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The biological events leading to the development of severe disease manifestations of dengue infections (dengue hemorrhagic fever/dengue shock syndrome, DHF/DSS) has been the focus of many investigations. Though DHF/DSS cases occur during primary dengue infections, the majority of severe dengue disease has been associated with persons experiencing a secondary heterotypic dengue infection. What do we know about the pathogenic processes that result in the exacerbation of dengue symptoms? Can these factors be identified in vitro and then correlated with clinical disease? The results of previous studies suggest that pre-existing DEN antibodies circulating in a person may be a risk factor in the development of DHF/DSS. However, other host and viral factors must be involved since only a small proprotion of the population residing in endemic dengue disease regions develop severe dengue disease.

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FOREWORD

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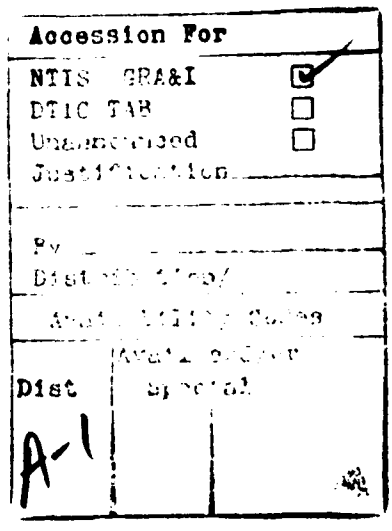

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INTRODUCTION

The biological events leading to the development of severe disease manifestations of dengue infections (dengue hemorrhagic fever/dengue shock syndrome, DHF/DSS) has been the focus of many investigations (1,8). Though DHF/DSS cases occur during primary dengue infections, the majority of severe dengue disease has been associated with persons experiencing a secondary heterotypic dengue infection (6,7). What do we know about the pathogenic processes that result in the exacerbation of dengue symptoms? Can these factors be identified *in vitro* and then correlated with clinical disease? The results of previous studies suggest that pre-existing DEN antibodies circulating in a person may be a risk factor in the development of DHF/DSS (9). However, other host and viral factors must be involved since only a small proportion of the population residing in endemic dengue disease regions develop severe dengue disease.

Antibody-dependent enhancement (ADE) of dengue virus (DEN) replication *in vitro* has been proposed as a pathogenic mechanism in the development of DHF/DSS. We believe that enhanced virus replication is an important part of DEN pathogenesis and that ADE is the result of the interplay of host cells, antibody and virus strain. We investigated DEN virus replication in order to define the parameters that could lead to enhanced growth in the presence of antibodies to flaviviruses.

SUMMARY OF PREVIOUS ACCOMPLISHMENTS FOR FY 1990

- Developed a sensitive ADE assay to examine the interplay of antibody, virus and host cells in DEN replication. Human promonocytic HL-CZ cells supported enhanced DEN replication better than K562 or U937 human cells at low MOIs (10^{-4}-10^{-6}).

- Determined that the sensitivity of the HL-CZ cells was related to the number of Fc-receptors (FcRs) and the FcR types (FcR II > FcR III > FcR I) expressed on the cell surface since blocking the FcRs by specific FcR monoclonal antibodies (MAbs) abrogated virus replication.

- Characterized the abilities of MAbs 4G2 and 3H5 to mediate virus neutralization and enhanced replication. Determined that the MAbs recognizing DEN envelope (E) glycoprotein epitopes were involved in NT and ADE and confirmed the observation that these activities were concentration related rather than epitope-directed.

- Compared the growth profiles of selected DEN viruses representing epidemiologically important genotypes using our ADE system. Viruses from endemic dengue region (Thailand) were more antibody-dependent than that of viruses from the dengue epidemic region (Caribbean).

- Attempted to define the antigenic epitopes that mediate ADE and NT by using antibodies raised against DEN-2 E glycoprotein synthetic peptides. We were able to determine that some antipeptide antibody pools were reactive in ADE and/or NT tests, though reactions appeared much weaker than the MAb controls.

- Continued to determine the nucleotide sequence encoding the non-structural (NS) regions of DEN-1 CV1636/77 virus. Of the regions examined thus far, it appeared that DEN-4 Dominica and DEN-1 CV1636/77 were very similar in the NS region, suggesting that the viruses have evolved closely or that there may be genomic recombination.

ACCOMPLISHEMENTS FOR FY 1991

Examination of FcR-expression in HL-CZ promonocytic and enhanced virus replication. Dr. Wu Tse Liu of the National Yang Ming Medical School, Taipei, Taiwan provided us with several lines of HL-CZ cells (14). We compared the virus yields of the uncloned, clone 3 and clone CCC-5 cells. The results of the enhanced growth profile of DEN-2 16681 virus were variable thus suggesting that the permissiveness of the cells to support enhanced virus replication could be intrinsically different. We investigated the discrepancy of virus yield of these cultures and determined that if the ADE results were grouped by >20% FcR-expression (rosetting) and compared with virus yield (>10^4 pfu/ml), the presence of rosetting cells was a factor in cell permissiveness (Table 1) as we had demonstrated before when comparing virus growth in U937, K562 or HuPBL cells. However, in a few cases, neither high nor low number of rosettes correlated with virus yield, thus implying that some other factors also affect virus replication. Therefore, in our analyses of ADE results, we only accepted the tests in which 1) virus control cultures (no antibody) contained no visible growth and 2) positive ADE controls of cultures containing antibody produced 10^3 pfu/ml virus yield.

Reactivities of anti-DEN-2 E glycoprotein synthetic peptide antibodies with DEN-1 and DEN-2 virus. We have previously determined the reactivities of mouse antibodies immunized with DEN-2 E glycoprotein peptides in PRNT and ADE assays. Though we were able to demonstrate some activity in sera obtained from mice immunized by i.m. and s.c. routes, there was variation between antibody specimens directed against the same peptide from heterologous mouse strains (19). To normalize antibody reactivity, sarcoma-primed BALB/C mice were immunized with individual DEN-2 E glycoprotein synthetic peptides and the resulting mouse ascites fluids (MAFs) were assessed (Table 2). To compare the anti-peptide antibodies on an equal basis, immune mouse ascites fluids (MAFs) were purified by elution from protein A columns and standardized to

1 mg/ml and examined by ELISA. The reactivities of the purified Igs were not appreciably different from crude MAFs suggesting that binding to virus antigen or peptide was related to the original strength of the MAF and was not affected by increased/decreased affinity of the antibody to the peptide.

In addition to testing each of the anti-peptide antibodies individually, we attempted to reconstitute antigenic binding sites by mixing the antibodies together (Table 3). Seven anti-peptide antibodies were mixed in various combinations and each tested for binding to antigen, for ability to neutralize virus and for mediating enhanced virus growth. Binding of MAFs, 1 μg and 10 μg of anti-peptide antibodies to DEN-2 Jamaica virus antigen were examined by ELISA, and these results reflect original MAF titers. HL-CZ cells were infected with DEN-1 16681 virus at MOI of 10^{-5}. Where the positive ADE and background culture controls cells met our acceptance criteria, the enhanced virus yields in the presence of 1 μg of anti-peptide antibodies was not consistent (Table 3). Neutralization activity of the anti-peptide antibodies against DEN-2 16681 virus was examined. One μg of an antibody was mixed with 1000 pfu of virus and incubated at 37 C for 1 hour. The surviving virus was ascertained by testing the virus/Ab mixes in the BHK-21 plaque assay (16) and the results reported as percentage of reduction of input virus (Table 3). Both anti-peptide mix 21 (antibodies to peptides 06, 240, 274, 17 and 361) and mix 22 (anti-peptides 240, 274, 17, and 361) neutralized 53% of the input virus, and anti-peptide mix 42 (antibodies to peptides 240 and 274) neutralized 100% of the input virus.

Cloning and sequencing the nucleotides encoding the non-structural DEN-1 CV1636/77 genes. The genome encoding the structural genes of DEN-1 CV1636/77 have been previously published (3). Last year we completed the nucleotide sequences encompassing NS4a, NS4b, and NS5 genomic regions of DEN-1 CV1636/77 and compared the results with the published sequences of DEN-2 (5), DEN-3 (18), and DEN-4 (15). We have completed the sequencing of the rest of the non-strucutural nucleotide regions for NS1, NS2a, NS2b, NS3 and the final 800 base pair sequence of the 3'-end of the viral RNA (Figure 1).

The similarity of the non-structural gene regions between the 4 DEN viruses are summarized in Figure 2. DEN-1, DEN-2, and DEN-3 share between 63%-68% similarity by nucleotide sequence comparison and 65%-78% similarity by their deduced amino acid sequences.over each of the non-strucutural gene regions. DEN-1 and DEN-4 however are very similar in NS3, NS4a, and NS4b regions (95%-98%); this is contrasted by a comparison of DEN-1 and DEN-4 over the NS5 region where similarity extends to only 78%. When the combined nucleotide and deduced amino acid sequences over NS3, NS4a, NS4b, and NS5 regions are examined, the similarity of 90% remains between DEN-1 and DEN-4 (Figure 3,4).

DISCUSSION

Studies to identify genomic correlates of DHF/DSS have primarily depended mouse, monkey and other laboratory experiments. Animals infected with DEN will respond by seroconversion to the infected virus but do not develop DHF/DSS. Therefore most disease parameters of infected humans are based on clinical observations, and epidemiological assements. The availability of genomic sequences of flavi- and dengue viruses, the synthesis of peptides corresponding to deduced amino acid sequences, and the development of molecular techniques, make it possible to begin studies to correlate biological activities with genomic variation.

Relevance of epitope mapping using anti-peptide antibodies. With the standardized ADE assay, we have been able to examine divergent aspects of the roles of antibody, virus and host cells. From these studies, we could determine that each component share roles in virus replication and that the ADE system developed could isolate many of these factors for further examination. In our attempts to identify the genomic regions that encode antigenic epitopes involved in biological responses using anti-peptide antibodies, we could identify the epitopes that mediate neutralization of the virus. However, the enhancing activity could not be located within a specific region using the anti-peptide antibodies. This does not mean ADE activity cannot be found, the non-or broad reactivity may only be a matter of using sub-optimal antibody concentrations, the inappropriate mix of the anti-peptides, the virus strain variability or the susceptibility of the host cell stage to virus replication. It is likely that in using anti-peptides to map strategic epitopes, a reactive result implies reconstitution of epitopes, whereas non-reactivity implies only that epitopes were not reconstituted.

Using anti-peptide sera directed against selected DEN-2 E glycoprotein regions, we have been able to demonstrate that some of the E regions will elicit antibody that will mediate enhanced virus replication, neutralization and enhancement, and neutralization alone. Though this series of experiments need to be repeated with other antibody mixes and other DEN viruses, the neutralization epitope defined by amino acids 240-274 is is the first direct association of specific E-glycoprotein regions with biological functions.

Analyses of the genetic relatedness of DEN viruses. The similarity of the non-structural genomic sequences of DEN-1 and DEN-4 viruses was unexpected. Published sequences of NS regions of DEN-2 and DEN-3 viruses led us to expect only 63%-68% homology among the DEN viruses. DEN-1 and DEN-4 viruses, however, appeared to be nearly identical from NS1 through NS5 and again at the 3'-end, suggesting that there may be a double-crossover genetic recombination. To preclude that possibility that the DEN stock cultures may have been contaminated with one or the other viruses, we plaque-picked purified virus from our CV1636/77 stock and found that they all

contained the same characteristics (data not shown). In addition, we are examining, by PCR amplification and sequencing, of other DEN-1 and DEN-4 strains in the 3'-end region to analyze the relationship.

Future studies. During this study, we were not able to achieve all the goals set forth in the original proposal. We would liked to have been able to get anti-DEN-1-peptide serum to analyze and work as we did with DEN-2 peptides. However, we were delayed by the unexpected complication of the DEN-1 sequence homology with DEN-4 and felt that was important finding to follow-up and analyze. We are planning to do work on examining patient serums that would recognize DEN-2 peptide mix 240/274 and to identifiy whether this region of the E-glycoprotein is a useful diagnostic tool.

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Tables

Table 1 Chi-square comparison of the relationship between rosette expression and virus replication in HL-CZ cells

Table 2 Reactivity of the mouse ascites fluids obtained from mice immunized with DEN-2 E glycoprotein synthetic peptides

Table 3 Mixtures of purified anti-DEN-2 synthetic peptide immunoglobulins and PRNT/ADE results

Figures

Figure 1 Location of CV1636/77 clones sequenced and the diagram of the similar regions between DEN-1 and DEN-4.

Figure 2 Percentage of homology of the non-structural region nucleotide and deduced amino acid sequences of DEN viruses.

Figure 3 Comparison of the nucleotide sequences comprising the non-structural genome regions of DEN-1, DEN-2, DEN-3 and DEN-4 viruses.

Figure 4 Comparison of the deduced amino acid sequences of the non-structural regions of the four DEN viruses.

TABLE 1

Chi-square comparison of the relationship between rosette expression and virus replication in HL-CZ cells

PFU VIRUS/% ROSETTE	> 20% ROSETTE	< 20% ROSETTE
> 10^3 VIRUS/ML	6*	1
< 10^3 VIRUS/ML	1	4

*p <0.001

TABLE 2 REACTIVITY OF ANTI-PEPTIDE ANTIBODIES AGAINST HOMOLOGOUS PEPTIDE, DENGUE-2 AND DENGUE-1 VIRUSES

PEPTIDE[a]	ANTIGEN USED IN ELISA[b]		
	PEPTIDE	DENGUE-2	DENGUE-1
1-2*	6400	1280	320
35	102400	128000	4000
3-8/1	100	<10	<10
4-6	400	40	10
04*	1600	160	10
142*	3200	640	10
167*	100	10	<10
06*	25600	5120	40
240#	1600	1280	80
274*	100	10	<10
16*	800	160	80
17#	3200	160	<10
361*	12800	640	80
437*	3200	20	80
+control	--	>12800	>12800
-control	--	<10	<10

[a] Roehrig et al (19).

[b] Each well of the ELISA plates were coated with either 1 ug of peptide, or gradient-purified virus antigen. The antibody titers as reported as positive were adjusted by subtracting 2 standard-deviations above background reactions.

* Synthetic peptides which are distinct by deduced amino acid sequence from DEN-2 Jamaica.

\# Synthetic peptides that are not distinct from DEN-2 Jamaica virus (>90% homology) but are in the NT/ADE region mapped by anti-peptide antibodies.

TABLE 3 ANTIBODY-DEPENDENT ENHANCEMENT (ADE) AND PLAQUE REDUCTION NEUTRALIZATION (PRNT) RESULTS

ANTI-PEPTIDE ANTIBODIES 100 NG[a]									PRNT[b]		ADE[c]
1-2	35	3/8-1	4-6	06	240	274	17	361	DEN1	DEN2	pfu/ml
■									20	35	250
	■								15	41	< 7
		■							19	32	< 7
			■						24	35	< 7
				■					15	32	>8300
					■				24	31	280
						■			31	32	4600
							■		27	36	>8300
									28	46	< 7
■	■	■	■	■	■	■	■	■	32	38	< 7
	■	■	■	■	■	■	■	■	36	42	3700
		■	■	■	■	■	■	■	42	56	260
			■	■	■	■	■	■	36	42	1400
				■	■	■	■	■	22	**53**	400
					■	■	■	■	18	**53**	< 7
						■	■	■	38	40	< 7
							■	■	10	19	< 7
		■	■	■	■	■	■		28	**54**	< 7
			■	■	■	■	■		16	**56**	< 7
				■	■	■	■		4	38	1500
					■	■	■		8	35	4000
						■	■		4	32	4500
									35	**100**	800
			■	■	■				16	27	5500
				■	■				0	10	3600
4G2 MAb*, flavivirus group reactive									96	97	>8300
3H5 MAb*, dengue-2 specific									12	**100**	8300
Virus control@									0	0	< 7

Legend for TABLE 3

Purified anti-DEN-2 peptide antibodies, used 100 ng of each anti-peptide in the mixes. Filled boxes indicate the anti-peptide serum used.

