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In Silico Identification of Epitope-Based Peptide Vaccine for Nipah Virus

Vikas Kaushik[1]

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Abstract
Nipah virus was first appeared in Malaysian 1998, which further found be outburst in neighbor countries i.e. Bangladesh, Singapore, and India. Currently there is no effective drug or vaccine available only supportive care and prevention are way to manage it. Epitope based vaccine could be the best way to cure Nipah virus infection. In this study, the proteome of Nipah virus was retrieve from UniProt database and were subjected to check for allergenicity using Allergen FP v.1.0 tool. NetMHCII 2.3 server screened epitopes from non-allergen proteins and Vaxijen tool was used to identify the most antigenic epitopes binds with MHC class II molecules. Two potent T cell epitopes LLFVFGPNL and KYKIKSNPL were found, which binds with HLA-DRB1*01:01 and HLA-DRB1*07:01 MHC class II alleles. PepstrMod and Swiss-Model server were used to build 3D structure model of epitopes and alleles, respectively. Further identified epitopes were docked with HLA alleles using AutoDock vina tool to confirm binding ability. The epitopes LLFVFGPNL and KYKIKSNPL had binding affinity of − 8.1 kcal/mol and − 5.7 kcal/mol with HLA-DRB1*01:01 and HLA-DRB1*07:01 alleles, respectively. Solidity of predicted epitope—allele docked complex were evaluating by molecular dynamics simulation.HLA distribution analysis was performed for predicted epitopes using the population coverage tool of Immune Epitope Database (IEDB). These predicted epitopes cover maximum number of populations in India as well as worldwide. Therefore, these epitopes could be potent vaccine candidates to counter Nipah virus by testing in wet lab.

Keywords Alleles · Epitopes · Nipah virus · MHC class II · Population coverage

Introduction

Nipahvirus (NiV) originates from the *Paramyxoviridae* family and genus *Henipavirus*. In 1999 it was isolated and recognized in Malaysia and Singapore during an outbreak of encephalitis mostly amongst farmers concerned to pigs and also the people having close contact to the same. Nipah virus named after the village of its origin, Sungai Nipah in Malaysia Peninsula. In the Malaysia and Singapore Nipah virus outbreak, transmission happened via interaction between people and pigs, while in Bangladesh and India, it occurred by absorption of date palm fluid which is contaminated and also through human-to-human transmission (Ang et al. 2018). There are as of now no drugs or vaccines available for either people or animals for Nipah virus infection in spite of the fact that WHO have distinguished Nipah as a priority disease for the WHO Research and Development. Intensive supportive care is recommended to cure Nipah virus infection. Nipah virus can also be communicated to human-to-human and animals to humans or through contaminated foods (WHO 2018). Humans infected with Nipah virus had a range of clinical presentations, which may range from infection (asymptomatic) to sever diseases related to respiratory system and may finally be converted to lethal encephalitis.

Fruit bats that belong to Pteropodidae family are nominated as the natural host of this virus. Nipah virus was first outbreaks in Malaysia, Bangladesh, Singapore, and India (Chua et al. 1999; Gurley et al. 2007; Paton et al. 1999; Chadha et al. 2006; Arankalle et al. 2011). Zoonotic communication of the Nipah virus through pigs and bats to human has also been reported of (Chua et al. 2000; Luby et al. 2009). Recently in May, 2018, a Nipah virus outbreak was reported from Kozhikode district of Kerala, India, in which 17 deaths and 18 confirmed cases found as of 1 June 2018 (WHO 2018).

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To solve the problem of Nipah virus infection, vital need of a vaccine that could potentially cure Nipah virus by providing immunity against it. Here, epitopes based vaccines design approach was used to find out potential vaccine candidate. This method is rather more precise, easy, economic, consumes less time, and harmless when compared to the vaccine designs conveniently available in the market (Kumar et al. 2015).In this study, six proteins from proteome of Nipah virus were checked for allergenicity. Non-allergen proteins were subjected for prediction of epitopes. Predicted epitopes will be subjected for immunogenic properties, structural modeling and the docking with corresponding MHC II alleles to investigate the strong binding interaction. Population coverage analysis of predicted epitopes was also performed.

