD HLA-DQ7 (DQB1*0301) 11.701 U1-snRNP 3 LLQRQKATV 12.965 26.41 MCTD-MCTD HLA-DQ7 (DQB1*0301) 11.701 U1-snRNP 3 SPTGNEAM 12.065 26.41 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 SKRSGKFG 15.01 3.10 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 SKRSGKFG 15.01 3.10 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 SKRSGKFG 15.01 3.10 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 SKRSGKFG 15.01 3.16 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 RPRRLGGG 28.58 63.48 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 RPRRLGGG 28.56 63.48 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 27.561 <t< td=""><td></td><td></td><td></td><td></td><td></td><td>FAQTLHPSL</td><td>14,356</td><td>31.43</td></t<>						FAQTLHPSL	14,356	31.43
BP-MCTD HLa-Da7 (DaB1*0301) 11.701 U1-snRNP 3 LLQRQKATV 12,573 27.53 BP-MCTD HLa-Da7 (DQB1*0301) 11.701 U1-snRNP 3 LLQRQKATV 12,406 27.36 MCTD-MCTD HLa-DR1 (DRB1*0101) 8.009 U1-snRNP 3 SKRSSKPRG 12,013 26.3 MCTD-MCTD HLa-DR1 (DRB1*0101) 8.009 U1-snRNP 3 SKRSSKPRG 15,071 33.0 MCTD-MCTD HLa-DR1 (DRB1*0101) 8.009 U1-snRNP 3 SKRSSKPRG 15,071 33.0 MCTD-MCTD HLa-DR1 (DRB1*0101) 8.009 U1-snRNP 3 YKHADGKK1 18,186 37.69 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 RPRRLGGG 28.56 63.48 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 SKRSKPRG 666 18.76 25.36 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 ultscheeteeteeteeteeteeteeteeteeteeteeteeteet						ITQSLNSGF	12,997	28.46
BP-MCTD HLA-DQ7 (DQB1*0301) 11.701 U1-snRNP 3 LRHTVTARQ 12.465 27.36 BP-MCTD HLA-DQ7 (DQB1*0301) 11.701 U1-snRNP 3 SKRSGKPRG 15.071 33.0 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 SKRSGKPRG 15.071 33.0 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 YKHADGKKI 12.187 25.39 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 YKHADGKKI 13.69 28.19 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 YKHADGKKI 13.69 28.36 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 RPRLGGGL 22.48 27.36 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 RPRLGGGL 27.92 27.92 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 RPRLGGGL 27.94 27.94 27.94 27.94 27.94 27.94 27.94 27.94 27.94 27.94 27.						LLQRQKATV	12,573	27.53
BP-MCTD HLA-DQ7 (DQB1*0301) 11.701 U1-snRNP 3 ADFDFHTGL 12.406 27.16 BP-MCTD HLA-DQ7 (DQB1*0301) 11.701 U1-snRNP 3 SKRSGKPRG 12,013 3.00 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 SKRSGKPRG 12,013 3.00 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 SKRSGKPRG 1.87 25.99 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 YKHADGKKI 181.16 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 RPRRLGGGL 25.33 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 u11-snRNP 2 RPRLGGGL 27.961 62.22 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten LTGMPGIRG 39.33 31.13 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 27.961 62.22 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 27.961						LRHTVTARQ	12,495	27.36
BP-MCTD HLA-DQ7 (DQB1*0301) 11.701 U1-snRNP 3 IIDVLIATK 12.06 26.41 IIDVLIATK 12.013 30.0 WRPRRLGGG 15.071 33.0 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 WRPRLGGG 12.75 27.99 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 WRPRLGGG 12.75 25.39 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 YKHADGKKI 18.186 37.69 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 RPRRLGGG 25.38 25.38 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 3 30 (top ten 17.904 37.11 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 16.536 30.33 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 16.536 31.20 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 16.536 31.20 MCTD-B						ADFDFHTGL	12,406	27.16
BP-MCTD HLA-DQ7 (DQB1*0301) 11.701 U1-snRNP 3 SKRSGKPRG 15,071 26.3 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 WRPRRLGGG 12.75 27.92 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 YKHADGKKI 18.187 25.99 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 YKHADGKKI 18.186 27.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 YCGIAPYIR 13.569 28.19 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 RPRLGGGL 28.526 63.48 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top tan 12.243 25.36 31.11 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top tan 17.904 37.11 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top tan 16.53 31.29 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top tan 17.90						ISPTGNEAM	12.06	26.41
BP-MCTD HLA-DQ7 (DQB1*0301) 11.701 U1-snRNP 3 SKRSGKPRG 15,071 33.0 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 YKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 YKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 YKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 RPRRLGGGL 28.526 63.48 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 17.904 37.11 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 17.904 37.11 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 17.904 37.11 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 17.904 37.11 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 17.905 37.11 </td <td></td> <td></td> <td></td> <td></td> <td></td> <td>IIDVLIATK</td> <td>12,013</td> <td>26.3</td>						IIDVLIATK	12,013	26.3
MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 WRPRLGGG 12.75 27.92 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 YKHADGKKI 187 25.99 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 2 YKHADGKKI 18.186 37.69 9mer-HLA-B07 19.18 U1-snRNP 2 RPRLGGGL 28.19 28.19 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 ult-snRNP 2 APRDPIPYL 12.243 25.38 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 19.267 39.32 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 17.904 37.11 FTASPASIA IGEMPOIS YRAHSPAS 17.904 37.11 FTASPASIA 16.536 34.27 MRGLPGAVG ISO XGAIQGPPG IAFASPASIA 16.536 34.27 YCAIQGPPG IAFASPASIA 16.536 34.27 YAELSSRL 15.97 33.1 YCAIQGPPG IAFASPASIA IAFASPASIA	BP-MCTD	HLA-DQ7 (DQB1*0301)	11.701	U1-snRNP	ო	SKRSGKPRG	15,071	33.0
MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 VKHADGKKI 18.186 37.69 MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 VKHADGKKI 18.186 37.69 9mer-HLA-B07 19.18 U1-snRNP 2 RPRLGGcL 28.526 63.48 9mer-HLA-B07 19.18 U1-snRNP 2 RPRRLGGcL 28.526 63.48 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten LTGMPGIRG 19,267 39.93 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten LTGMPGIRG 19,267 39.93 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 17,904 37.11 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 16,536 34.27 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 17,904 37.11 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 17,904 37.11 <tr< td=""><td></td><td></td><td></td><td></td><td></td><td>WRPRRLGGG</td><td>12.75</td><td>27.92</td></tr<>						WRPRRLGGG	12.75	27.92
MCTD-MCTD HLA-DR1 (DRB1*0101) 8.009 U1-snRNP 3 YKHADGKKI 18.186 37.69 28.19 YCGIAPYIR 13.599 28.19 YCGIAPYIR 13.599 28.19 9mer-HLA-DR1 0 U1-snRNP 2 RPRRLGGGL 28.526 63.48 9mer-HLA-DR1 19.18 U1-snRNP 2 RPRRLGGL 28.526 63.48 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten LTGMPGIRG 19,267 39.33 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten LTGMPGIRG 19,267 39.31 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten LTGMPGIRG 17,904 37.11 FTASPASIA TGSPASIA 16,536 34.27 YAELSSRIL 15,995 31.29 YGALOGPPG 14.75 30.57 YGALOGPPG 14.75 30.57 YGALOGPPG 14.65 30.57 YGALOGPPG 14.65 30.56						DRDREHKRG	11.87	25.99
WCGIAPYIK 13.599 28.19 9mer-HLA-B07 19.18 U1-snRNP 2 RPRRLGGCL 28.526 63.48 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 17,904 37.11 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 17,904 37.11 RPRLS FTASPASIA 16,536 34.27 33.23 34.27 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten 17,904 37.11 RPRLS FTASPASIA 16,536 34.27 YAELSSRIL 16,536 34.27 RGLPGAVG FTASPASIA 16,509 31.29 YGAIQGPPG 14.75 30.55 MRGLPGAVG 14.75 30.36 YGAIQGPPG 14.75 30.36	MCTD-MCTD	HLA-DR1 (DRB1*0101)	8.009	U1-snRNP	ი	YKHADGKKI	18.186	37.69
9mer-HLA-B07 19.18 U1-snRNP 2 FVARVNYDT 12.243 25.38 9mer-HLA-B07 19.18 U1-snRNP 2 RPRRLGGGL 28.526 63.48 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten LTGMPGIRG 19,267 39.93 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten LTGMPGIRG 19,267 39.93 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten LTGMPGIRG 19,267 39.93 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten TTGMPGIRG 19,267 39.93 FTASPASIA TAELSSRIL 16,536 34.27 YGAIQGPYG 16,570 33.17 MRGLPGAVG T5.97 73.11 MRGLPGAVG 16,570 31.29 YGAIQGPPG 14.75 30.57 YGAIQGPPG 14.755 30.57						YCGIAPYIK	13.599	28.19
9mer-HLA-B07 19.18 U1-snRNP 2 RPRRLGGGL 28.526 63.48 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten LTGMPGIRG 19,267 39.93 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten LTGMPGIRG 19,267 39.93 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten TGMPGIRG 17,904 37.11 REQUENCES REALSSRIL 16,536 34.27 YAELSSRIL 16,536 34.27 RIGLPGAVG IS.97 RIGLPGAVG 15,095 31.29 YGAIQGPPG 14,75 30.57 LQGMAPAAG 14.75 30.36 14.75 30.36 14.75 30.36						FVARVNYDT	12.243	25.38
MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten APRDPIPYL 27.961 62.22 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten LTGMPGIRG 19,267 39.93 Sequences shown) YRRAHSPAS 17,904 37.11 YAELSSRIL 16,536 34.27 MRGLPGAVG 15,095 31.29 YGAIQGPPG 14,75 30.57 LQGMAPAAG 14,75 30.36		9mer-HLA-B07	19.18	U1-snRNP	2	RPRRLGGGL	28.526	63.48
MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten LTGMPGIRG 19,267 39.93 MCTD-BP HLA-DR1 (DRB1*0101) 8.009 alpha 1 type XVII 30 (top ten LTGMPGIRG 19,267 39.93 collagen (BP180) 71,1 YRAHSPAS 17,904 37.11 74LSSRIL 15,97 33.1 MRGLPGAVG 15,095 31.29 YGAIQGPPG 14,75 30.57 LQGMAPAAG 14,75 30.36 267 20.36 267						APRDPIPYL	27.961	62.22
collagen (BP180) sequences shown) YRRAHSPAS 17,904 37.11 FTASPASIA 16,536 34.27 YAELSSRIL 15.97 33.1 MRGLPGAVG 15,095 31.29 YGAIQGPPG 14.75 30.57 LQGMAPAAG 14.65 30.36	MCTD-BP	HLA-DR1 (DRB1*0101)	8.009	alpha 1 type XVII	30 (top ten	LTGMPGIRG	19,267	39.93
FIASPASIA 16,536 34.27 YAELSSRIL 15.97 33.1 MRGLPGAVG 15,095 31.29 YGAIQGPPG 14.75 30.57 LQGMAPAAG 14.65 30.36				collagen (BP180)	sequences shown)	YRRAHSPAS	17,904	37.11
YAELSSRIL 15.97 33.1 MRGLPGAVG 15,095 31.29 YGAIQGPPG 14.75 30.57 LQGMAPAAG 14.65 30.36						F IASPASIA	16,536	34.27
MIRGLPGAVG 15,095 31.29 YGAIQGPPG 14.75 30.57 LQGMAPAG 14.65 30.36						YAELSSRIL	15.97	33.1
YGAIQGPPG 14.75 30.57 LQGMAPAAG 14.65 30.36						MIRGLPGAVG	15,095	31.29
LQGMAPAAG 14.65 30.36						YGAIQGPPG	14.75	30.57
						LQGMAPAAG	14.65	30.36





