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SVM based Prediction of Major Histocompatibility Complex Binders: Identification and Analysis of *Dracunculus medinensis* Peptide

Sonu Mishra[1]*, Virendra Gomase[1], and Karbhari V Kale[2]

[1]*Department of Biotechnology, Mewar University, India*

[2]*Department of Computer Science and IT, Dr.Babasaheb Ambedkar Marathwada University, India*

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***Corresponding author:** Sonu Mishra, Department of Biotechnology, Mewar University, Chittorgarh, Rajasthan, 312901, India, Email: sonumishra1014@gmail.com; gomase.viren@gmail.com

Abstract

The largest human infecting parasite causes guinea worm disease, known as the disease and cause of poverty due to unavailability of the sanitized water. This is not lethal but causes the long term morbidity and motility in the infected human. In this research work, we predict the peptide binders of antigenic protein from *D. medinensis* sequence to MHC-I molecules are as 11mer_H2_Db, 10mer_H2_Db, 9mer_H2_Db, 8mer_H2_Db.Also study integrates prediction of peptide MHC class I binding; proteasomal C terminal cleavage and TAP transport efficiency by using sequence and properties of the amino acids. We also found the binding of peptides to different alleles by using Position Specific Scoring Matrix. NADH dehydrogenase subunit 6 (mitochondrion) from *D. medinensis* is 145 residues long with 137 nonamers having antigenic MHC binding peptides. PSSM based server will predict the peptide binders from *D.medinensis* of NADH dehydrogenase subunit 6 sequence to MHC-II molecules are as I_Ab.p, I_Ad.p, I_Ag7.p,I_Ak.p which are found antigenic epitopes region in NADH dehydrogenase subunit 6 (mitochondrion) from *D. medinensis.*

Keywords: Antigen; MHC; TAP; PSSM; NADH dehydrogenase subunit 6; Peptide

Abbreviations: MHC: Major Histocompatibility Complex; TAP: Transporter Associated with Antigen Processing; PSSM: Position Specific Scoring Matrices; SVM: Support Vector Machine

Introduction

The unique life cycle of the *D.medinensis* takes almost one and half years to complete with unusual six stages. This infection remains asymptomatic during the incubation period. This is one of the largest known human parasites which cause the high rate of the motility and morbidity in infected individuals for long time especially among the school going children's.

The female worm released the larvae after the incubation period. Cyclops (intermediate host) eats infected larvae which gets entry into the human while drinking the contaminated water where the larvae gets mature and complete their six stages of the life cycle and finally the infectious female releases the infectious larvae which induces a painful blister (1 to 6cm diameter) on the skin of lower limbs; the person develop a slight fever, local skin redness, swelling and severe pruritus around the blister. Other symptoms include diarrhea, nausea, vomiting and dizziness. The severity of the wound infections in the infected individual led to a more complications such as redness and swelling of the skin (cellulitis), boils (abscesses), generalized infection (sepsis), joint infections (septic arthritis) that can cause the joints to lock and deform (contractures), lock jaw (tetanus). The blister burst within 1 to 3 days and female worms one or more slowly comes out from the wounds which causes an excoriating burning sensation and pain .Immersing or pouring water over the blister provide pain reliever. But this the moment that adult female is exposed to the external environment. During emergence of the limbs in open water sources it recognizes the temperature difference and releases the milky white liquid in the water which contains millions of immature larvae, when larvae released in water are ingested by copepods where they mount twice and become infective larvae within two weeks [1-7]. However, Identification of MHC [Major Histocompatibility Complex] binding antigenic peptide molecule will improves the understanding of specificity of immune responses against the pathogen, which is one of the important steps for vaccines discovery.

MHC class I antigen

The presence of the Major histocompatibility complex class I (MHC-I) molecules has been seen on the on the surface of all nucleated cells and display a large array of peptide epitopes for surveillance by the CD8+ T cell repertoire. CD8+ T cell responses,

which are essential for the disease or infection control. The CD8+ T cells are actively and efficiently discriminate between the healthy and the infected cell through the recognition of peptides which are associated with MHC-I molecules present on the cell surface. The peptide with the length range of the 8-11 amino acids , are typically derived from protein antigens in the cytosol that arise from conventional as well as cryptic translational reading frames [8]. Proteins which are classically synthesized in the cytosol undergo proteasomal degradation and the resultant peptides are later on transported into the Endoplasmic Endoplasmic Reticulum (ER) and loaded onto MHC-I molecules [9]. Due to the loading of the peptide the class I MHC stabilizes and pass through to the cell surface where the circulating CD8+ T cells scans the complexes which is known as 'immune surveillance' [10-19]. Therefore, prediction of TAP binding peptides is important for identification of the MHC class-1 restricted T cell epitopes.