Methodology

Retrieval of Proteome Data

Full-genome sequence (18,252 nt) of Nipah virus amplified from lung tissue of human of West Bengal, India (Arankalle et al. 2011) were taken as sample in this study. UniProt database has been used for the complete retrieval of the proteome of the Nipah virus, which has proteome id UniProt UP000128950 (http://www.uniprot.org/proteomes/), which displays the sum of 6 coding sequence of protein.

Prediction of Allergic Properties of Proteins

The sequences of protein were then tested, for the prediction of allergenicity with the help of Allergen FP v.1.0 (Dimitrov et al. 2014).

T Cell Epitopes' Prediction

Non-allergen proteins of Nipah virus were subjected to NetMHCII 2.3 (Jensen et al. 2018) server to screen T cell epitopes which has the capability of binding having MHC class II molecules. To confirm higher confidence level of epitopes, Vaxijen (Doytchinova et al. 2007) tool was used in identification of epitopes having higher confidence level of binding with MHC class II alleles. High scorer epitopes having Vaxijen (Antigenicity) Score $\geq$ 1.1 were selected for analysis.

Epitopes' Toxicity Prediction

Toxicity of designated peptides were predicted through using Toxin Pred (Gupta et al. 2013) tool. Non-toxic peptides were selected for study.

Table 1 AllergenFP result of 6 proteins of Nipah virus

S. no.	UniProt id	Allergen FP
1	D2DEC2	Allergen
2	D2DEC0	Non-allergen
3	D2DEB7	Non-allergen
4	D2DEC1	Allergen
5	D2DEB9	Non-allergen
6	D2DEB8	Non-allergen

Molecular Modeling of Epitopes and HLA Alleles

PEPstrMOD server was used to build 3D structures of the predicted epitopes (Kaur et al. 2007). SWISS-MODEL server was utilized to build 3D structures of predicted corresponding HLA alleles (Waterhouse et al. 2018).

Epitopes' Molecular Docking and HLA Alleles

AutoDock Vina was used to perform the docking of selected epitopes with HLA alleles (Trott and Olson 2010). Among nine conformation generated by Vina tool, best one has been nominated based on lowest binding energy. Ligand and protein preparation were done by using AutoDock tool.

Molecular Dynamic Simulation Studies

Epitope-allele complex were subjected to simulation by utilizing NAMD (Phillips et al. 2005) implanted with program VMD (Visual Molecular Dynamics) (Humphrey et al. 1996).

Population Coverage Analysis

MHCPred was used to predict epitope quantitatively to major histocompatibility complexes (Guan et al. 2003), whereas the IED tool of population coverage was used to predict population coverage of the predicted epitopes which are MHC-II restriction based (Bui et al. 2006).

Results and Discussion

Allergenicity Prediction

Total six proteins were identified as having Non-allergen property as displayed in Table 1.

Table 2 Epitopes predicted based on NetMHCII 2.3 Server and VaxiJen (antigenicity) score

Protein Id	Peptide	Allele	Binding affinity (nM)	Vaxijen	Antigen/non-antigen
D2DEC0	LLFVFGPNL	DRB1_0101	532.1	2.3879	Antigen
	KYKIKSNPL	DRB1_0701	129.6	1.3649	Antigen
	WISIVPNFI	DRB1_0701	21.5	1.4793	Antigen
	ISIVPNFIL	DRB1_0701	84.1	1.9433	Antigen
D2DEB7	WSFAMGVAT	DRB1_0101	321.0	1.3526	Antigen
D2DEB9	INGVISKRL	DRB1_0701	28.0	1.1631	Antigen
	INGVISKRL	DRB1_1301	62.3	1.1631	Antigen

Antigenicity scale 1.1 and above were selected

Table 3 Template/crystal structure Pdb Id used in MHC class II alleles structure modeling