					14,629 17,629	30.32 26.40
		dystonin (BP230)	56 (top ten	FQAMENRML	12,030 21,334	44.22
			sequences shown)	YTALVTLMT	18,836	39.04
				IKQMEKDLA	17,855	37.01
				WHKEKADQL	17,566	36.41
				LAFLEAQAA	17,355	35.97
				YRAMVDSQQ	17,008	35.25
				IDKMVALAF	16,637	34.48
				RAAMQTQWS	16,464	34.12
				YIKFAGDSL	16,398	33.99
				YKSTIANLM	15,891	32.94
9mer-HLA-B07	19.18	alpha 1 type XVII	6	GPPGPVTTI	26,397	58.74
		collagen (BP180)		GPPGPPGAM	23,355	51.97
				GPPGPPGPV	23,008	51.2
				GPPGVSGAL	22,519	50.11
				GPRGPPGPS	22,357	49.75
				GPPGPPGSI	21,477	47.79
				GPRGPPGVS	21,201	47.18
				GPRGPPGPP	20,932	46.58
				GPPGDSRLL	20,217	44.99
		dystonin (BP230)	£	TPRSPLLRW	23,701	52.74



 Table S8A. Rankpep analysis of DH- and MCTD-derived autoantigens predicted to bind their HLA-associated alleles in a one- and two-disease model.