Proteasomal degradation

Proteasomal degradation is important step in the antigen-presentation process to regulate the balance between intracellular proteins [20]. Inside the proteasome by the action of proteinase the antigenic protein NADH dehydrogenase subunit 6 (mitochondrion) from *D. medinensis* are cleaved into oligopeptides [21] and then these oligopeptides are binds to the TAP, which transports these peptides into the ER.

TAP mediated peptide transport into ER(Endoplasmic Reticulum)

TAP is heterodimeric transmembrane protein, is a family of ABC transporter that transports antigenic peptide (NADH dehydrogenase subunit 6 (mitochondrion) from *D. medinensis* into ER [22] because most of the MHC binding peptides are unable to diffuse across membrane, but TAP protein is capable of transporting the peptide inside the ER where it binds to MHC class I molecules. These MHC-peptide complexes will be translocate on the surface of antigen presenting cells [23] and are recognized by T-cell receptors to elicit an immune response.

MHC class II antigen

The prediction of peptides binding to a MHC class II molecule is difficult due to different side chains and longer length found in the extracellular antigen presentation [24-26]. In the MHC class II antigen presentation process, antigenic protein NADH dehydrogenase subunit 6 (mitochondrion) from D. medinensis are ingested by antigen-presenting cells through the process of endocytosis or phagocytosis, then cleaved by cathepsins a class of protease into oligopeptides in the endosomes, than are fuse with lysosomes containing MHC class II molecules [27] and present them at the cell surface for recognition by T cells [28-36]. Where T helper cells trigger an immune response by inflammation and swelling due to phagocytes or may lead to an antibody-mediated immune response via B-cell activation. Since MHCs have a key role in immune system by stimulating cellular and humoral immunity against NADH dehydrogenase subunit 6 (mitochondrion) from *D. medinensis* and are used for controlling specific immunological processes by creating peptides to bind to specific MHC alleles and this binding affinity to specific peptides are used for designing synthetic peptide vaccines [37-40].

Materials and Methods

Predictions of MHC class I binding peptide

MHC binding peptide is predicted using neural networks trained on C terminals of known epitopes. By using RANKPEP we predict peptide binders to MHCI molecules from protein sequences or sequence alignments using Position Specific Scoring Matrices (PSSMs) whose C terminal end is likely to be the result of proteosomal cleavage.

Prediction of antigenic peptides by cascade SVM based TAPPred method

By using TAPPred we predict TAP binders on the basis of sequence and the properties of amino acids. We found the MHCI binding regions. The binding affinity of NADH dehydrogenase subunit 6 (mitochondrion) from D.medinensis having 145 amino acids shows 137 nonamers.

Predictions of MHC class II binding peptide

MHC peptide binding of NADH dehydrogenase subunit 6 (mitochondrion) from *D. medinensis* predicted using neural networks trained on C terminals of known epitopes. By using RANKPEP we predict peptide binders to MHCII molecules from protein sequences or sequence alignments using Position Specific Scoring Matrices (PSSMs). MHC molecule binds to some of the peptide fragments generated after proteolytic cleavage of antigen.

Results and Interpretation

In this research work, we predict the peptide binders of NADH dehydrogenase subunit 6 (mitochondrion) from *D. medinensis* sequence to MHC-I molecules are as 11mer_H2_Db, 10mer_H2_Db, 9mer_H2_Db, 8mer_H2_Db (Table 2). MHC molecule binds to peptide fragments which are generated after proteolytic cleavage of antigen tend to be high-efficiency binders. TAP is an important transporter that involved in the translocation of peptides from cytosol to ER. TAP binds and translocate selective peptides for binding to specific MHC molecules. Therefore, predicting binding affinity of those peptides toward the TAP transporter is crucial to identify the MHC class-1 restricted T cell epitopes. Cascade based support vector machine shows 42 High affinity TAP binder residues at N and C termini using sequence and properties of the amino acids of NADH dehydrogenase subunit 6 (mitochondrion) from *D.medinensis* (Table 3). This method integrates prediction of peptide MHC class I binding; proteasomal C terminal cleavage and TAP transport efficiency by using sequence and properties of the amino acids. We also found the binding of peptides to different alleles by using Position Specific Scoring Matrix. NADH dehydrogenase subunit 6 (mitochondrion) from *D. medinensis* is 145 residues long with 137 nonamers having antigenic MHC

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binding peptides. PSSM based server will predict the peptide binders of NADH dehydrogenase subunit 6 (mitochondrion) from D. medinensis sequence to MHCII molecules are as I_Ab.p, I_Ad.p,I_Ag7, I_Ak which are found antigenic epitopes region in NADH dehydrogenase subunit 6 (mitochondrion) from *D. medinensis* (Table 1).