Allele name	Template structure (Pdb Id)	Crystal structure/model
HLA-DRB1*01:01	4AH2	Crystal structure
HLA-DRB1*07:01	3C5 J	Model
HLA-DRB1*13:01	6CQL	Model

Table 4 Docking results of epitopes with HLA allele structures using AutoDock vina

Allele	Epitope	Binding energies (Kcal/mol)
LLFVFGPNL	HLA-DRB1*01:01	−8.1
KYKIKSNPL	HLA-DRB1*07:01	−5.7
WISIVPNFI	HLA-DRB1*07:01	−4.7
ISIVPNFIL	HLA-DRB1*07:01	−4.6
WSFAMGVAT	HLA-DRB1*01:01	0.0
INGVISKRL	HLA-DRB1*07:01	−3.9
INGVISKRL	HLA-DRB1*13:01	−4.8

T Cell Epitope Prediction

NetMHCII 2.3 server predicted T-cell epitopes with binding affinity from protein sequence against HLA class II alleles. VaxiJen server further assessed these epitopes were annotated on the basis scores ≥ 1.1, to predict antigenicity to elicit potent immune responses as shown in Table 2. Binding affinity of epitopes LLFVFGPNL and KYKIKSNPL with alleles HLA-DRB1*01:01 and HLA-DRB1*07:01 were 532.1 nm and 129.6 nm were predicted by NetMHCII 2.3 server.

Molecular Modeling of Epitopes and HLA Alleles

PEPstrMOD web server built 3D structures of the predicted epitopes. HLA-DRB1*07:01 and HLA-DRB1*13:01 homology model having template PDB Id 3C5J and 6CQL as shown in Table 3 built 3D structures of the HLA alleles using Swiss-Model server. Alleles HLA-DRB1*01:01 had crystal structure with PDB Id 4AH2 respectively. The quality of the homology model of alleles was verified with the help of Ramachandran plot. This plot was drawn by using Swiss-Model server which validates the model having > 90%, of the whole residues covering mostly the favored regions. Similarly, Kamthania and Sharma performed modeling of T-cell epitopes of Nipah virus' antigenic proteins nulceocapsid, phosphoprotein, matrix, fusion, glycoprotein, L protein, W protein, V protein and C protein along with their corresponding MHC class I alleles (Kamthania and Sharma 2015).

Molecular Docking of Epitopes and HLA Alleles

Using AutodockVina, the molecular docking between epitopes and alleles was performed. The binding affinities of epitopes with alleles were shown in Table 4.

Docked complex of epitopes and allele were shown in Figs. 1 and 2. As Similar, Ali et al. (Ali et al. 2015) docked epitopes VPATNSPEL, NPTAVPFTL and LLFVFGPNL of Nulceocapsid, V protein and Fusion protein of Nipah virus with their corresponding alleles HLA-B7, HLA-B*2705 and HLA-A2 MHC class I allele and found considerable binding energy.

Molecular Dynamics Simulation

NAMD was used for the molecular dynamics' simulation of the docked complex, which shows the firmness of the complex structure. RMSD's maximum value for the peptide

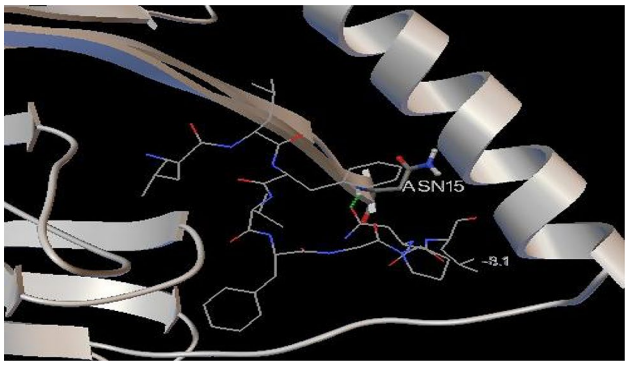

Fig. 1 Docked complex of peptide LLFVFGPNL with HLA-DRB1*01:01 allele. Complex depicting epitope formed one H-bond with ASN15 of allele. Epitope is represented as lines and colored as atom type