Disease 1	МНС	Performance	Disease 2	Protein	Total sequences
DH	HLA-DQ2 (DQA1*0501/DQB1*0201)	0.88 ± 0.06	DH	transglutaminase 3	685
	HLA-DQ8 (DQA1*0301/DQB1*0302)	0.72 ± 0.06		transglutaminase 3	685
	HLA-DQ2 (DQA1*0501/DQB1*0201)	$\textbf{0.88} \pm \textbf{0.06}$	MCTD	U1-snRNP	429
	HLA-DQ8 (DQA1*0301/DQB1*0302)	0.72 ± 0.06		U1-snRNP	429
MCTD	HLA-DR1 (DRB1*0101)	0.75 ± 0.04	MCTD	U1-snRNP	429
	9mer-HLA-B07	na		U1-snRNP	429
	HLA-DR1 (DRB1*0101)	0.75 ± 0.04	DH	transglutaminase 3	685
	9mer-HLA-B07	na		transglutaminase 3	685



Total predicted binders	Threshold	High binding score	Low binding score	% optimal high	% optimal low
0	31.451	29.276	16.04	40.74	22.32
3	12.635	15.737	14.644	30.63	28.5
4	31.451	20.599	13.862	40.09	26.98
0	12.635	-	_	_	-
3 2 17 1	8.009 19.18 8.009 19.18	18.186 28.526 19.6 21.332	12.243 27.961 8.343 -	37.69 63.48 40.62 47.47	25.38 62.22 17.29 -

Table S8B. F model.	² eptide sequences of DH- ar	nd MCTD-derived	l autoantigens predictec	d to bind their HLA-:	associated alleles in	ו a one- and	two-disease
Disease	MHC	Threshold	Autoantigen	Total predicted binders	Top binders	Score	% optimal
MCTD	HLA-DR1 (DRB1*0101)	8.009	U1-snRNP	З	YKHADGKKI YCGIAPYIR EVADVAVDT	18.186 13.599 12.243	37.69 28.19 25.30
	9mer-HLA-B07	19.18	U1-snRNP	2	RPRRLGGGL APRNPIPVI	28.526 28.526 27 961	63.48 62.20
MCTD-DH	HLA-DR1 (DRB1*0101)	8.009	transglutaminase 3	17	MTIIYNGTL	19.6 16.633	40.62 34.47
					FILLFNPWL YVQEDAGII	15,353 15.052	31.82 31.2
					YDPMGNPLD WKNSVNSHT	14,795 11 181	30.67
					FDILPSRSG	11,107	23.02
					FAEVNADRI	10,445	21.65 20.02
					FPAIKAMLS	10,045 9.733	20.02
					FAGTLNTAL	9,729	20.16
					WKDSATMSL	9,673	20.05
					LQASNGNTL	9,352 0,352	19.38
					CVLMVEGSG	9,057	18.77
					CNKFPAIKA	8,643 0 426	17.91
					FREMATEN	0,430 343	17.20
	9mer-HLA-B07	19.18	transglutaminase 3	-	APIGRYTMA	21,332	47.47
HD-HD	HLA-DQ2 (DQA1*0501/ DOR1*0201)	31.451	transglutaminase 3	0			
	DQB1*0302) DQB1*0302)	12.635	transglutaminase 3	e	DFSCNKFPA ALRSLGIPS SATMSLIDE	15.737 14.828 14.644	30.63 28.86 28.5
DH-MCTD	HLA-DQ2 (DQA1*0501/	31.451	U1-snRNP	0			0.00
	DQB1*0302) DQB1*0302)	12.635	U1-snRNP	4	IKRIHMVYS RERARRERE FEDPRDAPP PSEAGDAPP	20,599 16,863 13,862	40.09 32.82 32.33 26.98