Table 1: Peptide binders of NADH dehydrogenase subunit 6 (mitochondrion) from D. medinensis to MHC-II molecules.

MHC-II Allele	RANK	POS.	N	SEQUENCE	C	MW (Da)	SCORE	% OPT.
I_Ab	1	47	LYV	WYSYYVCLL	FLS	1168.42	12.487	35.04%
I_Ab	2	17	SMS	YFSFDPMKS	ALF	1103.27	10.081	28.29%
I_Ab	3	96	CMS	FDLYDYGGM	GLG	1062.17	8.903	24.99%
I_Ab	4	48	YVW	YSYYVCLLF	LSG	1152.39	7.98	22.40%
I_Ab	5	119	VYY	FWLVGVLLF	YLN	1052.36	7.618	21.38%
I_Ad	1	50	WYS	YYVCLLFLS	GIF	1102.37	9.332	17.56%
I_Ad	2	66	IIV	YFSSIGFCE	VFS	1034.17	7.484	14.08%
I_Ad	3	61	SGI	FVIIVYFSS	IGF	1056.28	6.352	11.95%
I_Ad	4	22	SFD	PMKSALFLV	FSL	987.27	4.957	9.33%
I_Ad	5	9	VLV	SMLFASMSY	FSF	1018.22	3.374	6.35%
I_Ag7	1	120	YYF	WLVGVLLFY	LNF	1068.36	8.163	19.97%
I_Ag7	2	137	SFL	TFMGALRSF		1011.21	7.908	19.35%
I_Ag7	3	94	FFC	MSFDLYDYG	GMG	1092.2	6.486	15.87%
I_Ag7	4	49	VWY	SYYVCLLFL	SGI	1102.37	6.209	15.19%
I_Ag7	5	38	GLL	PVISCNLYV	WYS	989.2	6.128	14.99%
I_Ak	1	79	FSL	DFFSFLLCV	YFS	1072.3	17.533	43.94%
I_Ak	2	43	ISC	NLYVWYSYY	VCL	1229.4	9.359	23.46%
I_Ak	3	121	YFW	LVGVLLFYL	NFI	1018.31	8.731	21.88%
I_Ak	4	59	FLS	GIFVIIVYF	SSI	1052.33	8.001	20.05%
I_Ak	5	100	DLY	DYGGMGLGL	VVS	863.98	7.069	17.72%

Matrix: I_Ab.p.mtx, Consensus: YYAPWCNNA, Optimal Score: 35.632, Binding Threshold: 9.52; Matrix: I_Ad.p.mtx, Consensus: QMVHAAHAE, Optimal Score: 53.145, Binding Threshold: 7.10; Matrix: I_Ag7.p.mtx, Consensus: WYAHAFKYV, Optimal Score: 40.873.

Binding Threshold: 7.54; Matrix: I_Ak.p.mtx, Consensus: DFWCWECCC, Optimal Score: 39.9, Binding Threshold: 14.17). (All rows highlighted in red represent predicted binders & A peptide highlighted in violet has a C-teminus predicted by the cleavage model used).

Table 2: Peptide binders of NADH dehydrogenase subunit 6 (mitochondrion) from D. medinensis to MHC-I molecules, having C-terminal ends are proteosomal cleavage sites.