PRNT by BHK-21 semi-micro assay. Average plaques of DEN virus in each 24-well = 26. Serum and virus were incubated at 37 C for 1 hour. Percentage of neutralization shown here. >50 % reduction shown in **bold face.**

ADE assay with HL-CZ cells and MOI of 10^{-5}. Cells were infected and incubated for 4 days at 37 C in 5% CO_2. Virus replication was assessed by plaque titration in BHK-21 semi-micro assay. Results are the average of 3 experiments.

* The amount of 4G2 used for PRNT = 10 ug, for ADE = 1 ug. 3H5 used for PRNT = 1 ug, for ADE = 100 ng.

@ Virus control = only virus without antibody for PRNT and ADE.

ABSTRACT

ASTMH 1991

206 THE NON-STRUCTURAL GENOME OF DENGUE-1 VIRUS CV1636/77: COMPARISON OF THE NUCLEOTIDE AND DEDUCED AMINO ACID SEQUENCES WITH THE OTHER DENGUE SEROTYPES.

Chu MC, Putvatana R, and Trent DW. Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, Centers for Disease Control, Ft. Collins, Colorado 80526

The determination of the entire nucleotide and deduced amino acid sequences of the DEN-1 Jamaica CV1636/77 virus together with the known sequences of DEN-2, DEN-3 and DEN-4 viruses provide a complete sequence database of the DEN serotype complex. We have previously presented analyses of the nucleotide sequences encoding the structural and the non-structural NS3-NS4-NS5 regions. Sequence analyses of the entire genomic RNA and cloned cDNA of DEN-1 reveal that the genomic RNA contains 10,641 nucleotides and encodes an open reading frame of 10,224 nucleotides that translate into 3408 amino acid residues. A comparison of the DEN-1 sequence with DEN-2 (Jamaica; Deubel *et al.*, 1988), and DEN-3 (H87; Osatomi *et al.*, 1990) reveal that the genomic sequences encoding the structural (C-prM-M-E) and some of the non-structural (NS1, NS3, and NS5) regions are conserved (>70% homology). The 3'non-coding regions of DEN-1, DEN-2, DEN-3, and DEN-4 (Dominica; Mackow *et al.*, 1987) are of different nucleotide lengths comprising 387, 455, 448, and 385 base pairs respectively. The entire non-structural sequences for DEN-1 and DEN-4 share >90% identity. These results reveal a close evolutionary relationship between Caribbean DEN-1 and DEN-4 viruses which cannot be detected by conventional serological methods. Thus the sequence database of all the DEN virus serocomplex will be a useful tool in studying the genetic variation and evolution of these viruses.

Prepared for ASTMH 1991

ABSTRACT

Antibody-dependent enhancement (ADE) of dengue (DEN) virus infection in human mononuclear cells in vitro has been standardized using a human promonocytic cell line HL-CZ, purified monoclonal antibodies (MAbs), and select DEN viruses. Characterization of the Fc-receptors (FcRs) expressed on HL-CZ cells have indicated that subsets of FcR mediate ADE better than others. Using this standardized system, we have compared the ability of mouse anti-DEN 2 envelope (E) peptides to elicit virus neutralization and ADE. Peptides 1-2, 437 appear to elicit ADE activity in contrast to other peptides that appear to elicit neutralization but not ADE. Though these assays need to be repeated, it appears that differential functions may be attributed to particular E genomic regions. The comparison of the nucleotide sequences of DEN-1 RNA encoding the non-structural proteins to the other DEN sequences has revealed that DEN-4 and DEN-1 share > 90% similarity in NS3 and NS4a, 4b genome regions. DEN-3 and DEN-1 have a deletion in in NS5 that is conserved in other DEN-1 and DEN-3 isolates. These genomic sequence comparisons indicate that non-structural region differences need to be studied as well for our understanding of DEN replication and pathogenesis.

PUBLICATIONS

1. Chu MC, Huang GH, Collins ND, and Trent DW. An experimental model for analyzing antibody-dependent enhanced growth of dengue virus in human promonocytic HL-CZ cells. Submitted for publication.

2. Chu MC, Putvatana R, Huang GH, Roehrig JT, and Trent DW. Analyses of the reactivities of anti-dengue-2-E glycoprotein antibodies to dengue-1 and dengue-2 viruses. Manuscript in preparation.

3. Chu MC, Putvatana R, Repik P and Trent DW. Similarities of the dengue-1 CV1636/77 and dengue-4 Caribbean viruses: genomic sequence comparison and oligonucleotide fingerprinting. Manuscript in preparation.

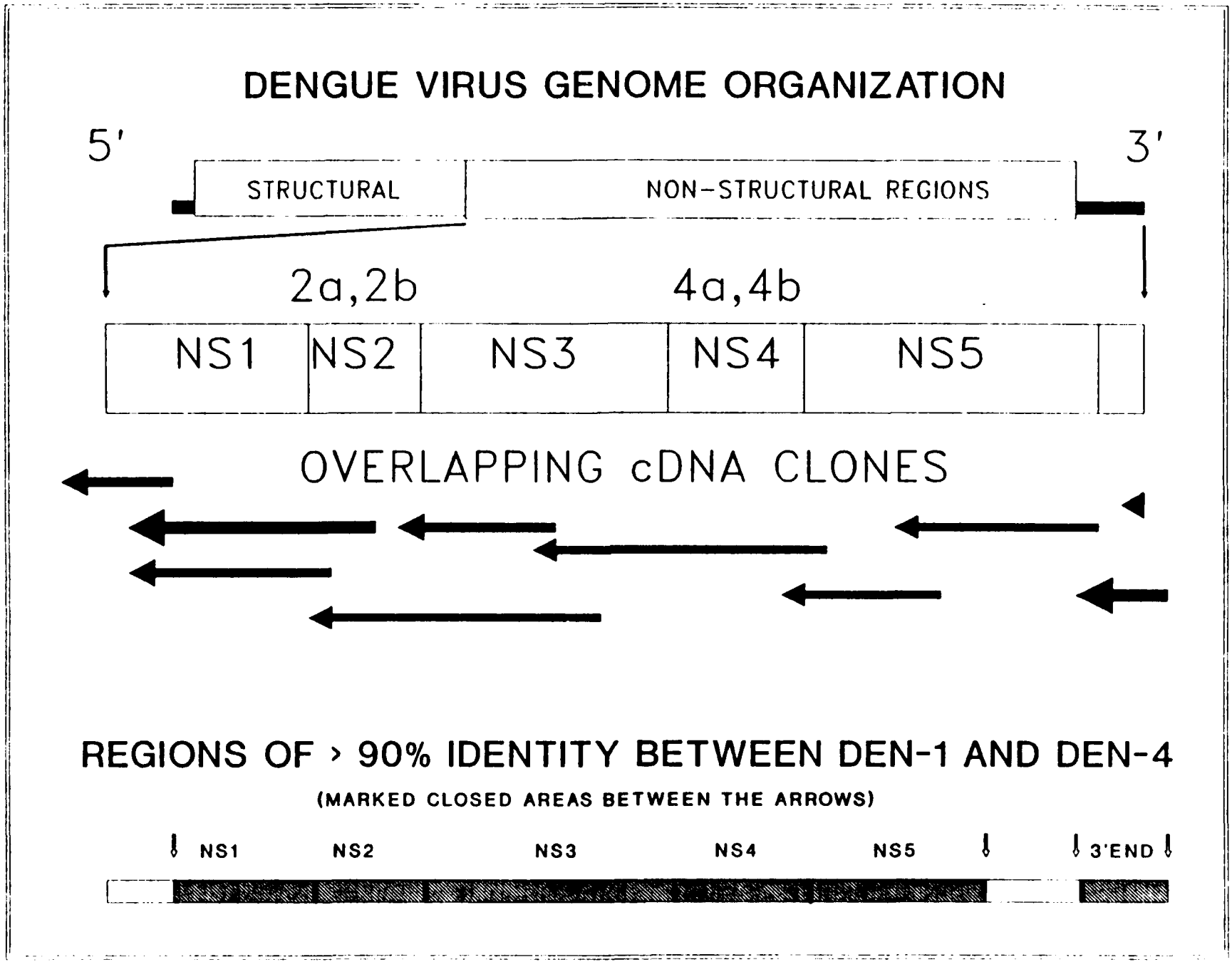
DENGUE VIRUS GENOME ORGANIZATION
5'
3'
STRUCTURAL
NON-STRUCTURAL REGIONS
2a,2b
4a,4b
NS1
NS2
NS3
NS4
NS5
OVERLAPPING cDNA CLONES
REGIONS OF > 90% IDENTITY BETWEEN DEN-1 AND DEN-4
(MARKED CLOSED AREAS BETWEEN THE ARROWS)
NS1
NS2
NS3
NS4
NS5
3'END

FIGURE 1

COMPARISON OF THE NON-STRUCTURAL GENOME OF DENGUE-1 CV1636/77 WITH DEN-2, DEN-3, AND DEN-4

	DEN-2		DEN-3		DEN-4	
	NT	AA	NT	AA	NT	AA
NS1	68%	59%	69%	59%	97%	84%
NS2a	36%	34%	38%	39%	99%	98%
NS2B	59%	53%	59%	55%	98%	95%
NS3	69%	71%	70%	74%	98%	95%
NS4a	64%	68%	61%	65%	99%	95%
NS4B	68%	83%	69%	82%	98%	97%
NS5	70%	75%	71%	81%	73%	79%
3'-END	67%		72%		97%	

FIGURE 2

FIGURE 3

COMPARISON OF THE NS1 NUCLEOTIDE SEQUENCES OF DENGUE VIRUSES

NS1

2427

```
DEN-1   GAC UCG GGA UGU GUA AUC AAC UGG AAA GGC AAA GAA CUG AAA UGU GGC AGU GGC AUU UUU
DEN-2   ..U AGU ..U ..C ..U G.G .G. ... ... AAU ... ... ... ... ... ... ..C ... ..C ..C
DEN-3   ... AU. ..G ... ..C ..A ... ... ... ... ... ... ..C ... ... ..A ... ..A ... ..C
DEN-4   ... AU. ..U ... ..G G.G UCA ... .GU ..G ... ... U.. ..G ... ..A ..C ..A ... ...
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2487

```
DEN-1   GUC ACU AAU GAA GUC CAC ACU UGG ACA GAG CAA UAC AAA UUC CAG GCU GAC UCC CCA AAA
DEN-2   A.. ..A G.. A.C ..G ... ..A ... ... ..A ... ..U ..G ... ..A C.A ..A ... ..U UC.
DEN-3   ... ... ... ..G ... ... ..C ... ... ... ... ... ... ..U ..A ..A ... ... ..C ...
DEN-4   ... GU. G.C A.C ..G ... ... ... ... ..A C.G ... ... ..U ..A C.A ..G ... ... GCG
```

2547

```
DEN-1   AGA CUG UCA GCA GCC AUU GGG AAG GCA UGG GAG GAG GGG GUG UGU GGA AUU CGA UCA ACC
DEN-2   .A. ..A G.U U.. ..U ..C CAA ..A ..U CAU ..A ... ..C A.U ... ... ..C ..C ... GUA
DEN-3   ... G.. G.. A.. ... ... .CA GGC ..U ... ... A.U ..A ... ..C ... ... A.G ... ..A
DEN-4   ... ..A G.G U.U ..A ..A UUA ..U ..C CAC A.A ..U ... ..C ... ... ... A.. ... ...
```

2607

```
DEN-1   AGC AGG CUU GAA AAU GUC AUG UGG AAG CAA AUA ACC AAG GAG CUA AAC UAU GUU CUC UGG
DEN-2   .CA ..A U.G ..G ... C.G ... ... ..A ... ... ..A CCA ..A U.G ..U C.C A.. ..A .CA
DEN-3   .C. ..A A.G ..G ..C C.. U.. ... ... ... ... G.. ..U ..A ..G ... ..C A.A U.A ...
DEN-4   .CG ... ..G ... ... ... ... ... ... ... ... ... ..C ... ... ... ... ... ... ...
```

2667

```
DEN-1   GAA GGA GGA CAU GAC CUC ACU GUA GUG GCU GGG GAU GUG AAG GGG GUG UUG ACC AAA GGC
DEN-2   ... AAU .AG GTA A.G U.G ..C A.U A.. A.A ..A ..C A.U ..A ..A A.C A.. CAG GC. ..A
DEN-3   ... AAC .AC AU. A.A U.A ..G ... ..U .UA ..C ..C A.A .CU ... ..C ..A GAG C.. ..G
DEN-4   ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
```

2727

```
DEN-1   AAG AGA GCC CUC ACA CCC CCA GUG AGU GAU CUG AAA UAU UCA UGG AAG ACA UGG GGA AAA
DEN-2   ..A C.. U.U U.G CGG ... .AG CCC .C. ..G ... ..G ..C ... ... ..A ... ... ... ..G
DEN-3   ..A ... A.A ..A ... ..A .A. CCC .UG ..G ..A ... ... ..U ... ..A ... ... ..U UUG
DEN-4   ... ... ..A ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
```

2787