model.											
Disease 1	МНС	Performance	Disease 2	Protein	Total sequences	Total predicted binders	Threshold	High binding score	Low binding score	% optimal high	% optimal low
OCP	HLA-DQ7 (DQB1*0301)	ра	OCP	alpha 1 type XVII collagen (BP180)	1489	4	11.701	19.68	11.938	43.09	26.14
	HLA-DQ7 (DQB1*0301)	na		β4 integrin	1814	14	11.701	20.182	11.829	44.19	25.9
	HLA-DR4 (DRB1*0401)	0.68 ± 0.01		alpha 1 type XVII collagen (BP180)	1489	76	4.853	18.832	4.855	42.71	11.01
	HLA-DR4 (DRB1*0401)	0.68 ± 0.01		β4 integrin	1814	84	4.853	19.344	4.867	43.87	11.04
	HLA-DQ7 (DQB1*0301)	na	MCTD	UI-snRNP	429	ю	11.701	15.071	11.87	33	25.99
	HLA-DR4 (DRB1*0401)	0.68 ± 0.01		UI-snRNP	429	9	4.853	12.955	6.599	29.38	14.97
MCTD	HLA-DR1 (DRB1*0101)	0.75 ± 0.04	MCTD	U1-snRNP	429	ю	8.009	18.186	12.243	37.69	25.38
	9mer-HLA-B07 HLA-DR1 (DRB1*0101)	na 0.75 ± 0.04	OCP	U1-snRNP alpha 1 type XVII collagen (BP180)	429 1489	2 30	19.18 8.009	28.526 19.267	27.961 8.273	63.48 39.93	62.22 17.15
	HLA-DR1 (DRB1*0101)	0.75 ± 0.04		β4 integrin	1814	29	8.009	17.695	8.039	36.68	16.66
	9mer-HLA-B07	na		alpha 1 type XVII collagen (BP180)	1489	o	19.18	26.397	20.217	58.74	44.99
	9mer-HLA-B07	na		β4 integrin	1814	5	19.18	27.886	20.604	62.05	45.85



ble S9B. Peptide sequences of DH- and MCTD-derived autoantigens predicted to bind their HLA-associated alleles in a one- and two-di odel.
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model.							
Disease	MHC	Threshold	Autoantigen	Total predicted binders	Top binders	Score	% optimal
MCTD-MCTD	HLA-DR1 (DRB1*0101)	8.009	U1-snRNP	ю	YKHADGKKI YCGIAPYIR	18.186 13.599	37.69 28.19
	9mer-HLA-B07	19.18	U1-snRNP	7	FVARVNYDT RPRRLGGGL	12.243 28.526	25.38 63.48
	HI A_DR4 (DRR1*0101)	8 000	alnha 1 trua XVII	30 (ton ten	APRDPIPYL I tgmdgibg	27.961 10 267	62.22 30 03
		0000	collagen (BP180)	sequences shown)	YRRAHSPAS	17,904	37.11 37.07
					YAELSSRIL	15.97	33.1 33.1
					MRGLPGAVG	15,095 14 75	31.29 30.57
					LQGMAPAAG	14.65	30.36
					IKGEPGAPG	14,646	30.36
					UKAEANGUL WKWI I GI I I	14,629 12,638	30.32 26.19
		8.009	84 integrin	29 (top ten	WKELQVKLL	17,695	36.68
			•	sequences shown)	IRALDSPRG	17,581	36.44
					YSSLVSCRT	16,281	33.75
					YQLLNGGEL YRAISGVHK	15,387 14 592	31.89 30.24
					LAALISVSL	13.672	28.34
					FTALSPDSL	13,477	27.93
					WARLLLAAL	12,948	26.84
					YTQYRTQDY	12.79	26.51
					WRPDSTHLL	12,782	26.49
	9mer-HLA-B07	19.18	alpha 1 type XVII	თ	GPPGPVTTI GPPGPPGAM	26,397 23 355	58.74 51.97
					GPPGPPGPV	23.008	51.2
					GPPGVSGAL	22,519	50.11
					GPRGPPGPS	22,357	49.75
					GPPGPPGSI	21,477	47.79
					GPRGPPGVS	21,201	47.18
					GPRGPPGPP	20,932	46.58
					GPPGDSRLL	20,217	44.99
		19.18	β4 integrin	5	APRSAKPAL	27,886	62.05
					RPRRPNGDI	26,186	58.27
					SPRGLRTEV	24,271	54.01
					APGPNSTVL	21,118	46.99
					RPIGPMKKV	20,604	45.85
OCP-OCP	HLA-DQ7 (DQB1*0301)	11.701	alpha 1 type XVII	14	IRRSILPYG	19.68	43.09
			collagen (BP180)		FDYSELASH	19.381	42.44