MHC-I Allele	RANK	POS.	N	SEQUENCE	C	MW (Da)	SCORE	% OPT.
8mer_H2_Db	1	68	VYF	SSIGFCEV	FSL	822.94	22.661	43.17%
8mer_H2_Db	2	38	GLL	PVISCNLY	VWY	890.07	12.523	23.86%
8mer_H2_Db	3	57	LLF	LSGIFVII	VYF	843.08	8.163	15.55%
8mer_H2_Db	4	76	CEV	FSLDFFSF	LLC	991.13	8.108	15.45%
8mer_H2_Db	5	45	CNL	YVWYSYYV	CLL	1101.27	7.867	14.99%
8mer_H2_Db	6	55	VCL	LFLSGIFV	IIV	877.1	5.124	9.76%
8mer_H2_Db	7	103	DYG	GMGLGLVV	SDM	726.92	4.278	8.15%
8mer_H2_Db	8	82	DFF	SFLLCVYF	SFF	973.21	3.602	6.86%
8mer_H2_Db	9	109	LGL	VVSDMYLV	YYF	907.09	2.083	3.97%
8mer_H2_Db	10	94	FFC	MSFDLYDY	GGM	1035.15	1.865	3.55%
9mer_H2_Db	1	86	FLL	CVYFSFFCM	SFD	1128.4	19.178	38.08%
9mer_H2_Db	2	15	FAS	MSYFSFDPM	KSA	1106.29	17.399	34.55%
9mer_H2_Db	3	68	VYF	SSIGFCEVF	SLD	970.12	12.268	24.36%
9mer_H2_Db	4	76	CEV	FSLDFFSFL	LCV	1104.29	11.102	22.04%
9mer_H2_Db	5	67	IVY	FSSIGFCEV	FSL	970.12	9.504	18.87%
9mer_H2_Db	6	131	YLN	FISSFLTFM	GAL	1074.31	8.837	17.55%

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9mer_H2_Db	7	81	LDF	FSFLLCVYF	SFF	1120.39	8.767	17.41%
9mer_H2_Db	8	121	YFW	LVGVLLFYL	NFI	1018.31	8.298	16.48%
9mer_H2_Db	9	73	IGF	CEVFSLDFF	SFL	1088.26	7.597	15.08%
9mer_H2_Db	10	83	FFS	FLLCVYFSF	FCM	1120.39	6.513	12.93%
10mer_H2_Db	1	25	PMK	SALFLVFSLL	GLL	1091.37	9.355	15.89%
10mer_H2_Db	2	130	FYL	NFISSFLTFM	GAL	1188.41	8.663	14.72%
10mer_H2_Db	3	18	MSY	FSFDPMKSAL	FLV	1124.33	8.113	13.78%
10mer_H2_Db	4	58	LFL	SGIFVIIVYF	SSI	1139.41	6.333	10.76%
10mer_H2_Db	5	34	FSL	LGLLPVISCN	LYV	1010.26	6.237	10.60%
10mer_H2_Db	6	42	VIS	CNLYVWYSYY	VCL	1332.54	5.48	9.31%
10mer_H2_Db	7	45	CNL	YVWYSYYVCL	LFL	1317.57	4.949	8.41%
10mer_H2_Db	8	40	LPV	ISCNLYVWYS	YYV	1206.42	4.116	6.99%
10mer_H2_Db	9	93	SFF	CMSFDLYDYG	GMG	1195.34	2.565	4.36%
10mer_H2_Db	10	85	SFL	LCVYFSFFCM	SFD	1241.56	2.081	3.54%
11mer_H2_Db	1	96	CMS	FDLYDYGGMGL	GLV	1232.38	15.09	18.98%
11mer_H2_Db	2	122	FWL	VGVLLFYLNFI	SSF	1279.59	13.674	17.20%
11mer_H2_Db	3	44	SCN	LYVWYSYYVCL	LFL	1430.73	13.575	17.08%
11mer_H2_Db	4	42	VIS	CNLYVWYSYYV	CLL	1431.67	11.283	14.19%
11mer_H2_Db	5	45	CNL	YVWYSYYVCLL	FLS	1430.73	9.818	12.35%
11mer_H2_Db	6	62	GIF	VIIVYFSSIGF	CEV	1226.49	8.649	10.88%
11mer_H2_Db	7	85	SFL	LCVYFSFFCMS	FDL	1328.64	7.987	10.05%
11mer_H2_Db	8	93	SFF	CMSFDLYDYGG	MGL	1252.39	7.881	9.91%
11mer_H2_Db	9	84	FSF	LLCVYFSFFCM	SFD	1354.72	7.856	9.88%
11mer_H2_Db	10	107	MGL	GLVVSDMYLVY	YFW	1240.48	7.436	9.35%

Matrix: 8mer_H2_Db.p.mtx; Consensus: QNWNCCTI; Optimal Score: 52.494; Matrix: 9mer_H2_Db.p.mtx; Consensus: FCIHNCDYM; Optimal Score: 50.365; Binding Threshold: 17.96; Matrix: 10mer_H2_Kd.p.mtx; Consensus: WYPPPGKTTL; Optimal Score: 44.281; Binding Threshold: 21.13; Binding Threshold: 33.04;

Matrix: 11mer_H2_Db.p.mtx, Consensus: CGVYNFYYCCY, Optimal Score: 79.495, Binding Threshold: 56.96. (All rows highlighted in red represent predicted binders & A peptide highlighted in violet has a C-teminus predicted by the cleavage model used).