```
DEN-1   GCA AAA AUC UUC ACC CCA GAA GCA AGA AAU AGC ACA UUU UUA AUA GAC GGA CCA GAC ACC
DEN-2   ..G ... ..G C.. U.. A.. ..G U.U CAC ... CAG ..C ... C.U ..U ..U ..C ..U ..A .CA
DEN-3   ... ... ..A G.G ..A G.U ... A.. CA. ... UC. U.U ..C A.. ... ..U ..G ..A AG. ..A
DEN-4   ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
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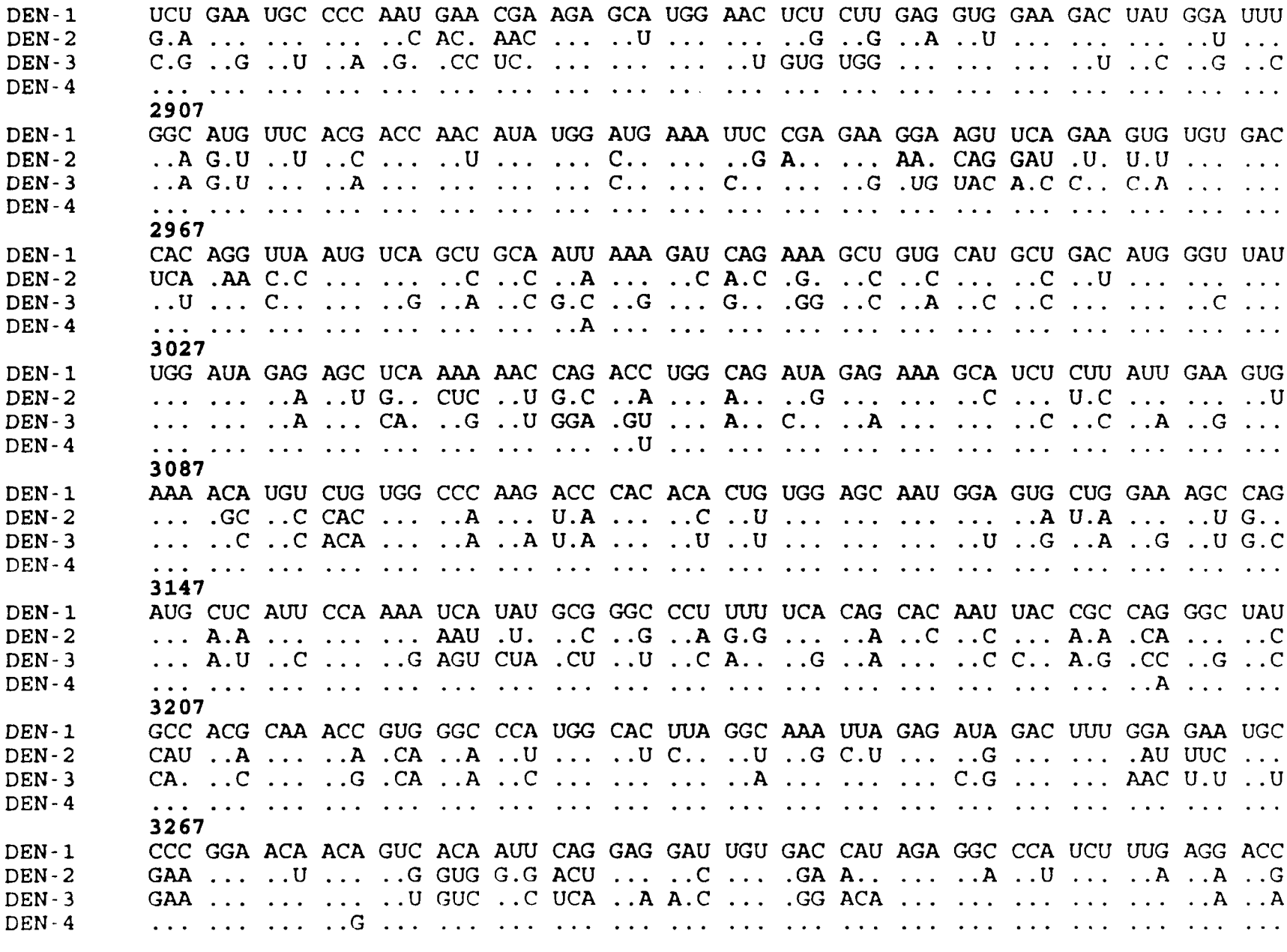
DEN-1 UCU GAA UGC CCC AAU GAA CGA AGA GCA UGG AAC UCU CUU GAG GUG GAA GAC UAU GGA UUU
DEN-2 G.A ... ...C AC. AAC ... ..U ... .G ..G ..A ..U ... ...U ...
DEN-3 C.G ..G ..U ..A .G. .CC UC. ... ...U GUG UGG ... ...U ..C ..G ..C
DEN-4 ... ...
2907
DEN-1 GGC AUG UUC ACG ACC AAC AUA UGG AUG AAA UUC CGA GAA GGA AGU UCA GAA GUG UGU GAC
DEN-2 ..A G.U ..U ..C ... ..U ... ... C.. ... ..G A.. ... AA. CAG GAU .U. U.U ... ...
DEN-3 ..A G.U ... ..A ... ... C.. ... C.. ... ..G .UG UAC A.C C.. C.A ... ...
DEN-4 ... ...
2967
DEN-1 CAC AGG UUA AUG UCA GCU GCA AUU AAA GAU CAG AAA GCU GUG CAU GCU GAC AUG GGU UAU
DEN-2 UCA .AA C.C ... .C ..C ..A ... ..C A.C .G. ..C ..C ... ..C ..U ... ...
DEN-3 ..U ... C.. ... ..G ..A ..C G.C ..G ... G.. .GG ..C ..A ..C ..C ... .C ...
DEN-4 ... ...A ... ...
3027
DEN-1 UGG AUA GAG AGC UCA AAA AAC CAG ACC UGG CAG AUA GAG AAA GCA UCU CUU AUU GAA GUG
DEN-2 ... .A ..U G.. CUC ..U G.C ..A ... A.. ..G ... .C ... U.C ... .U
DEN-3 ... .A ... CA. ..G ..U GGA .GU ... A.. C.. ..A ... .C ..C ..A ..G ...
DEN-4 ... ...U ... ...
3087
DEN-1 AAA ACA UGU CUG UGG CCC AAG ACC CAC ACA CUG UGG AGC AAU GGA GUG CUG GAA AGC CAG
DEN-2 ... .GC ..C CAC ... ..A ... U.A ... ..C ..U ... ...A U.A ... ..U G..
DEN-3 ... ..C ..C ACA ... ..A ..A U.A ... ..U ..U ... ...U ..G ..A ..G ..U G.C
DEN-4 ... ...
3147
DEN-1 AUG CUC AUU CCA AAA UCA UAU GCG GGC CCU UUU UCA CAG CAC AAU UAC CGC CAG GGC UAU
DEN-2 ... A.A ... ... AAU .U. ..C ..G ..A G.G ... ..A ..C ..C ... A.A .CA C
DEN-3 ... A.U ..C ... ..G AGU CUA .CU ..U ..C A.. ..G ..A ... ..C C.. A.G .CC ..G ..C
DEN-4 ... ...A ... ...
3207
DEN-1 GCC ACG CAA ACC GUG GGC CCA UGG CAC UUA GGC AAA UUA GAG AUA GAC UUU GGA GAA UGC
DEN-2 CAU ..A ... ..A .CA ..A ..U ... ..U C.. ..U ..G C.U ... ..G ... ... .AU UUC ...
DEN-3 CA. ..C ... ..G .CA ..A ..C ... ...A ... ... C.G ... ... AAC U.U ..U
DEN-4 ... ...
3267
DEN-1 CCC GGA ACA ACA GUC ACA AUU CAG GAG GAU UGU GAC CAU AGA GGC CCA UCU UUG AGG ACC
DEN-2 GAA ... ..U ... ..G GUG G.G ACU ... ..C ... .GA A.. ... ..A ..U ... ..A ..A ..G
DEN-3 GAA ... ...U GUC ..C UCA ..A A.C ... .GG ACA ... ...A ..A
DEN-4 ... ...G ... ...

```
DEN-1     ACC ACU GCA UCU GGA AAA CUA GUC ACG CAA UGG UGC UGC CGC UCC UGC ACG AUG CCU CCC
DEN-2     ... ... ..C ... ... ... ..C A.A ..A G.. ... ... ... ..A ... ... ..A C.A ..A ..U
DEN-3     ..A ..A .UG ..A ..G ..G U.G A.A CAC G.. ... ..U ... ... ..G ... ..A C.U ... ...
DEN-4     ... ... ... ... ... ... ... ... ... ... ATG GT. ... ... ... ... ... ... ... ...
          3387
DEN-1     UUA AGG UUC UUG GGA GAA GAU GGG UGC UGG UAU GGG AUG GAG AUU AGG CCC UUG AGU GAA
DEN-2     C.. ..A .AU AGA ..U ..G ... ..A ... ... ..C ... ... ..A ..C ..A ..A ... .AA ..G
DEN-3     C.G C.A .A. A.. ... ... ..C ..C ... ... ... ..C ... ..A ..C ..A ... A.T .A. ..G
DEN-4     ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
          3447
DEN-1     AAA GAA GAG AAC AUG GUC AAA UCA CAG GUG ACG GCC
DEN-2     ... ... ... ..U U.. ... ..C ..C UU. ..C ..A ...
DEN-3     ... ... ... ... ... ..A ..G ..U .UA .CC U.A ..A
DEN-4     ... ... ... ... ... ... ... ... ... ... ... ...
```

COMPARISON OF THE NS2a NUCLEOTIDE SEQUENCES OF DENGUE VIRUSES

NS2a

3484

DEN-1 GGA CAG GGC ACA UCA GAA ACU UUU UCU AUG GGU CUG UUG UGC CUG ACC UUG UUU GUG GAA
DEN-2 ... ..U ..G CAG AUU ..C .AC ... ..A C.A ..A G.C ... G.A A.. G.A C.. ..C C.. ...
DEN-3 ..G AGU ..A .AG GUG ..C .AC ..C A.A ... ... G.C ... ..U U.. G.A A.C C.C U.U ...
DEN-4 ... ...

3544

DEN-1 GAA UGC UUG AGG AGA AGA GUC ACU AGG AAA CAC AUG AUA UUA GUU GUG GUG AUC ACU CUU
DEN-2 ... AUG C.C ... .CC C.. ..A GGA .C. ... ..U GCA ... C.G C.A ..U .CA G.A U.. U..
DEN-3 ..G GUG A.. ..A G.. .A. U.U GGG .AA ... ...U GC. .GG ..U C.C U.. ..G U..
DEN-4 ... ...

3604

DEN-1 UGU GCU AUC AUC CUG GGA GGC CUC ACA UGG AUG GAC UUA CUA CGA GCC CUC AUC AUG UUG
DEN-2 GUG A.A U.G ..U ACT ..G AA. A.G UCC .UU .GA ... CUG GG. A.. .UG A.G G.U ... G..
DEN-3 GUG CUC C.. C.. UCA ..G CAA A.A ... ... .GA .G. A.G GCG .AC A.A ... ..A ... A.U
DEN-4 ... ... U.. ... ...

3664

DEN-1 GGG GAC ACU AUG UCU GGU AGA AUA GGA GGA CAG AUC CAC CUA GCC AUC AUG GCA GUG UUC
DEN-2 ..C .CU ..C ... A.G .A. GAC ... ..U ATG GGA G.G ACU UAU CUU GC. C.A CU. .CA GCU
DEN-3 ... UC. .AC GCC ... .AC ... ..G ..G ATG GGC C.. ACU UAC CUA GCU C.A AUU .CA ACA
DEN-4 ... ...

3724

DEN-1 AAG AUG UCA CCA GGA UAC GUG CUG GGU GUG UUU UUA AGG AAA CUC ACU UCA AGA GAG ACA
DEN-2 UUC .AA UU AG. CC. ACT U.U GCA .C. .GA C.A C.C UU. .G. AAA CUG ACC UCC A.. GA.
DEN-3 UUU .AA AUU .AG CC. .U. U.. GCU UUG .GA ..C ..C CU. .GG AAA CUG AC. UCU AGA GA.
DEN-4 ... ... A.. ... ...

3784

DEN-1 GCA CUA AUG GUA AUA GGA AUG GCC AUG ACA ACG GUG CUU UCA AUU CCA CAU GAC CCU AUG
DEN-2 UU. A.G ... .CC .CC AU. GGA AUC GCA CUC CUU UCC .AA AGC .CC AU. .CA ..G A.C ..U
DEN-3 AAU U.. U.. C.G GG. .UU GG. UUG GCC .UG G.A .CA ACG .U. CGA .UG .CA ..G GAC ..U
DEN-4 ... ... .U. ...

3844

DEN-1 GAA CUC AUU GAU GGA AUA UCA CUG GGA CUA AUU UUG CUA AAA AUA GUA ACA CAG UUU GAC
DEN-2 CUU GAA C.G AC. .AU GCG .U. GCC CUG GGC ..G A.. G.C CTC .A. A.. GUG AGA AA. AUG
DEN-3 ... .AA ..G .CG AAU GG. AUU GCU UUG GGG C.C A.. GCU CUU .A. C.G .U. ACA CAA UUU
DEN-4 ... ... AG. ... ...

```
DEN-1    AAC ACC CAA GUG GGA ACC UUA GCU CUU UCC UUG ACU UUC AUA AGA UCA ACA AUG CCA UUG
DEN-2    G.A .AG U.C CAA UUG G.A G.G A.. A.C AUG GCU .UC C.G UGU GUC C.. .AU GCA GUG A.A
DEN-3    G.A ..A U.C CAA CU. UGG ACG ..A U.A GUU .CC CUA ACG UGU UC. AAU ... ..U UUC AC.
DEN-4    ... ... ... ... ..G ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
         3964
DEN-1    GUC AUG GCU UGG AGG ACC AUU AUG GCU GUG UUG UUU GUG GUC ACA CUC AUU CCU UUG UGC
DEN-2    U.G CAA AAC GCA U.. .AG G.G .GU UGC ACA A.A ..G .CA .CG GUG UC. G.. U.. CCA CUG
DEN-3    U.G .CU .U. GCC U.. .GA .CA GCC A.. C.. A.U ..A .CC .GA .UU GCG C.. UUG CCA GUG
DEN-4    ... ... ... ... ... ... ... ... ... ... ... ... ... .A. ... ... ... ... ... ...
         4024
DEN-1    AGG ACA AGC UGU CUU CAA AAA CAG UCU CAU UGG GUA GAA AUA ACA GCA CUC AUC CUA GGA
DEN-2    CUC UU. .CA .CC UCA ..G C.G A.A G.G G.. ... A.. CC. C.G G.. UUG ACG ..A AA. ..U
DEN-3    U.C CAG UCU .CG AGC AUG .GG A.A A.A G.. ... C.C CC. ..G ..U .UG GCA GCU A.G ...
DEN-4    ... ... ... ... ... . . ... ... ... ... ... .C. ... ... ... ... ... ... ... ...
         4084                                                                    4137
DEN-1    GCC CAA GCU CUG CCA GTG UAC CUA AUG ACU CUU AUG AAA GGA GCC UCA AGA AGA
DEN-2    CU. A.U CCA ACA G.C A.U .UU ... .C. ..C ... UC. .G. ACC AG. AAG .A. .AG
DEN-3    .UU .C. C.C ..A ... C.U UUU A.U U.C .G. ..G .AA G.U AC. CU. AA. ..G ...
DEN-4    ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
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COMPARISON OF THE NS2B NUCLEOTIDE SEQUENCES OF DENGUE VIRUSES

NS2B

4138

DEN-1	UCU	UGG	CUC	UUG	AAC	GAG	GGC	AUA	AUG	GCU	GUG	GGU	UUG	GUU	AGU	CUC	UUA	GGA	UGC	GCU
DEN-2	AGC	...	.CG	C.A	..U	...	.CU	..C	...	..A	..C	..G	A..	..G	..C	A.U	...	.CC	A.U	U..
DEN-3	AGC	...	.CA	C..	..U	...	..G	G.G	...	..A	..U	..A	C.U	..G	..C	A.U	C..	.CU	A.U	U..
DEN-4	...	...	..U	C.U	...	...	...	...	...	...	...	...	...	...	...	...	...	...	A..	...

4198

DEN-1	CUU	UUA	AAG	AAU	GAU	GUC	CCU	UUA	GCU	GGC	CCA	AUG	GUG	GCA	GGA	GGC	UUA	CUU	CUG	GCG
DEN-2	..C	C..	...	...	..C	A.U	..C	A.G	A.A	..U	...	U.A	...	..U	...	..G	C.C	..	ACU	.U.
DEN-3	..C	C.U	.G.	...	...	..G	..C	A.G	...	..A	...	U.A	...	..U	..G	..C	..G	..G	A.A	...
DEN-4	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...

4258

DEN-1	GCU	UAC	GUG	AUG	AGU	GGU	AGC	UCA	GCA	GAU	CUG	UCA	CUA	GAG	AAG	GCC	GCC	AAU	GUG	CAG
DEN-2	UG.	...	...	C.C	.C.	..A	C.A	..G	..C	...	U..	GA.	..G	...	.GA	..U	...	G..	..A	A.A
DEN-3	UGC	...	..C	..A	.C.	..C	.CG	...	...	..C	..C	A.U	G..	..A	..A	..A	..A	G..	..A	ACA
DEN-4	...	...	A..	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...

4318

DEN-1	UGG	GAU	GAA	AUG	GCA	GAC	AUA	ACA	GGC	UCA	AGC	CCA	AUC	AUA	GAA	GUG	AAG	CAG	GAU	GAA
DEN-2	...	..A	..U	CA.	...	..A	...	U..	..A	AGC	...	...	...	C.G	UC.	A.A	.CA	AUA	UCA	...
DEN-3	...	..G	...	GA.	..C	..G	CA.	...	..A	GUG	UC.	.AC	.AU	U..	AUG	A.C	.CA	GUU	...	..U
DEN-4	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...

4378

DEN-1	GAU	GGC	UCU	UUC	UCC	AUA	CGG	GAC	GUC	GAG	GAA	ACC	AGU	AUG	AUA	ACC	CUU	UUG	GUG	AAA
DEN-2	...	...	AGC	A.G	..G	...	AAA	A.U	.AA	...	...	GAA	CAA	.CA	C.G	...	A.A	C.C	A.C	.G.
DEN-3	...	..A	A.A	A.G	AGA	...	AAA	..U	.A.	...	ACU	GAG	.AC	..C	U..	..A	G.G	C.U	U.A	...
DEN-4	...	...	...	...	...	...	...	...	...	...	...	...	.A.	...	...	...	...	...	...	...

4438

DEN-1	CUG	GAC	CUG	AUA	ACA	GUG	UCA	GGU	CUC	UAC	CCC	UUG	GCA	AUU	CCA	GUC	ACA	AUG	ACC	UUA
DEN-2	AC.	.GA	U..	U.G	GUG	A.C	...	..A	G..	.UU	..A	G.A	U.G	..A	...	A.U	..G	GCA	G.A	GC.
DEN-3	ACA	.CA	..A	C..	.U.	..A	...	..C	A..	.UU	..A	.AC	U.C	..A	..C	.CA	...	...	UUG	G.C
DEN-4	...	.CA	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...

4498 **4527**

DEN-1	UGG	UAC	AUG	UGG	CAA	GUG	AAA	ACA	CAA	AGA
DEN-2	...	...	C..	...	G..	...	..G	.A.	...	C.G
DEN-3	...	C.U	.CU	...	...	AA.	C..	..C	...	...
DEN-4	...	...	...	...	...	...	...	...	...	...

COMPARISON OF THE NS3 NUCLEOTIDE SEQUENCES OF DENGUE VIRUSES