(Continued)						
27.47	12.112	RRSQMSPQG				
28.29	12.471	WRPDSTHLL				
28.6	12.611	GWSGQTCNC				
30.19	13.312	YMLRENLMA				
30.66	12518					
30.10 31.38	14.019 13.835	WWLIPLLLL KVOARTTEG				
33.94	14.965					
43.34	19.108	YWIQGDSES	sequences shown)			
43.87	19.344	YRTQDGTAQ	84 (top ten	β4 integrin		
29.68	13,088	LRGEVGLPG				
30.24	13,332	YAAENSDSF				
31.95	14,086	WWKWLLGLL				
32.37	14,274	YAKTASLGG				
36.01	15,877	FRGIVGPPG				
37.78	16,655	HVWSSTLPA				
38.02	16,763	YGAIQGPPG				
38.55	16.995	VAGNGGI I G				
42.71	18,832	YHNNMI TQS	76 (top ten	alpha 1 type XVII	4853	HLA-DR4 (DRB1*0401)
25.9	11,829	VIRRVLDGG				
26.51	12,108	ADQDARGMV				
27.68	12.643	SCVOCOAWG				
28.54	13 035					
31.15 20.75	14.228	IYUVULKAL Vennu den				
32.05	14.639	FRQQPNAGK				
32.6	14.888	IRRVLDGGK				
34.86	15.922	DVPAGTATL				
36.85	16.829	YCACCKACL				
40.36	18.434	APRSAKPAL				
41.37	19.100	NYSAIHPGL				
44.19	20.182	DINITYON CAN DINITYON	4	p4 Integrin		
26.14	11,938	APGPAGPAG				
27.14	12,396	DIHSYGSSG				
27.16	12,403	LSSYLHTAG				
29.32 28 21	10.001					
29.63	13.531	SSQSVSGTY				
29.83	13.625	IRGPPGPSG				
30.32	13.849	SLGAGGAFG				
34.23	15.634	VWSSTLPAG				
35.55	16.234	AGPAGLPGH				
36.56 35 0	16.697 16 308	STDASHSKG				

Table S9B. (Co	ontinued)						
Disease	МНС	Threshold	Autoantigen	Total predicted binders	Top binders	Score	% optimal
					KMFQKTRTG	11.537	26.17
OCP-MCTD	HLA-DQ7 (DQB1*0301)	11.701	U1-snRNP	ი	SKRSGKPRG	15,071	33.0
					WRPRRLGGG	12.75	27.92
					DRDREHKRG	11.87	25.99
	HLA-DR4 (DRB1*0401)	4,853	U1-snRNP	6	YIREFEDPR	12,955	29.38
					GYLMEAAPE	9,074	20.58
					GGLGGTRRG	7,653	17.36
					TVKGWRPRR	7,229	16.4
					WDPHNDPNA	6,835	15.5
					YMESEGGDG	6,599	14.97





and oneσ .⊑ Table S10A. Rankpep analysis of MMP- and MCTD-derived autoantigens predicted to bind their HLA-associated alleles two-disease model.

Disease 1	MHC	Performance	Disease 2	Protein	Total sequences	Total predicted binders	Threshold	High binding score	Low binding score	% optimal high	% optima low
MMP	HLA-DQ7	na	MMP	β4 integrin	1814	14	11.701	20.182	11.829	44.19	25.9
		na	MCTD	U1-snRNP	429	З	11.701	15.071	11.87	33.00	25.99
MCTD	HLA-DR1 (1001)	0.75 ± 0.04	MCTD	U1-snRNP	429	З	8.009	18.186	12.243	37.69	25.38
	HLA-DR1 (PDB1+0101)	na 0.75 ± 0.04	MMP	U1-snRNP β4 integrin	429 1814	2 29	19.18 8.009	28.526 17.695	27.961 8.039	63.48 36.68	62.22 16.66
	(DRB1 0101) HLA-DR1 (DRB1*0101)	0.75 ± 0.04		alpha 1 type XVII collagen	1489	30	8.009	19,267	8,273	39.93	17.15
	9mer-HLA-B07	na		(BP180) β4 integrin	1814	ıΩ.	19.18	27.886	20.604	62.05	45.85
	9mer-HLA-B07	Па		alpha 1 type XVII collagen (BP180)	1489	6	19.18	26,397	20,217	58.74	44.99