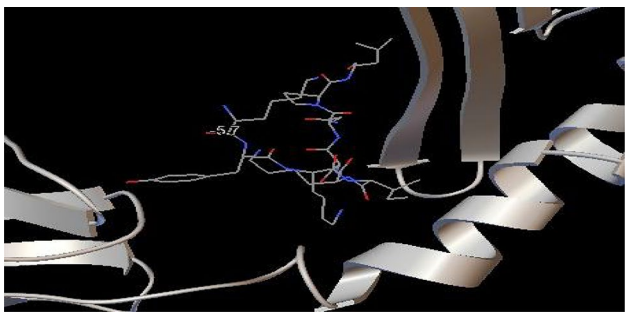

Fig. 2 Docked complex of peptide KYKIKSNPL with HLA-DRB1*07:01 allele. Epitope is represented as lines and colored as atom type

LLFVFGPNL—HLA-DRB1*01:01 allele complex was at 1.34 Å (Fig. 3), whereas peptide KYKIKSNPL—HLA-DRB1*07:01 allele complex was at 1. 46 Å (Fig. 4). As similar, Ravichandran et al. (2018) performed molecular dynamics simulation of docked complex of predicted epitope ELRSELIGY of phosphoprotein and YPLLWSFAM of nulceocapsid protein of Nipah virus with HLA-C*12:03 alleles.

Toxicity Prediction of Predicted Epitopes

Epitopes LLFVFGPNL and KYKIKSNPL having VaxiJen (Antigenicity) Score 2.3879 and 1.3649, respectively having lowest binding energy with their respective alleles, were chosen to predict toxicity and also conservancy analysis. Prediction of toxicity of epitopes as shown in the Table 5 was done using Toxin Pred.

Analysis of Population Coverage

IEDB tool was used to predict population coverage analysis of the epitopes and their corresponding MHC-II alleles. Epitopes and MHCPred were provided to IEDB population coverage tool as input. Epitopes LLFVFGPNL and KYKIKSNPL have shown the elicitation of the immune response of 28.63–22.06% total world population as shown in the Figs. 5 and 6. Epitopes LLFVFGPNL and KYKIKSNPL have population coverage 35.82 and 11.72 in India. The results of the population coverage analysis show the epitopes distribution in the different regions.

Conclusion

Two potent T cell epitopes LLFVFGPNL and KYKIKSNPL were identified having antigenicity Score 2.3879 and 1.3649 and had strong binding affinity with MHC class II alleles. These epitopes had lowest binding − 8.1 kcal/mol and − 5.7 kcal/mol with HLA-DRB1*01:01 and HLA-DRB1*07:01 alleles. These predicted epitopes cover maximum number of populations in India as well as worldwide. Therefore, these epitopes can

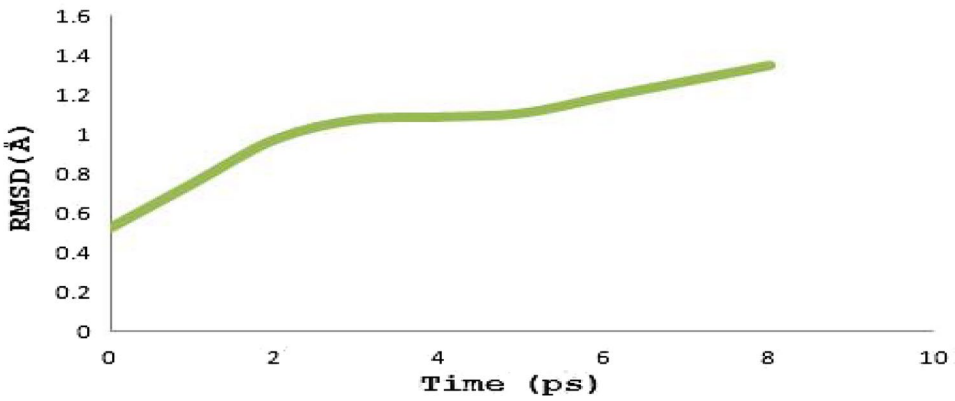

Fig. 3 Graph displaying RMSD for Peptide LLFVFGPNL—HLA-DRB1*01:01 allele complex, resulted in highest peak at 1.34 Å