```
          NS3
          4528
DEN-1     UCA GGA AGC CUG UGG GAC GUC CCC UCA CCC GCU GCC ACU CAA AAA GCC GCA CUG UCU GAA
DEN-2     G.U ... GUA U.. ... ... ... ..U ... ... C.A C.A GUG GG. ... ... .A. ... GAA ..U
DEN-3     ..C ..C GU. ..A ... ... ..A ... AGC ... C.A .AG ..A ..G ... ..G .A. ... GAA ...
DEN-4     ... ... GC. ... ... ... ... ... ... ... ... ... A.. ... ... ... ... ... ...
          4588
DEN-1     GGA GUG UAC AGG AUC AUG CAA AGA GGG UUA UUC AGG AAA ACU CAG GUU GGA GUA GGG AUA
DEN-2     ... .CC ..U ..A ... .A. ... ... ... A.U C.U G.A U.C U.. ... A.. ... .CC ..A G.U
DEN-3     ..G ... ..U ... ... .AA ..G CA. ..A A.U ..U G.. ... ..C ..A ..G ..G ..U ..A G..
DEN-4     ... ... ... ... ... ... ... ... ... ... ... G.. ... ... ... ... ... ... ... ...
          4648
DEN-1     CAC AUG GAA GGU GUA UUU CAC ACA AUG UGG CAU GUA ACA AGA GGA UCA GUG AUC UGC CAC
DEN-2     U.. .AA ... ..A AC. ..C ..U ... ... ... ..C ..C ... C.U ..U G.U ..U C.G AUG ..U
DEN-3     ..G .AA ... ... ..U ..C ... ..C ... ... ..C ..C ... ... ..G G.. ... U.G ACA ...
DEN-4     ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... AUC AGU GAU ... ...
          4708
DEN-1     GAG ACU GGG AGA UUG GAG CCA UCU UGG GCU GAC GUC AGG AAU GAC AUG AUA UCA UAC GGU
DEN-2     A.A GGG AA. ..G A.U ..A ... ..A ... ..A ... ... .AG ..A ... C.A ... ... ..U ..A
DEN-3     A.U GGG AAA ... C.. ..A ... AAC ... ... AG. ..G .AA ..A ..U C.. ..U ... ... ..A
DEN-4     ... ... ... ... ... ... ..G ... ... ... ... ... ... G.A ... ... ... ... ... ...
          4768
DEN-1     GGG GGA UGG AGG CUU GGA GAC AAA UGG GAC AAA GAA GAA GAC GUU CAG GUC CUC GCC AUA
DEN-2     ..A ..C ... .A. ..A .A. .GA G.. ... A.G G.. .G. ..G ..A ..C ..A ... ..G ..A U.G
DEN-3     ..A ... ... ..A U.G A.U .CA C.. ... C.A ..G .GG ..G ..G ..G ... ..U A.T ... G..
DEN-4     ... ... ... ... ... U.G ... ... ... ... ... ... ... ... ... ... ... ... ... ...
          4828
DEN-1     GAA CCA GGA AAA AAU CCU AAA CAU GUC CAA ACG AAA CCU GGC CUU UUC AAG ACC CUA ACU
DEN-2     ... ..U ... ... ... ..A .G. GCC ... ... ... ... ... ..A ... ... ..A ... AAC ..C
DEN-3     ..G ..G UUU ..G ..C ..A ..G A.C U.U ... ..C .UG ..A ..C A.. ..U C.. ..A AC. ..A
DEN-4     ... ... A.. ... ... ... ... ... ... ... ... ... ... A.. ... ... ... ... ... ...
          4888
DEN-1     GGA GGA AUU GGA GCA GUA ACA UUA GAU UUC AAA CCC GGA ACG UCU GGU UCU CCC AUC AUC
DEN-2     ... ACC ..A ..C ..C ... U.U C.G ..C ..U UCC ..U ... ... ..A ..A ... ..A ..U G..
DEN-3     ..G .A. ..A ... ... A.U G.. C.G ... ... ..G ..U ... ..U ..A ..A ... ... ... ..A
DEN-4     ... .A. ... ... ... ... ... ... ... ... ... ... ... ... ..A ... ... ... ... ...
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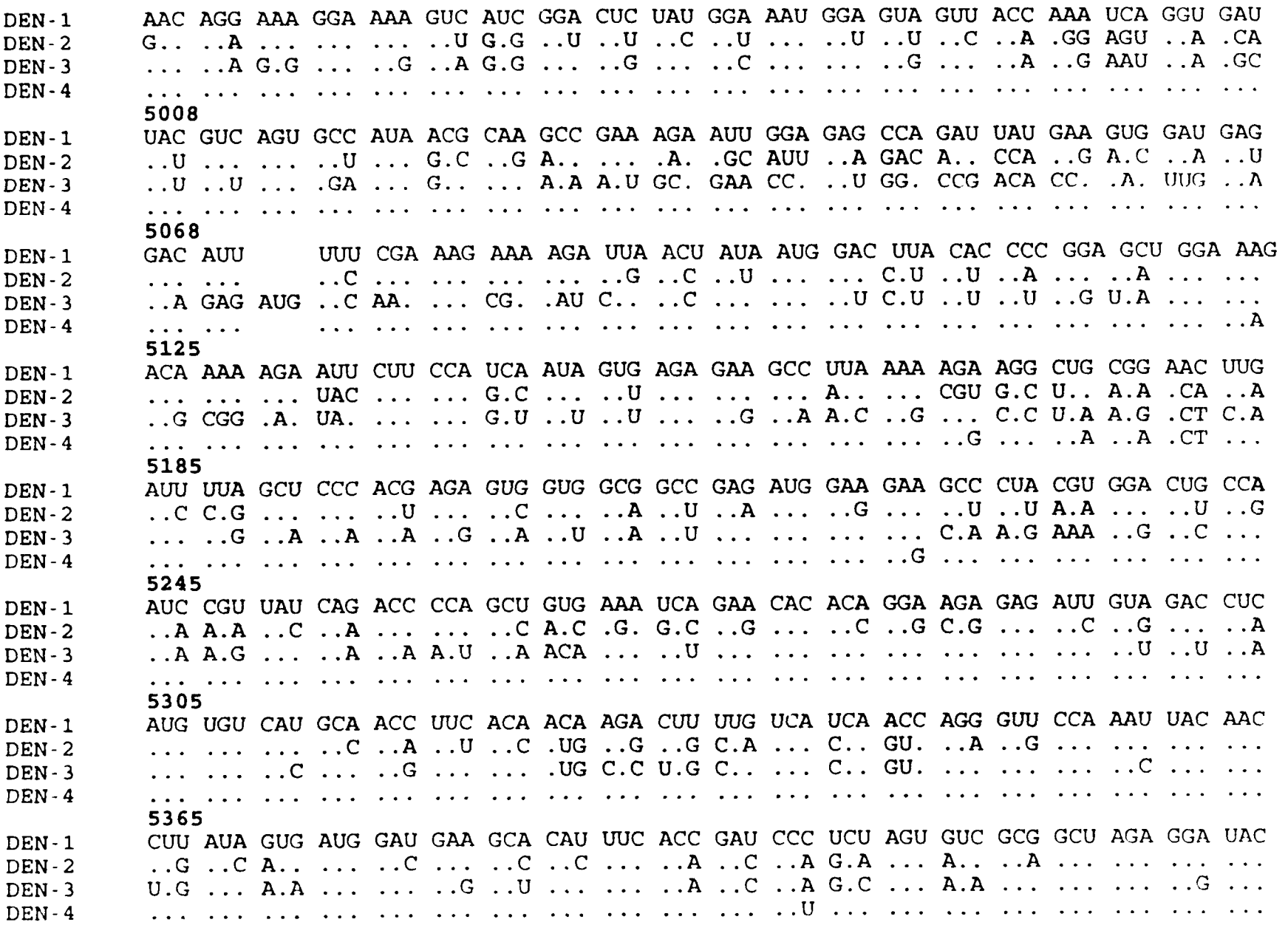
DEN-1 AAC AGG AAA GGA AAA GUC AUC GGA CUC UAU GGA AAU GGA GUA GUU ACC AAA UCA GGU GAU
DEN-2 G.. ..A ... ...U G.G ..U ..U ..C ..U ... ..U ..U ..C ..A .GG AGU ..A .CA
DEN-3 ... ..A G.G ... ..G ..A G.G ... ..G ... ..C ... .G ... ..A ..G AAU ..A .GC
DEN-4 ... ...
5008
DEN-1 UAC GUC AGU GCC AUA ACG CAA GCC GAA AGA AUU GGA GAG CCA GAU UAU GAA GUG GAU GAG
DEN-2 ..U ... .U ... G.C ..G A.. ... .A. .GC AUU ..A GAC A.. CCA ..G A.C ..A ..U
DEN-3 ..U ..U ... .GA ... G.. ... A.A A.U GC. GAA CC. ..U GG. CCG ACA CC. .A. UUG ..A
DEN-4 ... ...
5068
DEN-1 GAC AUU UUU CGA AAG AAA AGA UUA ACU AUA AUG GAC UUA CAC CCC GGA GCU GGA AAG
DEN-2 ... .C ... ...G ..C ..U ... ... C.U ..U ..A ... ..A ... ...
DEN-3 ..A GAG AUG ..C AA. ... CG. .AU C.. ..C ... .U C.U ..U ..U ..G U.A ... ...
DEN-4 ... ...A
5125
DEN-1 ACA AAA AGA AUU CUU CCA UCA AUA GUG AGA GAA GCC UUA AAA AGA AGG CUG CGG AAC UUG
DEN-2 ... ... UAC ... ... G.C ... ..U ... ... A.. ... CGU G.C U.. A.A .CA ..A
DEN-3 ..G CGG .A. UA. ... ... G.U ..U ..U ... ..G ..A A.C ..G ... C.C U.A A.G .CT C.A
DEN-4 ... ...G ... ..A ..A .CT ...
5185
DEN-1 AUU UUA GCU CCC ACG AGA GUG GUG GCG GCC GAG AUG GAA GAA GCC CUA CGU GGA CUG CCA
DEN-2 ..C C.G ... .U ... ..C ... ..A ..U ..A ... ..G ... ..U ..U A.A ... ..U ..G
DEN-3 ... ..G ..A ..A ..A ..G ..A ..U ..A ..U ... ... C.A A.G AAA ..G ..C ...
DEN-4 ... ...G ... ...
5245
DEN-1 AUC CGU UAU CAG ACC CCA GCU GUG AAA UCA GAA CAC ACA GGA AGA GAG AUU GUA GAC CUC
DEN-2 ..A A.A ..C ..A ... .C A.C .G. G.C ..G ... ..C ..G C.G ... ..C ..G ... ..A
DEN-3 ..A A.G ... ..A ..A A.U ..A ACA ... ..U ... ...U ..U ..A
DEN-4 ... ...
5305
DEN-1 AUG UGU CAU GCA ACC UUC ACA ACA AGA CUU UUG UCA UCA ACC AGG GUU CCA AAU UAC AAC
DEN-2 ... ...C ..A ..U ..C .UG ..G ..G C.A ... C.. GU. ..A ..G ... ...
DEN-3 ... .C ... ..G ... ... .UG C.C U.G C.. ... C.. GU. ... ...C ... ...
DEN-4 ... ...
5365
DEN-1 CUU AUA GUG AUG GAU GAA GCA CAU UUC ACC GAU CCC UCU AGU GUC GCG GCU AGA GGA UAC
DEN-2 ..G ..C A.. ... ..C ... ..C ..C ... ..A ..C ..A G.A ... A.. ..A ... ...
DEN-3 U.G ... A.A ... .G ..U ... .A ..C ..A G.C ... A.A ... ...G ...
DEN-4 ... ...U ... ...

