



# First study of complete genome of Dengue-3 virus from Rajasthan, India: genomic characterization, amino acid variations and phylogenetic analysis



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## ABSTRACT

First study on the complete genome characterization of Dengue-3 virus is reported from dengue endemic state Rajasthan, India. The genome of 10,672 base pairs was studied with reference to global and the regional genomes of Dengue-3 virus. 388 variations were observed in the nucleotide sequences with reference to the NCBI genome, including 34 variations in the amino acids. Of these 34 AA variations, 4 variations showed AA substitution in Envelope proteins and 1 in Anchored capsid region. The remaining 29 variations were observed in amino acids constituting non structural (NS) proteins. The reported mutations, especially those leading to amino acid variations in non-structural proteins of virus may influence the clinical profile of patients and accuracy of ongoing diagnostic tests. Reported amino acid variations in virus envelope may influence the immune response of patients. Phylogenetic studies showed similarity of reported genome with genomes from India, Pakistan and China.

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## 1. Introduction

Dengue Fever (DF) with Dengue Hemorrhagic Fever (DHF) is spreading fast world wide (390 million cases annually) (Bhatt et al., 2013) including India as one of the endemic countries (more than 90,000 cases in 2015) ([www.nvbdc.gov.in](http://www.nvbdc.gov.in)). In India, although the disease burden due to dengue is increasing yet there have been very few studies on its genomic constitution and no studies from the disease endemic state Rajasthan. So far, some studies on the partial genomic segments (Kukreti et al., 2009, 2008; Domingo et al., 2006) and some studies on complete genomes of Dengue-1 and Dengue-3 viruses have been published (Patil et al., 2011; Dayaraj et al., 2011; Anoop et al., 2012; Sharma et al., 2011). Dengue is single stranded positive sense RNA genome and is one of the fastest mutating arbo-viruses (Drake, 1993; Holmes and Burch, 2000). A significant variation in its nucleotide sequence which leads to amino acid alterations may facilitate the synthesis of modified viral proteins in the host cell interfering the normal immune response of the dengue patient. Owing to increasing disease burden due to dengue, periodic genomic surveillance of circulating dengue viruses is a necessity.

The state of Rajasthan, India is one of the worst affected states from dengue. The disease was first reported from the state in the year 1969 (Padbidri et al., 1973) and Dengue-3 was reported as the causative virus type (Padbidri et al., 1973). So far, no part or complete genome sequence of any of the dengue strains has been reported from Rajasthan, India. We have studied whole

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genome of Dengue-3 virus from a DHF patient, analysed its phylogeny and have studied nucleotide sequence variations and corresponding amino acid variations. Present paper reports the details.

## 2. Results

### 2.1. Comparison of sequence variations between cell line passaged and un-passaged samples

The serum sample from the DHF patient was subjected to nucleotide sequence determination directly as well as after passaging in C6/36 cell lines of *Aedes albopictus* mosquitoes. In both the cases (direct as well as cell passaged sample) the same observations of nucleotide sequences and the associated amino acid variations were observed.

### 2.2. Whole genome characterization of Dengue-3 virus

Complete genome of Dengue-3 virus was sequenced. In total 10,674 base pairs (bp) in un-passaged sample and 10,672 bp in passaged sample were analysed for their nucleotide sequence. The polyprotein gene range in case of unpassaged genome was from 88 to 10,260 while that of passaged genome was from 86 to 10,258. The entire assembled sequence has been deposited in the Gen Bank (unpassaged: Accession no.: KU216209; passaged: Accession no.: KU216208). The pair-wise nucleotide alignment using BLAST showed that in first 5 best matches, observed genome resembled the complete genome sequences of India, Pakistan, China and Sri Lanka (Table 1). The observed sequence which is first complete genome of Dengue-3 virus from Rajasthan, India showed 98–99% identity with reported Indian genomes. The phylogenetic analysis of the genome is shown in Fig. 1.

### 2.3. Variations in nucleotide sequence of observed genome with reference to global and regional genomes

The whole genomes of the DENV-3 virus (unpassaged: Accession no.: KU216209; passaged: Accession no.: KU216208) were subjected to mutation analysis. These genomes were compared taking two reference whole genomes sequences into consideration: one with NCBI reference genome (Global genome, Accession no.: NC\_001475.2) and another with genome of nearest phylogeny (Regional genome, Accession no.: JQ922556.1). The mutations in the nucleotide sequences were of two types; Substitution and Insertion type. As many as 388 variations were observed in the reported genome sequence when compared with the NCBI reference genome (global genome) and 109 variations were observed when compared with the regional genome (genome of nearest phylogeny) (Table 2).