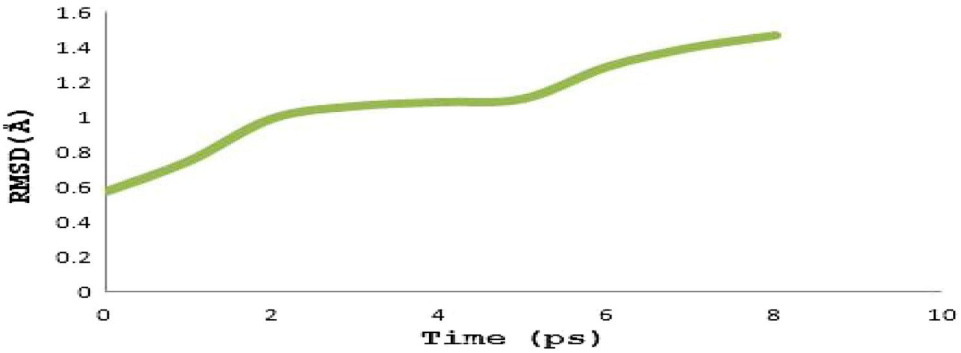

Fig. 4 Graph displaying RMSD for Peptide KYKIKSNPL—HLA-DRB1*07:01 allele complex, resulted in highest peak at 1.46 Å

Table 5 Selected vaccine candidates using MHC Pred tool to check their binding affinity to the maximum number of HLA alleles and toxicity prediction through Toxin Pred tool

Epitope	No. of HLA binders	HLA-allele with predicted IC50 value (nM)	Toxicity score	Toxicity prediction
LLFVFGPNL	2	HLA-DRB1*01:01 (105.20) HLA-DRB1*07:01 (281.19)	−0.96	Non-toxin
KYKIKSNPL	2	HLA-DRB1*01:01 (1.69) HLA-DRB1*04:01 (229.09)	−0.70	Non-toxin