Disease	MHC	Threshold	Autoantigen	Total predicted	Top binders	Score	% optimal
				binders			
MCTD-MCTD	HLA-DR1 (DRB1*0101)	8.009	U1-snRNP	n	YKHADGKKI	18.186	37.69
					YCGIAPYIR	13.599	28.19 67.60
				(12.243	25.38
	9mer-HLA-B07	19.18	U1-snRNP	N	RPRRLGGGL	28.526	63.48
					APRDPIPYL	27.961	62.22
MCTD-MMP	HLA-DR1 (DRB1*0101)	8.009	84 integrin	29 (top ten	WKELQVKLL	17,695	36.68
			-	sequences shown)	IRALDSPRG	17,581	36.44
					YSSLVSCRT	16,281	33.75
					YQLLNGGEL	15,387	31.89
					YRQISGVHK	14,592	30.24
					LAALISVSL	13,672	28.34
					FTALSPDSL	13,477	27.93
					WARLLLAAL	12,948	26.84
					YTQYRTQDY	12.79	26.51
					WRPDSTHLL	12,782	26.49
		8.009	alpha 1 type XVII	30 (top ten	LTGMPGIRG	19,267	39.93
			collagen (BP180)	sequences shown)	YRRAHSPAS	17,904	37.11
					FTASPASIA	16,536	34.27
					YAELSSRIL	15.97	33.1
					MRGLPGAVG	15,095	31.29
					YGAIQGPPG	14.75	30.57
					LQGMAPAAG	14.65	30.36
					IKGEPGAPG	14,646	30.36
					LKAEANGDL	14,629	30.32
					WKWLLGLLL	12,638	26.19
	9mer-HLA-B07	19.18	84 integrin	ភ	APRSAKPAL	27,886	62.05
			•		RPRRPNGDI	26,186	58.27
					SPRGLRTEV	24,271	54.01
					APGPNSTVL	21,118	46.99
					RPIGPMKKV	20,604	45.85
		19.18	alpha 1 type XVII	6	GPPGPVTTI	26,397	58.74
			collagen (BP180)		GPPGPPGAM	23,355	51.97
			- -		GPPGPPGPV	23,008	51.2
					GPPGVSGAL	22,519	50.11
					GPRGPPGPS	22,357	49.75
					GPPGPPGSI	21,477	47.79
					GPRGPPGVS	21,201	47.18
					GPRGPPGPP	20,932	46.58
					GPPGDSRLL	20,217	44.99
MMP-MMP	HLA-DQ7 (DQB1*0301)	31.451	β4 integrin	14	LPPSGKPMG	20.182	44.19
)		YRYTVKARN	19.166	41.97
					NYSAIHPGL	19.047	41.7





40.36	36.85	34.86	32.6	32.05	31.15	29.75	28.54	27.68	26.51	25.9	43.09	42.44	36.56	35.9	35.55	34.23	30.32	29.83	29.63	29.32	28.31	27.16	27.14	26.14	33.0	27.92	25.99	
18.434	16.829	15.922	14.888	14.639	14.228	13.589	13,035	12,643	12,108	11,829	19.68	19.381	16.697	16.398	16.234	15.634	13.849	13.625	13.531	13.391	12,928	12,403	12,396	11,938	15,071	12.75	11.87	
APRSAKPAL	YCACCKACL	DVPAGTATL	IRRVLDGGK	FRQQPNAGK	IYQVQLRAL	YSDDVLRSP	RAQSQEGWG	SCVQCQAWG	ADQDARGMV	VIRRVLDGG	IRRSILPYG	FDYSELASH	STDASHSRG	ILDANLPSH	AGPAGLPGH	VWSSTLPAG	SLGAGGAFG	IRGPPGPSG	SSQSVSGTY	NTNAYSAGS	YRRAHSPAS	LSSYLHTAG	DIHSYGSSG	APGPAGPAG	SKRSGKPRG	WRPRRLGGG	DRDREHKRG	
											14														ი			
											alpha 1 type XVII	collagen (BP180)													U1-snRNP			
											31.451														31.451			
											HLA-DQ7 (DQB1*0301)														HLA-DQ7 (DQB1*0301)			
																									MMP-MCTD			



Table S11A. Rankpep analysis of BP- and DH-derived autoantigens predicted to bind their HLA-associated alleles in a one- and two-disease model.

Disease 1	МНС	Performance	Disease 2	Protein	Total sequences
BP	HLA-DQ7 (DQB1*0301)	na	BP	alpha 1 type XVII collagen (BP180)	1489
	HLA-DQ7 (DQB1*0301)	na		dystonin (BP230)	2641
	HLA-DQ7 (DQB1*0301)	na	DH	transglutaminase 3	685
DH	HLA-DQ2 (DQA1*0501/DQB1*0201)	0.88 ± 0.06	DH	transglutaminase 3	685
	HLA-DQ8 (DQA1*0301/DQB1*0302)	0.72 ± 0.06		transglutaminase 3	685
	HLA-DQ2 (DQA1*0501/DQB1*0201)	0.88 ± 0.06	BP	alpha 1 type XVII collagen (BP180)	1489
	HLA-DQ2 (DQA1*0501/DQB1*0201)	$\textbf{0.88} \pm \textbf{0.06}$		dystonin (BP230)	2641
	HLA-DQ8 (DQA1*0301/DQB1*0302)	0.72 ± 0.06		alpha 1 type XVII collagen (BP180)	1489
	HLA-DQ8 (DQA1*0301/DQB1*0302)	0.72 ± 0.06		dystonin (BP230)	2641