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DEN-1   AUC UCG ACC AGG GUG GAA AUG GGA GAG GCA GCA GCC AUC UUC AUG ACC GCA ACC CCU CCC
DEN-2   ..U ..A ..U C.A ..A ..G ... ..U ..A ... ..U .GG ..U ... ... ..A ..C ..U ... ..G
DEN-3   ..A ..A ..U C.U ..A .G. ... ... ... ... ..C ..A ..U ... ... ..A ... ..A ..C ..U
DEN-4   ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
        5485
DEN-1   GGA GCG ACA GAU CCC UUU CCC CAG AGC AAC AGC CCA AUA GAA GAC AUC GAG AGG GAA AUU
DEN-2   ... AGU .G. ..C ..A ... ..U ... ... ..U GCA ... ..C AUG ..U GAG ..A ..A ... ..C
DEN-3   ... A.A G.U ... G.. ... ..U ... ... ... GCU ... ..U C.. ..U GAA ... ..A ..C ..A
DEN-4   ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
        5545
DEN-1   CCG GAA AGG UCA UGG GAC ACA GGG UUC GAC UGG AUA ACA GAC UAC CAA GGG AAA ACU GUG
DEN-2   ..U ..G C.U ..G ... A.U U.. ..A CAU ..A ... G.C ..G ..U .UU A.. ... ..G ... ..U
DEN-3   ... ... C.C ... ... A.U U.. ..C AAU ..A ... ..U ..U ... .UU GUU ... ..G ..A ...
DEN-4   ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
        5605
DEN-1   UGG UUU GUU CCC AGC AUA AAA GCU GGA AAU GAC AUU GCA AAU UGU UUG AGA AAG UCG GGA
DEN-2   ... ... ... ..A ..U ... ... ..A ... ... ... ..A ... GC. ... C.U ..G ..A AAU ...
DEN-3   ... ... ..C ..U ... ... ... ..C ... ... .U. ..A ... ..C ... ... C.G ..A AAU ...
DEN-4   ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
        5665
DEN-1   AAG AAA GUU AUC CAG UUG AGU AGG AAA ACC UUU GAU ACA GAG UAU CCA AAA ACG AAA CUC
DEN-2   ... ... ..G ..A ..A C.C ... ... ..G ..U ... ..C U.U ... ... GUU ..G ..U .G. GC.
DEN-3   ... ..G ..C ..U ..A C.C ..C ... ..G ... ... ..C ... ..A ... .A. ..G ..C ... ..G
DEN-4   ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
        5725
DEN-1   ACG GAC UGG GAC UUU GUG GUC ACU ACA GAC AUA UCU GAA AUG GGG GCC AAU UUU AGA GCU
DEN-2   CAA ..U ... ... ... ... ... ..A ..U ... ..U ..A ... ... ..U ... ..C ..C .AG ...
DEN-3   .AU ..U ... ... ... ... ..G ..A ... ... ..U ..A ... ... ..A ... ... ..C .U. ..A
DEN-4   ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ..C
        5785
DEN-1   GGG AGA GUG AUA GAC CCU AGA AGA UGC CUC AAG CCA GUU AUC CUA ACA GAU GGG CCA GAG
DEN-2   .AA ..G ..U ... ... ..C ... C.U ... A.G ..A ... ... ..A U.. ... ... ..C GA. ...
DEN-3   .AU ... ... ..C ... ..A ... ... ..U ... ... ..G ..G ..U U.G ... ... ..A ..C ...
DEN-4   ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
        5845
DEN-1   AGA GUC AUU UUA GCA GGU CCU AUU CCA GUG ACU CCA GCA AGC GCU GCU CAG AGA AGA GGG
DEN-2   C.G ..G ..C ..G ... ..A ... ..G ... ... ..C .AC U.U ..U ..A ..G ..A ... ... ...
DEN-3   C.G ..G ..C C.G ..U ..A ..A ..G ... ..C ..C GU. ..G ... ... ..G ..A ..G ... ...
DEN-4   ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
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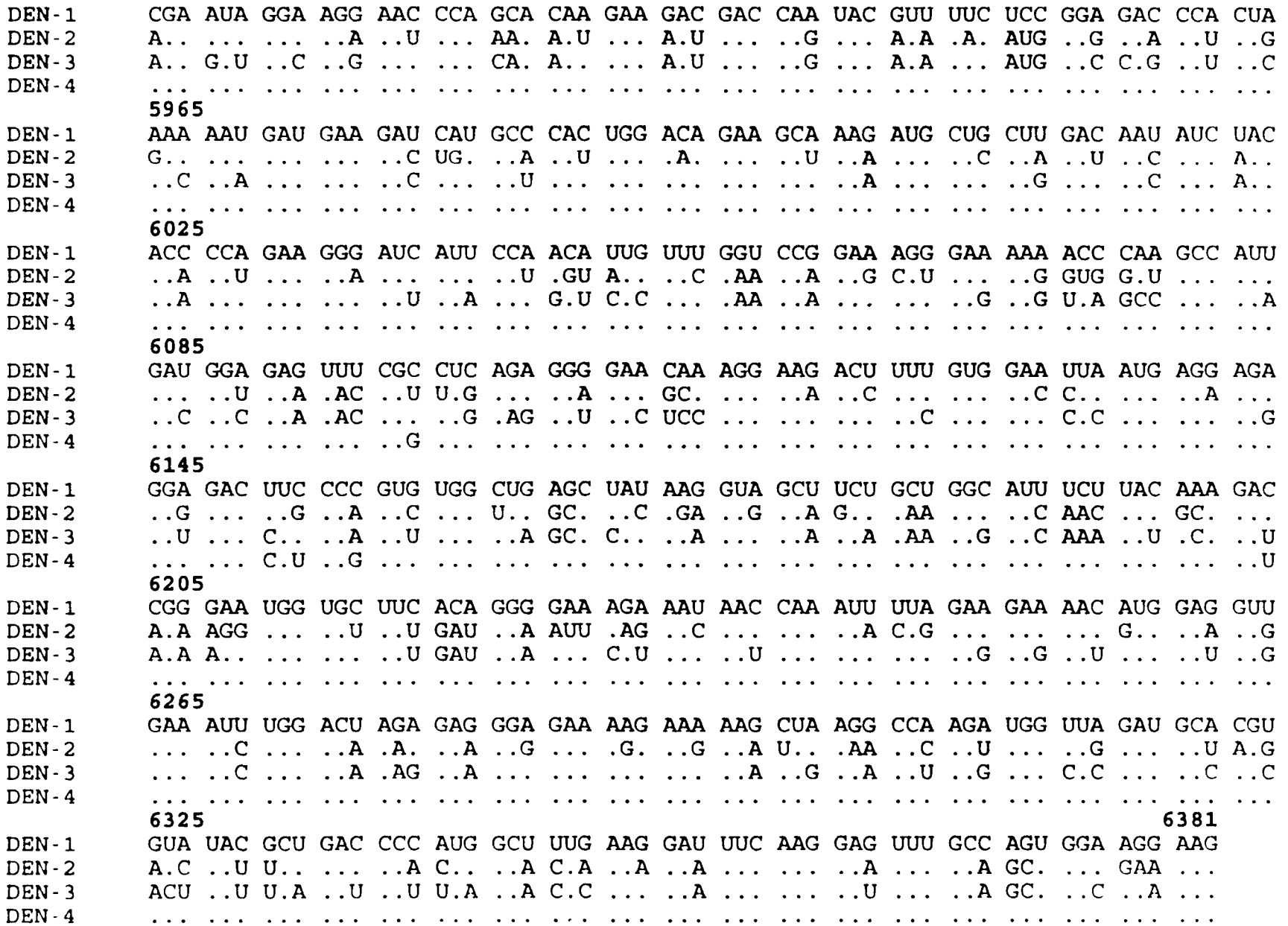
DEN-1 CGA AUA GGA AGG AAC CCA GCA CAA GAA GAC GAC CAA UAC GUU UUC UCC GGA GAC CCA CUA
DEN-2 A.. ... .A ..U ... AA. A.U ... A.U ... ..G ... A.A .A. AUG ..G ..A ..U ..G
DEN-3 A.. G.U ..C ..G ... ... CA. A.. ... A.U ... ..G ... A.A ... AUG ..C C.G ..U ..C
DEN-4 ... ...
5965
DEN-1 AAA AAU GAU GAA GAU CAU GCC CAC UGG ACA GAA GCA AAG AUG CUG CUU GAC AAU AUC UAC
DEN-2 G.. ... ...C UG. ..A ..U ... .A. ... ..U ..A ... ..C ..A ..U ..C ... A..
DEN-3 ..C ..A ... .C ... ..U ... ...A ... .G ... ..C ... A..
DEN-4 ... ...
6025
DEN-1 ACC CCA GAA GGG AUC AUU CCA ACA UUG UUU GGU CCG GAA AGG GAA AAA ACC CAA GCC AUU
DEN-2 ..A ..U ... ..A ... .U .GU A.. ..C .AA ..A ..G C.U ... ..G GUG G.U ... ...
DEN-3 ..A ... ...U ..A ... G.U C.C ... .AA ..A ... .G ..G U.A GCC ... ..A
DEN-4 ... ...
6085
DEN-1 GAU GGA GAG UUU CGC CUC AGA GGG GAA CAA AGG AAG ACU UUU GUG GAA UUA AUG AGG AGA
DEN-2 ... ..U ..A .AC ..U U.G ... ..A ... GC. ... ..A ..C ... .C C.. ... ..A ...
DEN-3 ..C ..C ..A .AC ... ..G .AG ..U ..C UCC ... ...C ... ... C.C ... .G
DEN-4 ... ...G ... ...
6145
DEN-1 GGA GAC UUC CCC GUG UGG CUG AGC UAU AAG GUA GCU UCU GCU GGC AUU UCU UAC AAA GAC
DEN-2 ..G ... ..G ..A ..C ... U.. GC. ..C .GA ..G ..A G.. .AA ... ..C AAC ... GC. ...
DEN-3 ..U ... C.. ..A ..U ... ..A GC. C.. ..A ... ..A ..A .AA ..G ..C AAA ..U .C. ..U
DEN-4 ... ... C.U ..G ... ...U
6205
DEN-1 CGG GAA UGG UGC UUC ACA GGG GAA AGA AAU AAC CAA AUU UUA GAA GAA AAC AUG GAG GUU
DEN-2 A.A AGG ... ..U ..U GAU ..A AUU .AG ..C ... .A C.G ... ... G.. ..A ..G
DEN-3 A.A A.. ... .U GAU ..A ... C.U ... ..U ... ...G ..G ..U ... ..U ..G
DEN-4 ... ...
6265
DEN-1 GAA AUU UGG ACU AGA GAG GGA GAA AAG AAA AAG CUA AGG CCA AGA UGG UUA GAU GCA CGU
DEN-2 ... ..C ... ..A .A. ..A ..G ... .G. ..G ..A U.. .AA ..C ..U ... ..G ... ..U A.G
DEN-3 ... ..C ... ..A .AG ..A ... ...A ..G ..A ..U ..G ... C.C ... ..C ..C
DEN-4 ... ...
6325
6381
DEN-1 GUA UAC GCU GAC CCC AUG GCU UUG AAG GAU UUC AAG GAG UUU GCC AGU GGA AGG AAG
DEN-2 A.C ..U U.. ... ..A C.. ..A C.A ..A ..A ... .A ... ..A GC. ... GAA ...
DEN-3 ACU ..U U.A ..U ..U U.A ..A C.C ... ..A ... .U ... ..A GC. ..C ..A ...
DEN-4 ... ...

COMPARISON OF THE NS4a NUCLEOTIDE SEQUENCES OF DENGUE VIRUSES

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          NS4a
          6382
DEN-1     AGU AUA ACU CUC GAC AUC CUA ACA GAG AUU GCC AGU UUG CCA ACU UAC CUU UCC UCU AGG
DEN-2     UC. U.G ..C ..G A.. C.A AUC ... ..A ..G .GU ..G C.A ... ... .U. ATG A.U CAG .A.
DEN-3     UCA ..C G.C ..U ..U C.U G.G ... ..A ..A .GA ..A G.. ..U UCA C.. U.A G.. CAC ..A
DEN-4     ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
          6442
DEN-1     GCC AAG CUC GCC CUU GAU AAC AUA GUC AUG CUC CAC ACA ACA GAA AGA GGA GGG AGG GCC
DEN-2     ..A .GA GA. ..A ..G ..C ... U.. .CU G.. ..G ..U ..C G.U ..G GC. ..U ..A ... ..G
DEN-3     A.G .GA AA. ... ..G ..C ..U U.G ..G ... ..G ... ..G U.. ... CAU ..C ..U ... ...
DEN-4     ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
          6502
DEN-1     UAU CUU CAC GCC CUG AAC GAA CUU CCG GAG UCA CUG GAA ACA CUC AUG CUU GUA GCU UUA
DEN-2     ..C AA. ..U ..U ..C .GU ... ..G ... ... A.C ... ..G ... ..G C.U U.A C.G ACA C.C
DEN-3     ..C AGG ..U ..A G.. G.G ... ..A ..A ..A A.G A.. ... ... ... U.A ..C C.G .GA C.G
DEN-4     ... .AA ... ... ... ... ... ... A.. ... ... ... ... ... ... ... ... ... ... ...
          6562
DEN-1     CUA GGU GCU AUG ACA GCA GGU AUC UUC CUG UUU UUC AUG CAA GGG AAA GGA AUA GGG AAA
DEN-2     ..G .CC A.A G.. ... .G. ..A ... ... U.A ..C ..A ... AGC ..A ... ..U ... ... ..G
DEN-3     A.G AUC UUG U.A ... .GU ..A GCA A.G ..C ..C ..G ..A UC. ..U ... ..G ..U ..A ..G
DEN-4     ... ... ... ... ... ... ..C ... ... ... ... ... ... ... ... ... ... ... ... ...
          6622
DEN-1     UUG UCA AUG GGU UUG AUA ACC AUU GCG GUG GCU AGU GGC UUG CUC UGG GUA GCA GAA AUU
DEN-2     A.. A.C C.. ..A A.. UGU UG. ..A AUC AC. ... ... AU. C.C ..A ... UAU ... C.G ..A
DEN-3     ACU ... ..A ..A C.C ..U UGU G.A AUU .CU U.C ..C ... A.. U.A ... A.G ..U ..U G.C
DEN-4     ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
          6682
DEN-1     CAA CCC CAG UGG AUA GCG GCC UCA AUC AUA CUA GAG UUU UUU CGC AUG GUA CUG UUG AUA
DEN-2     ... ..A ..C ... ... ..A ..U ... ..A ... ..G ... ... ... .U. ..A ..U ... C.C ..U
DEN-3     .C. .U. ..A ... ..C ... TCG G.U ..A G.C ..G ... ... ... AUG ... ..G U.. C.C ...
DEN-4     ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
          6742
DEN-1     CCG GAA CCA GAA AAA CAA AGG ACC CCA CAA GAC AAU CAA UUG AUC UAC GUC AUA UUG ACC
DEN-2     ..A ... ... ... ... ..G ..A ..A ..C ... ... ..C ... ... .C. ... ..U G.C A.A G..
DEN-3     ..A ... ... ... ..G ..G ..A ..U ..C ... ... ..C ... C.C GCA ..U ... G.G A.A GG.
DEN-4     ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
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          6802                                                  6831
DEN-1     AUU CUC ACC AUC AUU GGU CUA AUA GCA GCC
DEN-2     ..C ... ..A G.G G.G .CC GC. .CC AUG ..A
DEN-3     ..A ..U ..A U.G GC. .CA A.. G.. ..G ...
DEN-4     ... ... ... ... ... ... ... ... ... ...
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COMPARISON OF THE NS4B NUCLEOTIDE SEQUENCES OF DENGUE VIRUSES

NS4b

6829

DEN-1 AAC GAG AUG GGG CUG AUU GAA AAA ACA AAA ACG GAU UUU GGG UUU UAC CAG GUA AAA ACA
DEN-2 ... ...U U.C C.G ... .C ..G .AA ..C C.C ..A ..G GGA AGC A.U .C. ..U
DEN-3 ..U ..A ... ..A ... U.G ... .CU ... ..G .GA ... ..A ..A A.G .CU A.A .A. CC. GGU
DEN-4 ... ...

6889

DEN-1 GAA ACC ACC AUC CUC GAU GUG GAC UUG AGA CCA GCU UCA GCA UGG ACG CUC
DEN-2 CAG GAA UCU ..G .G. .A. ... ..G ..C A.A ..U C.A C.U ..U ..A ... ...G
DEN-3 GUU GUU UCU CC. ... .G. UAU U.G ... ... CAC ... ..A ... ..C ... ..A U.G
DEN-4 ... ...

6940

DEN-1 UAU GCA GUA GCC ACC ACA AUU CUG ACU CCC AUG CUG AGA CAC ACC AUA GAA AAC ACG UCG
DEN-2 ... ..C ..G ..U ..A ... U.. G.U ..A ..A ... U.. ... ..U .G. ..U ... ..U U.C ..A
DEN-3 ..C ..C ..G ... ..A ... G.A A.A ..A ..A ... U.. ... ...G ..U U.C A.A
DEN-4 ... ...U ...

7000

DEN-1 GCC AAC CUA UCU CUA GCA GCC AUU GCC AAC CAG GCA GCC GUC CUA AUG GGG CUU GGA AAA
DEN-2 .UG ..U G.G ..C ... A.. ... .U ... ..A ..C A.A ..G ... .U ... ..G ...
DEN-3 ..A ..U G.G ..C ..G ... .A ..U ... ... .UG ... ..G ... ..U U.A .AC ...
DEN-4 ... ...