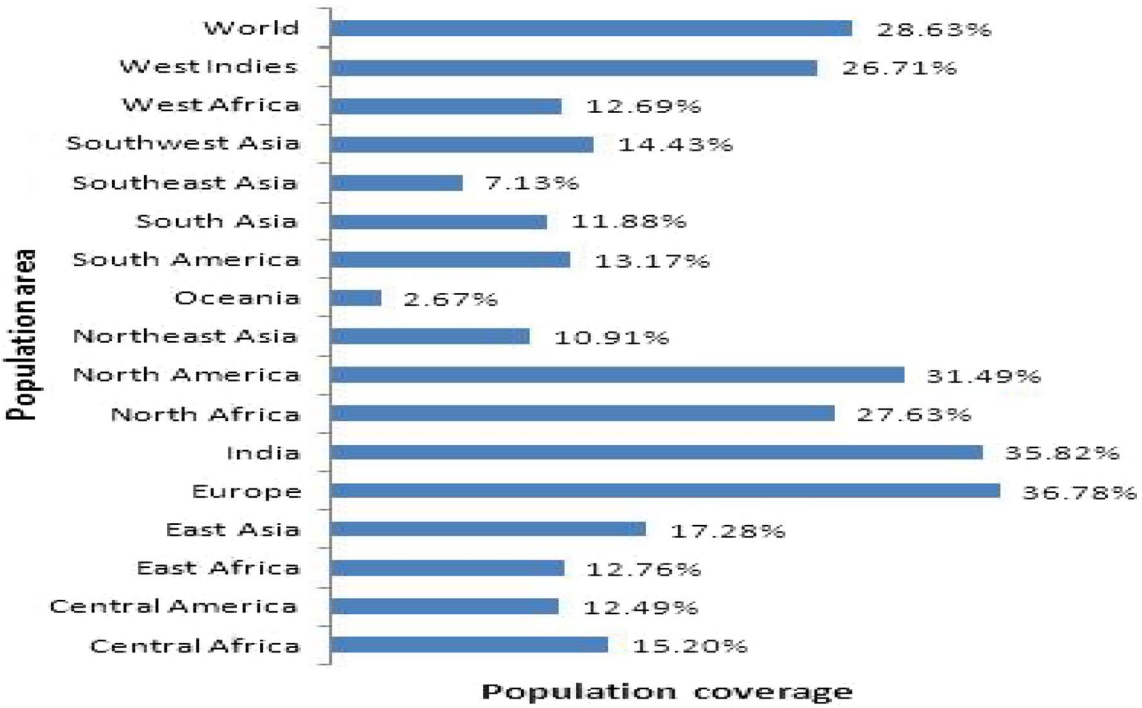

Fig. 5 Worldwide population conservancy analysis for epitope LLFVFGPNL through IEDB tool

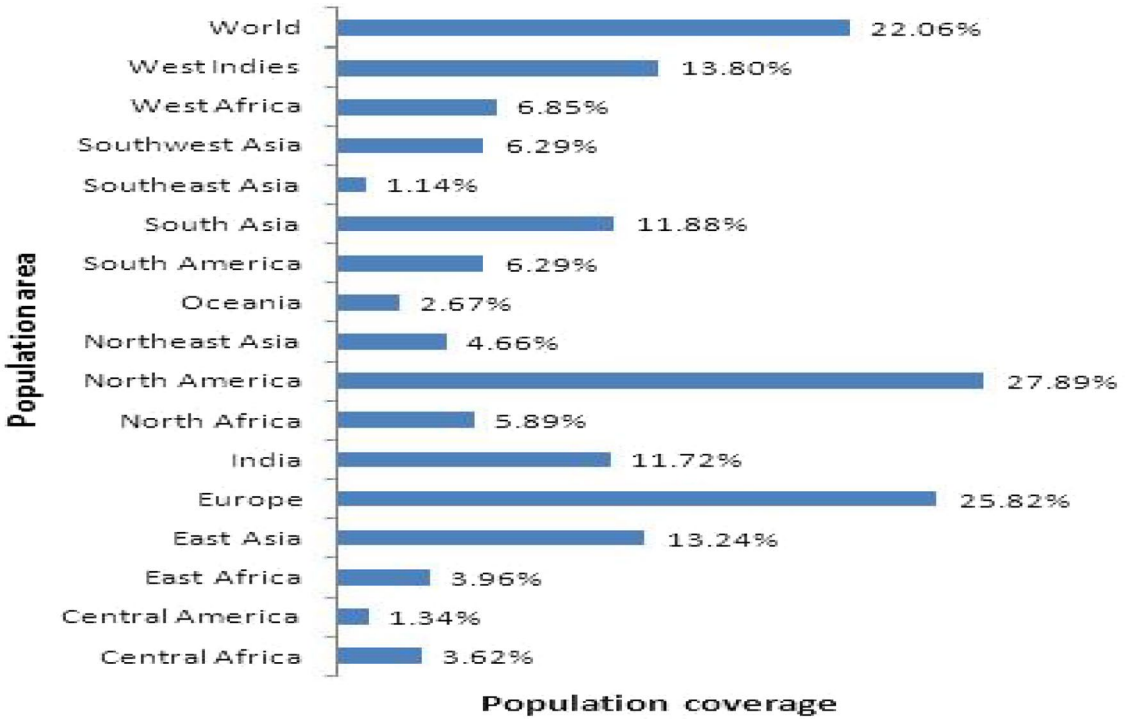

Fig. 6 Worldwide population conservancy analysis for epitope KYKIKSNPL through IEDB tool

be used in designing vaccines against Nipah virus after wet lab verification.

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Compliance of Ethical Standards

Conflict of interest The author hereby declares that they have "no conflict of interest".

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

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