Total predicted binders	Threshold	High binding score	Low binding score	% optimal high	% optimal low		
14	11.701	19.68	11.938	43.09	26.14		
12 6 0	11.701 11.701 31.451	16,983 20,579 -	12,013 11.92 -	37.19 45.06 -	26.3 26.1 -		
3	12.635	15.737	14.644	30.63	28.5		
1	31.451	32.97	_	45.89	-		
0	31.451	-	_	_	-		
8	12.635	18.587	13.11	36.18	25.52		
12	12.635	24,137	13,043	46.98	25.39		

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Disease	MHC	Threshold	Autoantigen	Total predicted binders	Top binders	Score	% optimal
BP-BP	HLA-DQ7 (DQB1*0301)	11.701	alpha 1 type XVII	14	IRRSILPYG	19.68	43.09
			collagen (BP180)		FDYSELASH	19.381	42.44
					STDASHSRG	16.697	36.56
					ILDANLPSH	16.398	35.9
					AGPAGLPGH	16.234	35.55
					VWSSTLPAG	15.634	34.23
					SLGAGGAFG	13.849	30.32
					IRGPPGPSG	13.625	29.83
					SSQSVSGTY	13.531	29.63
					NTNAYSAGS	13.391	29.32
					YRRAHSPAS	12,928	28.31
					LSSYLHTAG	12,403	27.16
					DIHSYGSSG	12,396	27.14
					APGPAGPAG	11,938	26.14
			dystonin (BP230)	12	FESYGHSSH	16,983	37.19
					NFDGDHACS	15.913	34.84
					YRDTYHPLD	14,818	32.45
					LTPSVTPAY	14,805	32.42
					IEPQVHSRL	14,386	31.5
					FAQTLHPSL	14,356	31.43
					ITQSLNSGF	12,997	28.46
					LLQRQKATV	12,573	27.53
					LRHTVTARQ	12,495	27.36
					ADFDFHTGL	12,406	27.16
					ISPTGNEAM	12.06	26.41
					IIDVLIATK	12,013	26.3
BP-MCTD	HLA-DQ7 (DQB1*0301)	11.701	transglutaminase 3	9	GSDSVWNFH	20,579	45.06
					DDNGVLAGN	17,095	37.43
					YVGRVLSAM	14,523	31.8
					DPRSWNGSV	13.59	29.76
					AEHPIKISY	13,343	29.22
					ITAVCKVPD	11.92	26.1
HD-HD	HLA-DQ2 (DQA1*0501/	31.451	transglutaminase 3	0			
				c		101	
	HLA-DU8 (DUA1~0301/ DOR1*0302)	CC0.21	transgiutaminase 3	ũ	DFSCNKFFA ALRSLGIPS	15./3/ 14.828	30.03 28.86
					SATMSI DPF	14 644	28.50
DH-MCTD	HLA-DQ2 (DQA1*0501/	31.451	alpha 1 tvpe XVII	£	RGREGPMGP	32.97	45.89
	DQB1*0201)		collagen (BP180)				
		31.451	dystonin (BP230)	0			
	HLA-DQ8 (DQA1*0301/	12.635	alpha 1 type XVII	ω	PGRPGIKGE	18,587	36.18
	DQB1*0302)		collagen (BP180)		PAGPAGLPG	17,805	34.66





31.59	29.23	27.56	26.99	26.95	25.52	46.98	39.26	35.14	30.18	30.13	30.11	30.06	29.26	27.79	27.11
16,228	15,018	14,162	13,865	13,846	13.11	24,137	20,169	18,052	15,507	15,481	15,471	15,444	15,033	14,276	13,926
NADSGLKAE	DRGPAGPPG	WGPAPAWCP	PKGDRGFPG	DRLQGMAPA	GAKGAMGPA	ITRAHAVAE	IKRCKETSE	PAYTPGFPS	VSWHYLINE	VQRVAKLRD	AYRAAMQTQ	DEIMALRNE	VRGIRVPPE	IVREKEAAE	VLKGVVDPE
						12									
						dystonin (BP230)									
						12.635									

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