Table 3: Cascade SVM based High affinity TAP Binders of NADH dehydrogenase subunit 6 (mitochondrion) proteins from *D. medinensis*.

Peptide Rank	Start Position	Sequence	Score	Predicted Affinity
1	83	FLLCVYFSF	8.641	High
2	70	IGFCEVFSL	8.64	High
3	50	YYVCLLFLS	8.637	High
4	131	FISSFLTFM	8.635	High
5	24	KSALFLVFS	8.621	High
6	92	FCMSFDLYD	8.615	High
7	128	YLNFISSFL	8.604	High
8	76	FSLDFFSFL	8.594	High
9	22	PMKSALFLV	8.545	High
10	53	CLLFLSGIF	8.538	High
11	95	SFDLYDYGG	8.514	High
12	61	FVIIVYFSS	8.475	High
13	57	LSGIFVIIV	8.468	High
14	14	SMSYFSFDP	8.463	High
15	135	FLTFMGALR	8.439	High
16	52	VCLLFLSGI	8.423	High

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17	36	LLPVISCNL	8.421	High
18	72	FCEVFSLDF	8.388	High
19	41	SCNLYVWYS	8.352	High
20	1	MLFFFVLVS	8.267	High
21	34	LGLLPVISC	8.233	High
22	51	YVCLLFLSG	8.215	High
23	66	YFSSIGFCE	8.171	High
24	94	MSFDLYDYG	7.945	High
25	17	YFSFDPMKS	7.704	High
26	56	FLSGIFVII	7.654	High
27	21	DPMKSALFL	7.542	High
28	87	VYFSFFCMS	7.537	High
29	124	VLLFYLNFI	7.481	High
30	62	VIIVYFSSI	7.476	High
31	102	GGMGLGLVV	7.172	High
32	27	LFLVFSLLG	7.113	High
33	38	PVISCNLYV	7.045	High
34	32	SLLGLLPVI	6.758	High
35	125	LLFYLNFIS	6.681	High
36	6	VLVSMLFAS	6.513	High
37	106	LGLVVSDMY	6.43	High
38	31	FSLLGLLPV	6.377	High
39	15	MSYFSFDPM	6.281	High
40	16	SYFSFDPMK	6.158	High
41	82	SFLLCVYFS	6.05	High
42	5	FVLVSMLFA	6.007	High

* TAPPred showing Cascade SVM based High affinity TAP Binders sites, their sequence, rank, position and scores are displayed in the tabular output are to be found 15 High affinity TAP Transporter peptide regions which represents predicted TAP binders residues which occur at N and C termini NADH dehydrogenase subunit 6 (mitochondrion) from *D. medinensis*.

* The RANKPEP consists of a list of selected peptides binding potential (score) to the MHC molecule from the query given at a selected threshold. Peptides shown here contain a C-terminal residue that is predicted to be the result of proteasomal cleavage and also focus on the prediction of conserved epitopes that help to avoid immune evasion resulting from mutation. Proteasomal cleavage options are only applied to the prediction of MHCI-restricted peptides.

* TAPPred showing Cascade SVM based High affinity TAP Binders sites, their sequence, rank, position and scores are displayed in the tabular output are to be found 42 High affinity TAP Transporter peptide regions which represents predicted TAP binders residues which occur at N and C termini NADH dehydrogenase subunit 6 (mitochondrion) from *D. medinensis.*

Conclusion

NADH dehydrogenase subunit 6 (mitochondrion) an antigenic proteins from D. medinensis involved multiple antigenic components to direct and empower the immune system to protect the host from the pathogenesis. Major histocompatibility complexes I and II (MHC-I and MHC-II) display specificity to bind with their respective epitopes. MHC class molecules are cell surface proteins that take active part in host immune reactions to response for almost all antigens. This knowledge of the immune responses to an antigen protein NADH dehydrogenase subunit 6 (mitochondrion) from *D. medinensis* clear that the whole protein is not necessary for raising the immune response, but a small fragment of antigen can induce immune response against whole antigen. This means the increase in affinity of MHC binding peptides may result in enhancement of immunogenicity of NADH dehydrogenase subunit 6 (mitochondrion) from *D. medinensis* hence are helpful *in silico* to design and develop highly predictive computational tools for the identification of T-cell epitopes. Finally, accurate prediction remains vital for the future to design synthetic peptide vaccine.

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