It was observed that when compared with the global genome (NC\_001475.2), the observed Rajasthan genome showed one insertion in the 5'UTR region (75th position; 75–76insT) and one insertion in the 3'UTR region (10436th position; 10,436–10437insA), both showing non-coding effects (Table 3). The rest of 386 mutations were of substitution type, belonged to the coding region. Similarly, when the observed genome was compared with genome of nearest phylogeny (JQ922556.1), it showed one insertion in the 5'UTR region (54th position; 54–55insT) and one in the 3'UTR region (10415th position; 10,415–10416insA). Rest of 107 mutations observed were of substitution type (Table 4). It was also observed that when observed genome was compared with global genome (NC\_001475.2), mutations were observed in membrane glycoprotein precursor M whereas when compared to genome of nearest phylogeny (JQ922556.1) this mutation was not observed.

**Table 1**

Alignments of reported genome of Rajasthan, India with other published genomes of nearby phylogeny.

| S.No | Gene Bank data   | Max score | Total score | Query cover | E value | Identity | Accession no. |
|------|--|-----------|-------------|-------------|---------|----------|---------------|
| 1    | Dengue virus 3 isolate DENV-3/IND/58760/2005, complete genome    | 18,714    | 18,802      | 99%         | 0.0     | 99%      | JQ922556.1    |
| 2    | Dengue virus 3 isolate D3/Pakistan/55505/2007, complete genome   | 18,628    | 18,715      | 99%         | 0.0     | 99%      | KF041255.1    |
| 3    | Dengue virus 3 strain GWL-25, complete genome                    | 18,626    | 18,713      | 100%        | 0.0     | 99%      | AY770511.2    |
| 4    | Dengue virus 3 isolate ND143 from India, complete genome         | 18,608    | 18,695      | 100%        | 0.0     | 99%      | FJ644564.1    |
| 5    | Dengue virus 3 D3/Pakistan/43298/2006, complete genome           | 18,583    | 18,760      | 99%         | 0.0     | 99%      | KF041259.1    |
| 6    | Dengue virus 3 isolate D3/Pakistan/52440/2006, complete genome   | 18,557    | 18,665      | 99%         | 0.0     | 99%      | KF014257.1    |
| 7    | Dengue virus 3 isolate D3/Pakistan/55709/2006, complete genome   | 18,557    | 18,665      | 99%         | 0.0     | 99%      | KF041256.1    |
| 8    | Dengue virus 3 isolate DEL-72, complete genome                   | 18,539    | 18,627      | 100%        | 0.0     | 99%      | GQ466079.1    |
| 9    | Dengue virus 3 isolate D3/45251/2009, complete genome            | 18,518    | 18,605      | 99%         | 0.0     | 99%      | KF041258.1    |
| 10   | Dengue virus 3 isolate D3/Pakistan/56/2008, complete genome      | 18,514    | 18,602      | 99%         | 0.0     | 99%      | KF041254.1    |
| 11   | Dengue virus 3 isolate ZJYW2009, complete genome                 | 18,500    | 18,587      | 100%        | 0.0     | 98%      | JF504679.1    |
| 12   | Dengue virus 3 strain GZ2D3, complete genome                     | 18,476    | 18,564      | 100%        | 0.0     | 98%      | JN662391.1    |
| 13   | Dengue virus 3 isolate GZ1D3, complete genome                    | 18,464    | 18,547      | 100%        | 0.0     | 98%      | GU353649.1    |
| 14   | Dengue virus 3 isolate 13GDZDVS30D, complete genome              | 18,417    | 18,504      | 99%         | 0.0     | 98%      | KF954948.1    |
| 15   | Dengue virus 3 isolate 13GDZDV30E, complete genome               | 18,411    | 18,499      | 99%         | 0.0     | 98%      | KF954949.1    |
| 16   | Dengue virus 3 isolate DENV-3/IND/59826/2005, complete genome    | 18,406    | 18,493      | 99%         | 0.0     | 98%      | JQ922557.1    |
| 17   | Dengue virus 3 isolate 13GDZSDV30A, complete genome              | 18,402    | 18,490      | 99%         | 0.0     | 98%      | KF954945.1    |
| 18   | Dengue virus 3 isolate 13GDZDV30B, complete genome               | 18,399    | 18,486      | 99%         | 0.0     | 98%      | KF954946.1    |
| 19   | Dengue virus 3 13GDZDV30C, complete genome                       | 18,397    | 18,484      | 99%         | 0.0     | 98%      | KF954947.1    |
| 20   | Dengue virus 3 isolate DENV-3/MZ/BID-V2418/1985, complete genome | 18,110    | 18,198      | 99%         | 0.0     | 98%      | FJ882575.1    |

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