7060

DEN-1 GGA UGG CCG CUC CAC AGA AUG GAC CUC GGU GUG CCG CUG UUA GCA AUG GGA UGC UAU UCU
DEN-2 ... .A U.G UCA .AG ..C C.. A.. ..A ..U ..C ..C C.U ..C ..U ... .C ..A
DEN-3 ... ... A.A UCG .A. ... ... U.G ..C ..A ..A ..A ..G ... C.. ..U ..C ... ..A
DEN-4 ... ...

7120

DEN-1 CAA GUG AAC CCA ACA ACC UUG ACA GCA UCC UUA GGC AUG CUU UUA GUC CAU UAU GCA AUA
DEN-2 ..G ..C ... ..U .U. ..U C.C ... ... G.U C.U CUU U.A U.G G.. .CA ... .C ..U
DEN-3 ... ... CU. ..U C.U .U. ..G G.A G.. CUU U.. ..A G.C ACA ... ...U
DEN-4 ... ... G.. ... ... .U. ... ...

7180

DEN-1 AUA GGC CCA GGA UUG CAG GCA AAA GCC ACA AGA GAG GCC CAG AAA AGG ACA GCU GCU GGG
DEN-2 ... ..G ... ... C.U ..A ... .A ..C ... ..A ..U ... .A G.. ..A ..A ..C
DEN-3 ... ..U ... ...U C.U ..A ..U ... ...A
DEN-4 ... ...

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DEN-1     AUC AUG AAA AAU CCC ACA GUG GAC GGG AUA ACA GUA AUA GAU CUA GAA CCA AUA UCC UAU
DEN-2     ... ... ... ..C ..A ... ..C ..U ..A ... ... ..G ..U ..C ... ..U ... ... C.. ...
DEN-3     ..A ... ..G ... ..A ..G ... ..U ..A ... .UG AC. ... ..C ... ..U ..U G.. ATA ...
DEN-4     ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
          7300
DEN-1     GAC CCA AAA UUU GAA AAG CAA UUA GGG CAG GUC AUG CUA CUA GUC UUG UGU GCU GGA CAA
DEN-2     ..U ... ... ... ... ... ..G ... ..A ..A ..A ... ..C ... A.. C.C ..C .UG ACU ...
DEN-3     ..U U.. ... ... ... ... ..A C.. ..A ... ..U ... ..C ..G ..T C.. ... ..A .UU ...
DEN-4     ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
          7360
DEN-1     CUA CUC UUG AUG AGA ACA ACA UGG GCU UUC UGU GAA GUC UUG ACU UUG GCC ACA GGA CCA
DEN-2     G.. U.A A.. ... ..G ..U ... ... ... C.G ... ..G .CU C.A ..C ..A ..G ..C ..G ..U
DEN-3     ..U U.G ..A ... ... ... U.. ... ..C ..G ... ... ..U CAU ..C C.A ... ... ... ...
DEN-4     ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
          7420
DEN-1     AUC UUG ACC UUG UGG GAG GGC AAC CCG GGA AGG UUU UGG AAC ACG ACC AUA GCC GUA UCC
DEN-2     ... .CC ..A C.. ... ..A ..A ..U ..A ..G ... ... ... ... ..U ... ..U ..A ..G ..A
DEN-3     ..A ACA ..A C.C ... ..A ..A UCA ..U ..G .A. ..C ... ... ..C ..G ... ..U ..U ...
DEN-4     ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
          7480
DEN-1     ACC GCC AAC AUU UUC AGG GGA AGU UAC UUG GCG GGA GCU GGA CUG GCU UUU UCA CUC AUA
DEN-2     .UG ..U ... ..C ..U ..A ..G ..C ... ... ..C ... ... ... ..U CUC ... ..C A.. ..G
DEN-3     .UG ..G ... ..C ..U ..A ..G ..C ..U ..A ..A ... ... ..G ..U ... C.. ..U A.. ..G
DEN-4     ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ... ...
          7540
DEN-1     AAG AAU GCA CAA ACC CCU AGG AGG
DEN-2     ... ..C A.. AC. .A. A.A ..A ..A
DEN-3     ..A UCA .UU GG. ..A GGA .A. ..A
DEN-4     ... ... ... ... ... ... ... ...
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COMPARISON OF THE NS5 NUCLEOTIDE SEQUENCES OF DENGUE VIRUSES

NS5

7564

DEN-1 GGA ACU GGG ACC ACA GGA GAG ACA CUG GGA GAG AAA UGG AAA ACA CAG UUA AAC CAA CUG AGC
DEN-2 ... .C .A. .U. ... ...U ... ..A ... ... .GC .GA ..G ... GC. ... G.A
DEN-3 ... ..A ... U.A CA. ..U ..A ..C U.A ... ..A ..G ... ... .AG A.A ... ..U ..G U.A UC.
DEN-4 ... ...G ... ..G .G. ... C.. ... UC. U.A GA.

7627

DEN-1 AAG UCA GAA UUC AAC ACC UAC AAA AGG AGU GGG AUU AUG GAG GUG GAC AGA UCC GAA GCC AAA
DEN-2 ..A AGU ... ..U C.G .U. ... ..G .AA ... ..A ..C CA. ..A ... ..G ... A.. UU. ..A ...
DEN-3 CG. AA. ..G ..U G.. CUU ... ..G .AA UCC ..A ..C .CC ..A ... ..U ... A.A ... ...
DEN-4 .G. AA. ..G ..U G.A GAG ..U ... ..A ... ..A ..A C.A ..A ... .G A.U ... .G

7690

DEN-1 GAG GGA UUG AAA AGA GGA GAA ACA ACC AAA CAU GCA GUG UCG AGA GGA ACA GCC AAA CUG AGG
DEN-2 ..A ..C A.C ... ...G GA. C.C ..C ..U ... ... C.. ..C U.. ..A ... .A
DEN-3 ..A ..G ..A ... ... .U. ..A C.C ... ..C ... ..C ... ..C .GC ..A ... ..U CAA
DEN-4 UCU .CC C.. ... GAU ..G UCU .A. .UG ..G ... .A ..U ... ..G U.C AGU ..G A.C ..A

7753

DEN-1 UGG UUU GUG GAG AGG AAC CUC GUG AAA CCA GAA GGG AAA GUC AUA GAC CUC GGU UGU GGA AGA
DEN-2 ... ..C ..C ... ..A ..U A.G ..C .C. ... ...G ..G G.G ... ...C ..C ...
DEN-3 ... ..C ... .A ... A.G ..C .UU ..C ... ..A .G. ... ... U.A ..C ... ...
DEN-4 ... A.. ..U ... ..A GGG A.G ..A ..G ... A.. ... G.. ..U G.. ..U ..U ..C ... ..G ...

7816

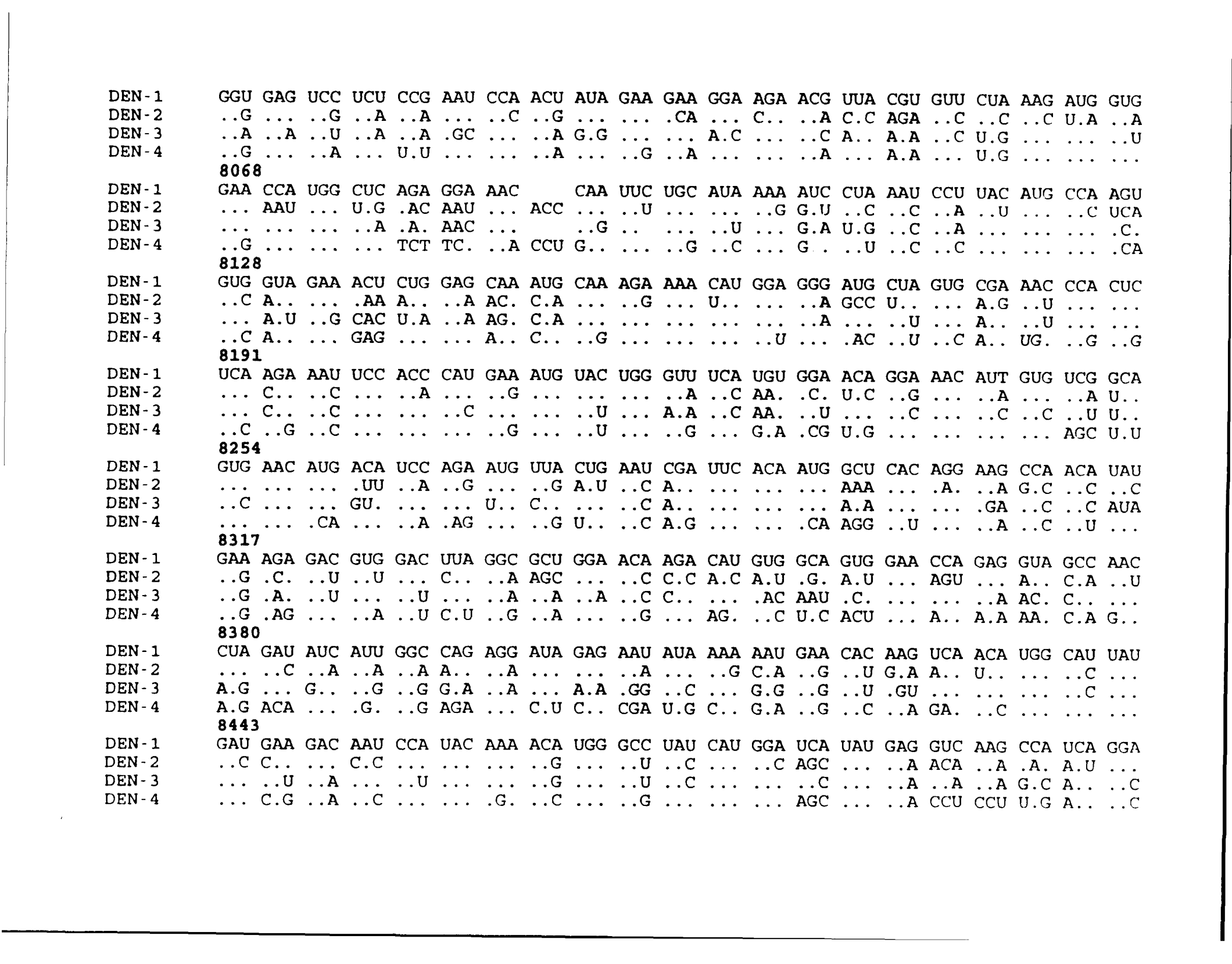
DEN-1 GGU GGC UGG UCA UAU UAU UGU GCU GGG CUG AAG AAA GUC ACU GAA GUG AAG GGA UAC ACA AAA
DEN-2 ..G ... ...C ... ... .GG ..A ..A ... ..U ..A .GA ... ..C ..A ..C CUG ... ...
DEN-3 ..A ... ...C ... ..A ..A ... ..A ... ..U ..A ... ... CGA ... ... .G. ...
DEN-4 ..A ..A ... ..U ... ..C AUG ..G ACA ..C ... ..C ..G ... ...A ..G ..U ... ...

7879

DEN-1 GGA GGA CCU GGA CAU GAG GAA CCU AUC CCA AUG GCG ACC UAU GGA UGG AAC CUA GUA AAG CUA
DEN-2 ... .A ... ..C ..A ... ..C ... ..C ... U.A ..A ... ..G ... ..U ... ..G CGU ..G
DEN-3 ..C ..C ..A ... ..C ..A ... ..A G.A ..U ... U.U ..A ..C ... .C A.. ..C ... U..
DEN-4 ... ..U ..A ... .A ... ..C ..U ..C ... ..U ..U ... ..U ... ..U U.G ..C ..A ..C

7942

DEN-1 CAC UCU GGA AAA GAU GUA UUU UUC ACA CCA CCU GAG AAA UGU GAU ACC CUU CUG UGU GAU AUU
DEN-2 ..A AG. ... GUU ..C ..U ..C ... ..C ..C ..A ..A ..G ... .A U.G U.. ... ..C ..A
DEN-3 AUG AG. ... ..G ... C.U ... .AU CUG ... .A ..G ... ...A U.. ... ..C ...
DEN-4 ..U ..A ..G GUU ..C U.G ..C .A. .A. ..C A.A ... C.. GUG ..C ..C ..G ..C ... ...


DEN-1 GGU GAG UCC UCU CCG AAU CCA ACU AUA GAA GAA GGA AGA ACG UUA CGU GUU CUA AAG AUG GUG
DEN-2 ..G ... ..G ..A ..A ... ..C ..G ... ... .CA ... C.. ..A C.C AGA ..C ..C ..C U.A ..A
DEN-3 ..A ..A ..U ..A ..A .GC ... ..A G.G ... ... A.C ... ..C A.. A.A ..C U.G ... .U
DEN-4 ..G ... ..A ... U.U ... .A ... ..G ..A ... .A ... A.A ... U.G ... ...
8068
DEN-1 GAA CCA UGG CUC AGA GGA AAC CAA UUC UGC AUA AAA AUC CUA AAU CCU UAC AUG CCA AGU
DEN-2 ... AAU ... U.G .AC AAU ... ACC ... ..U ... .G G.U ..C ..C ..A ..U ... ..C UCA
DEN-3 ... ...A .A. AAC ... ..G .. ..U ... G.A U.G ..C ..A ... ... .C.
DEN-4 ..G ... ... TCT TC. ..A CCU G.. ... ..G ..C ... G . ..U ..C ..C ... ... .CA
8128
DEN-1 GUG GUA GAA ACU CUG GAG CAA AUG CAA AGA AAA CAU GGA GGG AUG CUA GUG CGA AAC CCA CUC
DEN-2 ..C A.. ... .AA A.. ..A AC. C.A ... ..G ... U.. ... ..A GCC U.. ... A.G ..U ... ...
DEN-3 ... A.U ..G CAC U.A ..A AG. C.A ... ...A ... ..U ... A.. ..U ... ...
DEN-4 ..C A.. ... GAG ... ... A.. C.. ..G ... ...U ... .AC ..U ..C A.. UG. ..G ..G
8191
DEN-1 UCA AGA AAU UCC ACC CAU GAA AUG UAC UGG GUU UCA UGU GGA ACA GGA AAC AUT GUG UCG GCA
DEN-2 ... C.. ..C ... ..A ... ..G ... ...A ..C AA. .C. U.C ..G ... ..A ... ..A U..
DEN-3 ... C.. ..C ... .C ... .U ... A.A ..C AA. ..U ... ..C ... ..C ..C ..U U..
DEN-4 ..C ..G ..C ... ...G ... ..U ... ..G ... G.A .CG U.G ... ... AGC U.U
8254
DEN-1 GUG AAC AUG ACA UCC AGA AUG UUA CUG AAU CGA UUC ACA AUG GCU CAC AGG AAG CCA ACA UAU
DEN-2 ... ... .UU ..A ..G ... ..G A.U ..C A.. ... ... AAA ... .A. ..A G.C ..C ..C
DEN-3 ..C ... ... GU. ... ... U.. C.. ... ..C A.. ... ... A.A ... ... .GA ..C ..C AUA
DEN-4 ... ... .CA ... ..A .AG ... ..G U.. ..C A.G ... ... .CA AGG ..U ... ..A ..C ..U ...
8317
DEN-1 GAA AGA GAC GUG GAC UUA GGC GCU GGA ACA AGA CAU GUG GCA GUG GAA CCA GAG GUA GCC AAC
DEN-2 ..G .C. ..U ..U ... C.. ..A AGC ... ..C C.C A.C A.U .G. A.U ... AGU ... A.. C.A ..U
DEN-3 ..G .A. ..U ... ..U ... ..A ..A ..A ..C C.. ... .AC AAU .C. ... .A AC. C.. ...
DEN-4 ..G .AG ... ..A ..U C.U ..G ..A ... ..G ... AG. ..C U.C ACU ... A.. A.A AA. C.A G..
8380
DEN-1 CUA GAU AUC AUU GGC CAG AGG AUA GAG AAU AUA AAA AAU GAA CAC AAG UCA ACA UGG CAU UAU
DEN-2 ... ..C ..A ..A ..A A.. ..A ... .A ... ..G C.A ..G ..U G.A A.. U.. ... ..C ...
DEN-3 A.G ... G.. ..G ..G G.A ..A ... A.A .GG ..C ... G.G ..G ..U .GU ... ...C ...
DEN-4 A.G ACA ... .G. ..G AGA ... C.U C.. CGA U.G C.. G.A ..G ..C ..A GA. ..C ... ...
8443
DEN-1 GAU GAA GAC AAU CCA UAC AAA ACA UGG GCC UAU CAU GGA UCA UAU GAG GUC AAG CCA UCA GGA
DEN-2 ..C C.. ... C.C ... ...G ... ..U ..C ... ..C AGC ... ..A ACA ..A .A. A.U ...
DEN-3 ... ..U ..A ... ..U ... .G ... ..U ..C ... .C ... ..A ..A ..A G.C A.. ..C
DEN-4 ... C.G ..A ..C ... ... .G. ..C ... ..G ... ... AGC ... ..A CCU CCU U.G A.. ..C

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DEN-1   UCA GCC UCA UCU AUG GUG AAU GGC GUG GUG AGA UUG CUC ACA AAA CCA UGG GAU GUU AUC CCC
DEN-2   ... ..A ... ... ... ... ..C ..A ... ..C ... C.. ..G ... ... ..C ... ..C ..C G.. ..U
DEN-3   ... ... ..C ..C ... A.A ... ..A ..C ... .A. C.C ... ... ... ... ... ... ..G G.G ..A
DEN-4   ..U C.A ..C ..C ... ... ..C ..G ..A ..A .A. C.C ..A ... ... ..C ... ... ..G ..U ..A
        8569
DEN-1   AUG GUC ACA CAA AUA GCU AUG ACU GAU ACC ACA CCC UUC GGA CAA CAG AGA GUG UUU AAA GAG
DEN-2   ... ..G ... ..G ..G ..A ... ..A ..C ..G ..U ..A ..U ... ... ..A C.C ..U ..C ... ...
DEN-3   ... ..G ... ..G ..G ..A ... ..A ... ..A ..U ..A ..U ..C ..G ..A ... ..U ... ... ...
DEN-4   ... ..G ..U ..G U.. ..C G.. ..A ... G.A .UC .AT ..U ..C ... ..A ... ... ..C ... ...
        8632
DEN-1   AAA GUU GAC ACG CGC ACA CCA AGA GCA AAA CGA GGC ACA GCA CAA AUU AUG GAG GUG ACA GCC
DEN-2   ... ..G ... ... A.A ..C .A. GA. C.G ..G GA. ... ... AAG A.. C.G ... A.A A.C ..G ..A
DEN-3   ... ..G ... ..C A.G ... ..U ..G C.C .UG .C. ..A ... AG. A.G G.. ... ... A.C ... ..G
DEN-4   ..G ..G ..U ..C A.A ... ... CA. C.. ... .CC ..U ... CG. AUG G.. ... ACC AC. ... ...
        8695
DEN-1   AAG UGG UUA UGG GGU UUC CUU UCC AGA AAC AAA AAA CCC AGA AUC UGC ACA AGA GAG GAG UUC
DEN-2   G.. ... C.U ... AAA GAA ..A GGA .AG ..A ..G .C. ..U .GG ..G ..U ..C ... ..A ..A ...
DEN-3   G.. ... C.U ... A.G AC. ..G GGA .GG ... ... .G. ... ... U.A ... ... ..G ... ... ...
DEN-4   ..U ... C.G ... .CC C.C ... GGA .AG ..G ... ..U ... ... C.G ... ... ..G ..A ... ...
        8758
DEN-1   ACA AGA AAG GUU AGG UCA AAC GCA GCA AUA GGA GCA GUG UUC GUU GAU GAA AAC CAA UGG AAC
DEN-2   ... ... ... ..G ..A AGC ..U ... ..C U.G ..G ..C A.A ... AC. ... ..G ... A.. ... ..A
DEN-3   ... .AG ... ..C ..A A.C ... ... ..U ..G ..C ..U ..C ... ACA ..A ..G ... ... ... G..
DEN-4   .UC UC. ..A ... ..A ... ... ... ..C ... ..U CG. ..C ..U CAG ..A ... C.G GG. ... .CA
        8821
DEN-1   UCA GCA AAA GAA GCA GUG GAA GAC GAA AGG UUU UGG GAU CUC GUG CAC AGA GAG AGG GAG CUU
DEN-2   ..G ... CGU ..G ..U ..U ... ..U AGU ... ... ... ..G ..G ..U G.. ..G ..A ..A A.U ..C
DEN-3   AGU ..G .G. .CU ..U ..U ..G ... ... GAA ... ... A.A ..U ... G.. ... ..A C.U ..A ..C
DEN-4   ... ..C .GU ..A ..U ... A.U ... AGC C.. ... ... ..A ..G ..U G.. .A. ..A ..G .CC ..A
        8884
DEN-1   CAU AAA CAG GGA AAA UGU GCC ACG UGU GUC UAC AAC AUG AUG GGG AAG AGA GAG AAA AAA UUA
DEN-2   ... CUU G.A ... ..G ... .AA ..A ... ..G ... ... ... ... ..A ..A ... ... ..G ... C..
DEN-3   ..C ... .U. ..C ..G ... .GA .GC ..C ..U ... ... ... ... ..C ... ... ... ... ... C.U
DEN-4   ..C C.G G.A ..G ... ... .AA U.. ... ... ..U ... ... ... ..A ..A C.U ... ... ..G ...
        8947
DEN-1   GGA GAG UUU GGA AAG GCA AAA GGA AGU CGU GCA AUA UGG UAC AUG UGG CUG GGA GCA CGC UUU
DEN-2   ..G ... ..C ..C ... ... ... ..U ..C A.A ..C ... ... ... ... ... ... ... ... ... ..C
DEN-3   ... ... ... ..U ..A ... ... ..C ... A.G ..U ... ... ... ... ... U.. ... ..C A.G .AC
DEN-4   ... ... ... ..C .GA ..C ..G ... ..C ..A ... ..C ... ... ... ... ... ... ..G ..G ...
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DEN-1   CUA GAG UUC GAA GCC CUU GGU UUC AUG AAU GAA GAU CAC UGG UUC AGU AGA GAG AAU UCA CUC
DEN-2   U.. ... ..U ... ... ..A ..A ... U.. ... ... ... ... ... ... UCC ... .G. ..C ..C ..G
DEN-3   ..U ... ... ..G ..G ..C ..A ... C.. ... ... ..C ... ... ... UCG C.U ..A ..C ..U UA.
DEN-4   ..G ..A ..U ... ... ..G ... ... U.. ... ... ... ... ... ..U G.C ... ..A ... ... UGG
        9073
DEN-1   AGU GGA GUG GAA GGA GAA GGA CUG CAC AAA CUU GGA UAC AUA CUC AGA GAC AUA UCA AAG AUU
DEN-2   ... ... ... ... ... ... ..G ... ... ..G ..A ..C ... ..U U.A ... ... G.G AGC ... .AG
DEN-3   ... ... ..A ... ... ... ... ... ... ..G ..G ... ... ..C U.G ... ..U ..U ..C ... ..A
DEN-4   ... ... ... ... ..G ... ..U ... ... .G. U.G ... ..U ..C ..G GAG ..G ... GAC ... .AG
        9136
DEN-1   CCG GGG GGA AAU AUG UAU GCA GAU GAU ACA GCC GGA UGG GAC ACA AGA AUA ACA GAG GAU GAU
DEN-2   GAA ... ... GCA ... ..C ..C ... ..C ... ..A ... ... ... ... ... ..C ... CUA ..A ..C
DEN-3   ..C ..A ..A GCC ... ... ..U ... ..C ... ... ..U ... ... ... ... ... ... ..A ... ..C
DEN-4   GAU ..A .AC CUA ... ... ..U ... ..C ... ..A ..C ... ... ... ... ..C ..U ... ... ..C
        9199
DEN-1   CUU CAG AAU GAG GCU AAA AUC ACU GAC AUC AUG GAG CCU GAA CAU GCU CUA UUG GCU ACG UCA
DEN-2   U.A A.A ... ..A .AA .UG G.A ..A A.. CA. ... ..A GGA ... ..C AAG AA. C.A ..C GA. GCC
DEN-3   ..G ..C ... ... .AA ... ... ..A C.G CAG ... ..C ... ... ..C AGG .AG C.A ..G .AC G.U
DEN-4   ... ..A ... ... .AC CUG ... ..G ..A CAG ... .CU ..C C.C ..C AAG A.C C.A ..C .AA G.C
        9262
DEN-1   AUU UUU AAG CUG ACC UAC CAA AAC AAG GUG GUG ACC CUG CAA AGA CCA GCA AAA AAU GGA ACC
DEN-2   ..A ..C ..A U.A ..G ... ... ... ... ... ... CGU G.. ... ... ... A.. CC. .GA ..C ..A
DEN-3   ..A ..C ... ..C ..A ... ... ... ..A ... ..C .AA G.C ... C.. ... A.U CC. ..G ..C ..G
DEN-4   ... ..C ..A ..A ... ..U ... ... ..A ... ... UUU G.C .UC ... ..C A.. CCG .GA ... G.G
        9325
DEN-1   GUG AUG GAU GUU AUA UCC AGA CGU GAC CAG AGA GGA AGU GGA CAG GUC GGA ACU UAU GGC UUA
DEN-2   ..A ... ... A.C ... ..G ... A.A ... ..A ... ..C ... ..G ..A ... ..C ..C ... ... C.U
DEN-3   ..A ... ..C A.C ... ..U ..G AAA ... ..A ... ..C ... ... ... ..G ... ... ... ..U C.G
DEN-4   ..A ... ... A.C ... ... ..G AAA ..A ..A ... ..U ... ... ..A ..U ... ..A ... ..U ..G
        9388
DEN-1   AAT ACU UUC ACC AAU AUG GAG GUC CAA CUA AUA AGA CAA AUG GAG UCU GAA GGA GUC AUC ACA
DEN-2   ... ..A ... ... ..C ... ..A .CU ... U.. ..U ... ..G ... ... GGA ... ... A.. U.. .A.
DEN-3   ..C ..A ... ... ..C ... ..A .CC ..G ... ..C ... ... ... ..A GGA ... ..C ..G U.G U..
DEN-4   ..C ..A ... ... ..C ... ..A ..U ... ..C .GC C.C ... ... ..A G.. ... ... ... ... ...
        9451
DEN-1   CAA GAU GAC AUG CAG AAC CCA AAA GGU UUG AAA GAA AGA GUU GAG AAA UGG UCG AAA GAG UGU
DEN-2   AGC .U. C.G CAC .U. .CA GUC .C. GAA GAA .UC .CU GU. CAG A.C     ... .UA GC. AGU GUG
DEN-3   A.G .CA ... C.C G.. ... ..C C.U CCG C.A G.G A.G .A. A.. ACA C.. ... .U. G.. ACU AAA
DEN-4   ... ... ... ... ... ... ... ... ..G ... ... ... ... ... ... ... ... CUG ... ... ...
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DEN-1   GGU GUC GAC AGG CUG AAA AGA AUG GCA AUU AGC GGA GAU GAU UGU GUG GUG AAA CCA AUU AGU
DEN-2   ..G CGU ..A ... ..A UC. ... ... ..C ..C ..U ... ... ... ... ..U ..A ... ..U U.A GA.
DEN-3   ..A ..G ..G ... U.A ... ... ... ..C ..C ... ..G ... ... ..C ..A ... ... ... ..C GAC
DEN-4   ... ... ... ... U.A ..G ..G ... ... ..C ..U ... ..C ... ..C ... ... ..G ..C C.A GA.
        9577
DEN-1   GAC AGG UUC GCA ACA GCC UUA AUA GCU CUG AAU GAC AUG GGA AAA GUA AGA AAA GAC AUA CCG
DEN-2   ... ..A ..U ... .GU ..U ... .C. ... ..A ... ... ... ... ... ..U ..G ... ..U ... .AA
DEN-3   ... ..A ... ..C .AU ... C.G C.U ..C ... ..C ..U ... ... ..G ..U ..G ..G ... ... ..U
DEN-4   ... ... ..U .GC ..U U.. C.C C.C UUC U.. ..C C.G ... ... ..G ..G ..G ... ... ..U ...
        9640
DEN-1   CAG UGG GAA CCU UCA AAA GGA UGG AAU GAC UGG CAG CAA GUG CCU UUC UGU UCA CAC CAU UUC
DEN-2   ..A ... ... ... ... .G. ... ... ..C ..U ... ACA ... ... ... ... ... ... ... ... ..U
DEN-3   ..A ... C.G ..A ... ..G ... ... C.. ..U ... ..A ..G ..C ... ... ..C ..C ... ..C ..U
DEN-4   ... ... ... ..A ..U ..G ... ... ..A A.. ... ..A G.G ..U ... ..U ..C G.C ... ..C C.U
        9703
DEN-1   CAC CAG CUG AUC AUG AAG GAU GGG AGG GAA AUA GUG GUG CCA UGC CGC AAC CAA GAU GAA CUU
DEN-2   ..U G.. U.A G.. ... ..A ... ..U C.C .UG C.C ..A ..C ... ... A.A ... ... ... ... ..G
DEN-3   ..U G.A U.. ... ... ..A ... ..A ..A A.G U.G ..A ..U ..C ... A.A CC. ..G ..C ... ..A
DEN-4   ... A.. ACC U.U ... ... ... ..C C.C UC. C.. ..U ..U ... ..U A.A ... ..G ... ... ..G
        9766
DEN-1   GUG GCA AGG GCU AGA GUA UCA CAA GGC GCC GGA UGG AGC CUG AGA GAA ACU GCU UGC CUA GGC
DEN-2   A.U .GU ..A ..C C.. A.U ..C ..G ..A ... ..G ... UCU U.. .AG ..G ..G ..C ..U U.G ..G
DEN-3   A.A .G. ..A ..G ... A.C ..U ... ..A ..A .A. ... ... ..U ... ... ... ..A ..U ... ..G
DEN-4   A.A .G. ..A ..C ... A.C ..G ..G ..A ..U ... ... ... U.A ... ... ..A ..C ... ..G ...
        9829
DEN-1   AAG UCA UAU GCA CAA AUG UGG CAG CUG AUG UAC UUC CAC AGG AGA GAC CUG AGA CUA GCG GCU
DEN-2   ... ..U ..C ..C ... ... ... ACC ... ... ... ... ... ..A C.. ... ..C ... ..G ... ..A
DEN-3   ..A G.C ..C ..U ... ... ... ACU ..C ... ..U ..U ... ..A ... ..U ..U ... ... ..A U.C
DEN-4   ..A G.U ..C ..C ..G ... ... UCG ..U ... ... ... ... ..A .AG ..U ... C.U U.. ..C U.C
        9892
DEN-1   AAU GCU AUC UGU UCA GCC GUC CCA GUU GAU UGG GUC CCA ACC AGC CGC ACA ACC UGG UCA AUC
DEN-2   ... ... ..U ..C ..G ..A ... ..G UCA C.. ... ..U ... ..A ..U ..A ... ... ... ..C ..A
DEN-3   ..C ..C ..A ... ... ..A ..A ... ..C C.. ... ... ..C ..G ... A.A ..G ..A ... ..U ..U
DEN-4   .UG ..C ..A ..C ... ..A ..U ... ACG ..A ... U.U ... ..A ... A.A ... ..A ... ... ...
        9955
DEN-1   CAU GCC CAC CAC CAA UGG AUG ACA ACA GAA GAC AUG UUA UCA GUG UGG AAU AGG GUU UGG AUA
DEN-2   ..C ..U A.G ..U G.. ... ... ..G ..G ... ... ... C.G G.. ... ... ... ... ..C ... ..C
DEN-3   ... ..U ... ..U ..G ... ... ..U ... ... ... ... C.U A.U ..C ... ..C ... ..G ... ...
DEN-4   ..C ..U ..U ... ..G ... ... ..C ..U ... ..U ... C.C AA. ... ... ..C ..A ..G ... ...
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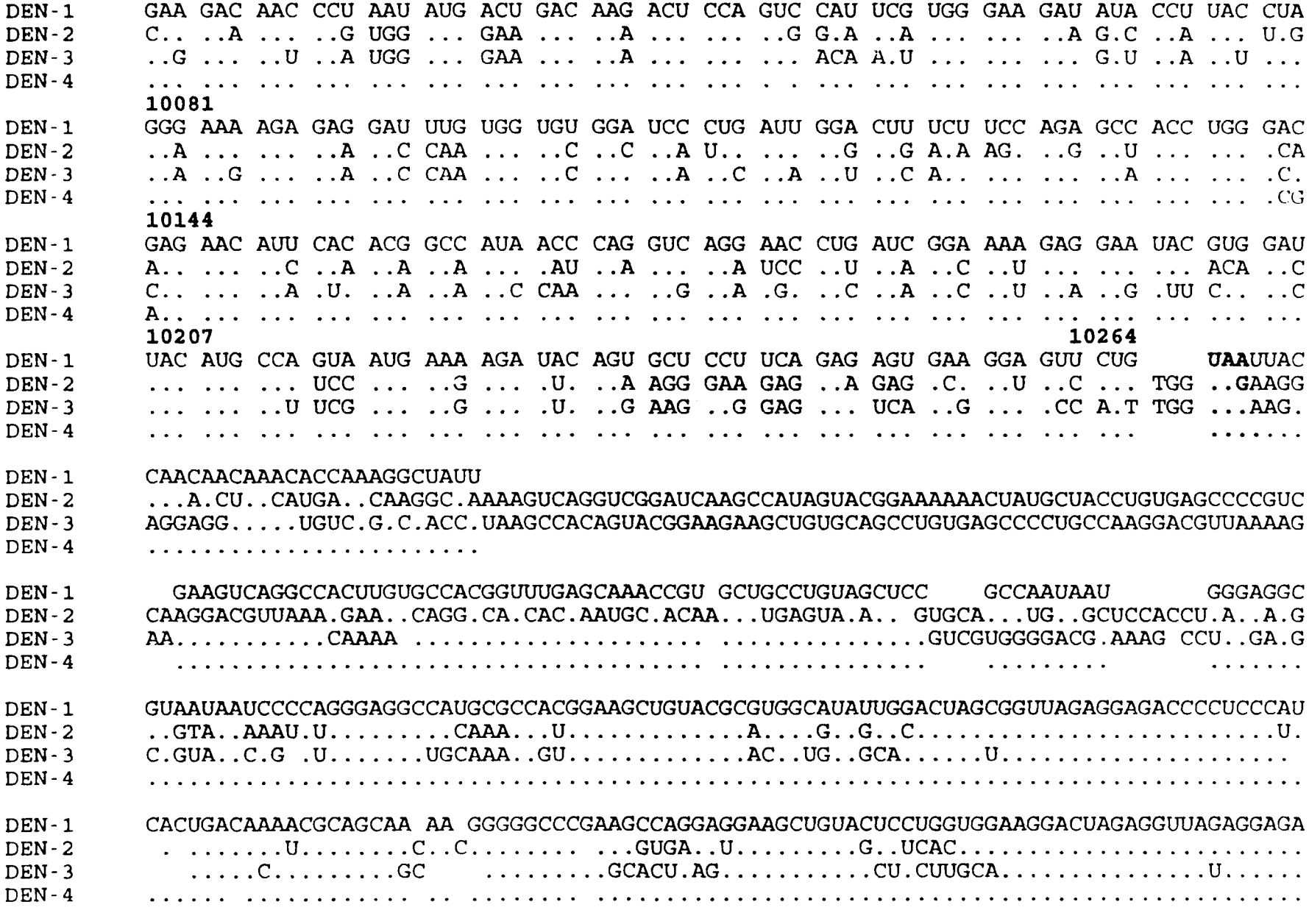
DEN-1 GAA GAC AAC CCU AAU AUG ACU GAC AAG ACU CCA GUC CAU UCG UGG GAA GAU AUA CCU UAC CUA
DEN-2 C.. ..A ... ..G UGG ... GAA ... ..A ... .G G.A ..A ... .A G.C ..A ... U.G
DEN-3 ..G ... ..U ..A UGG ... GAA ... ..A ... ... ACA A.U ... ... G.U ..A ..U ...
DEN-4 ... ...
10081
DEN-1 GGG AAA AGA GAG GAU UUG UGG UGU GGA UCC CUG AUU GGA CUU UCU UCC AGA GCC ACC UGG GAC
DEN-2 ..A ... .A ..C CAA ... ..C ..C ..A U.. ... ..G ..G A.A AG. ..G ..U ... ... .CA
DEN-3 ..A ..G ... ..A ..C CAA ... ..C ... ..A ..C ..A ..U ..C A.. ... .A ... ... .C.
DEN-4 ... ... .CG
10144
DEN-1 GAG AAC AUU CAC ACG GCC AUA ACC CAG GUC AGG AAC CUG AUC GGA AAA GAG GAA UAC GUG GAU
DEN-2 A.. ... ..C ..A ..A ..A ... .AU ..A ... ..A UCC ..U ..A ..C ..U ... ... ACA ..C
DEN-3 C.. ... ..A .U. ..A ..A ..C CAA ... ..G ..A .G. ..C ..A ..C ..U ..A ..G .UU C.. ..C
DEN-4 A.. ... ...
10207 10264
DEN-1 UAC AUG CCA GUA AUG AAA AGA UAC AGU GCU CCU UCA GAG AGU GAA GGA GUU CUG UAAUUAC
DEN-2 ... ... UCC ... ..G ... .U. ..A AGG GAA GAG ..A GAG .C. ..U ..C ... TGG ..GAAGG
DEN-3 ... .U UCG ... ..G ... .U. ..G AAG ..G GAG ... UCA ..G ... .CC A.T TGG ...AAG.
DEN-4 ... ...
DEN-1 CAACAACAAACACCAAAGGCUAUU
DEN-2 ...A.CU..CAUGA..CAAGGC.AAAAGUCAGGUCGGAUCAAGCCAUAGUACGGAAAAAACUAUGCUACCUGUGAGCCCCGUC
DEN-3 AGGAGG.....UGUC.G.C.ACC.UAAGCCACAGUACGGAAGAAGCUGUGCAGCCUGUGAGCCCCUGCCAAGGACGUUAAAAG
DEN-4 .....
DEN-1 GAAGUCAGGCCACUUGUGCCACGGUUUGAGCAAACCGU GCUGCCUGUAGCUCC GCCAAUAAU GGGAGGC
DEN-2 CAAGGACGUUAAA.GAA..CAGG.CA.CAC.AAUGC.ACAA...UGAGUA.A.. GUGCA...UG..GCUCCACCU.A..A.G
DEN-3 AA.....CAAAA ....GUCGUGGGGACG.AAAG CCU..GA.G
DEN-4 ....
DEN-1 GUAAUAAUCCCCAGGGAGGCCAUGCGCCACGGAAGCUGUACGCGUGGCAUAUUGGACUAGCGGUUAGAGGAGACCCCUCCCAU
DEN-2 ..GTA..AAAU.U.....CAAA...U.....A....G..G..C.....U.
DEN-3 C.GUA..C.G .U.....UGCAAA..GU.....AC..UG..GCA.....U.....
DEN-4 .....
DEN-1 CACUGACAAAACGCAGCAA AA GGGGGCCCGAAGCCAGGAGGAAGCUGUACUCCUGGUGGAAGGACUAGAGGUUAGAGGAGA
DEN-2 . .....U.....C..C..... ...GUGA..U.....G..UCAC.....
DEN-3 .....C.....GC .....GCACU.AG.....CU.CUUGCA.....U.....
DEN-4 ....

```
DEN-1     CCCCCCCAACAC AAAAACAGCAUAUUGACGCUGGGAAAGACCAGAGAUCCUGCUGUCUCUGCAACAUCAAUCCAGGCACAGA
DEN-2     .........A..A.....................................................CU..G.....U.............
DEN-3     ......GC.A.. ..........................G.....................CU..G.....U.............
DEN-4     ..........  ..........................................................C.................
                                                  10653     3'end length
DEN-1     GCGCCGCAAGAUGGAUUGGUGUUGUUGAUCCAACAGGUUCU          (387)
DEN-2     A....AG..A.....A.....C......AU..........U          (455)
DEN-3     A....AG..A.....A.....C.C....AU..........U          (448)
DEN-4     ........................................U          (385)
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FIGURE 4

COMPARISON OF THE DEDUCED NS1 AMINO ACID SEQUENCES OF DENGUE VIRUSES

NS1

```
DEN-1     DSGCVINWKG KELKCGSGIF VTNEVHTWTE QYKFQADSPK RLSAAIGKAW EEGVCGIRST
DEN-2     .....VS..N .......... I.DN...... .....PE..S K.AS..Q..H ...I.....V
DEN-3     .M........ .......... .......... .......... .VAT..AG.. .N........
DEN-4     .M...VS.S. .......... .VDN...... .....PE..A ..AS..LN.H KD........

DEN-1     TRLENVMWKQ ITNELNYVLW EGGHDLTVVA GDVKGVLTKG KRALTPPVSD LKYSWKTWGK
DEN-2     .......... ..P...HI.S .NEVK..IMT .CI..IMQA. ..S.R.QPTE ..........
DEN-3     ..M..LL... .A.....I.. .NDIK....V .CIT...EQ. ..T...QPME .........L
DEN-4     .......... .......... .......... .......... .......... ..........

DEN-1     AKIFTPEARN STFLIDGPDT SECPNERRAW NSLEVEDYGF GMFTTNIWMK FREGSSEVCD
DEN-2     ..MLST.SH. Q.......E. A.....N... .......... .V....I.L. L..KQDVF..
DEN-3     ...V.A.TQ. .S.I....S. P...SAS... .VW....... .V......L. L..VYTQL..
DEN-4     .......... .......... .......... .......... .......... ..........

DEN-1     HRLMSAAIKD QKAVHADMGY WIESSKNQTW QIEKASLIEV KTCLWPKTHT LWSNGVLESQ
DEN-2     SK........ NR........ ....AL.D.. KM....F... .S.H...S.. .........E
DEN-3     .......V.. ER........ ....Q..GS. KL........ ...T...S.. .........D
DEN-4     .......... .......... .......... .......... .......... ..........

DEN-1     MLIPKEYAGP FSQHNYRQGY ATQTVGPWHL GKLEIDFGEC PGTTVTIQED CDHRGPSLRT
DEN-2     .I...NF... V......P.. H...A..... ....M..DF. E....VVT.. .GN.......
DEN-3     .....SL... I......P.. H...A..... ....L..NY. E....V.S.N .GT.......
DEN-4     .....S.... .......... .......... .......... .......... ..........

DEN-1     TTASGKLVTQ WCCRSCTMPP LRFLGEDGCW YGMEIRPLSE KEENMVKSQV TA
DEN-2     .......I.E .......L.. ..YR...... ........K. ....L.N.L. ..
DEN-3     .TV....IHE .......L.. ..YM...... .......IN. ........LA S.
DEN-4     .........A MV.T...... .......... .......... .......... ..
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COMAPRISON OF THE DEDUCED NS2a AND NS2B AMINO ACID SEQUENCES OF DENGUE VIRUSES

```
          NS2a
DEN-1     GQGTSETFSM GLLCLTLFVE ECLRRRVTRK HMILVVVITL CAIILGGLTW MDLLRALIML
DEN-2     .H.QIDN..L ...GMA..L. .M..T..GT. .A..L.AVSF VTL.T.NMSF R..G.VMV.V
DEN-3     ...KVDN.T. .V...AILF. .VM.GKFGK. ...AG.LF.F VLLLS.QI.. RGMAHT...I
DEN-4     .......... S......... .......... .......... .......... ..........

DEN-1     GDTMSGRIGG QIH LAIMAV FKMSPGYVLG VFLRKLTSRE TALMVIGMAM TTVLSIPHDL
DEN-2     .A..TDD..M GVTY..LL.A ..VR.TFAA. LL......K. LMMAT..I.L LSQST..ETI
DEN-3     .SNA.D.M.M GLTY..LI.T ..IQ.FLA.. F......... NL.LGV.L.. AAT.RL.E.I
DEN-4     .......... ... ...... .....R.... .......... .......... ..........

DEN-1     MELIDGISLG LILLKIVTQF DNTQVGTLAL SLTFIRSTMP LVMAWRTIMA VLFVVTLIPL
DEN-2     L..T.ALA.. MMV....RNM EKY.LAVTIM AILCVPNAVI .QN..KVSCT I.AA.SVS..
DEN-3     EQMAN..A.. .MA..LI... ETY.LW.ALV ...CSNTIFT .TV....ATL I.AGIS.L.V
DEN-4     ....S..... .......... .......... .......... .......... ....D.....
                                                    NS2B
DEN-1     CRTSCLQKQS HWVEITALIL GAQALPVYLM TLMKGASRRS WLLNEGIMAV GLVSLLGSAL
DEN-2     LL..SQ..AD  .IPLALTIK .LNPTAIF.T ...RTSKK.. .P...A.... .M..I.A.S.
DEN-3     .QS.SMR.TD  .LPM.VAAM .VPP..LFIF S.KDTLK... .P....V... ....I.A.S.
DEN-4     .......... ..A....... .......... .......... .P........ ..........

DEN-1     LKNDLPLASP MVAGGLLLAA YVMSGSSADL SLEKAANVQW DEMADITGSS PIIEVKQDED
DEN-2     ....I.MTG. L......TVC ..LT.R.... E..R..D.K. EDQ.EIS... ..LSITIS..
DEN-3     ....V.M.G. L......I.C ..IT.T.... TV....D.T. E.E.EQ..V. HNLMITV.D.
DEN-4     ...CV...G. .......... .M........ .......... .......... ..........

DEN-1     GSFSIRDVEE TSMITLLVKL DLITVSGLYP LAIPVTMTLW YMWQVKTQR
DEN-2     ..M..KNE.. EQTL.I.IRT G.LVI..VF. VS..I.AAA. .L.E..K..
DEN-3     .TMR.K.D.T ENIL.V.L.T A.LI...IF. YS..A..LV. HT..KQ...
DEN-4     .......... .N........ A......... .......... .........
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COMPARISON OF THE DEDUCED NS3 AMINO ACID SEQUENCE OF DENGUE VIRUSES

NS3

```
DEN-1   SGSLWDVPSP AATQKAALSE GVYRIMQRGL FRKTQVGVGI HMEGVFHTMW HVTRGSVICH
DEN-2   A.V..... PPVG..E.ED .A...K...I LGYS.I.A.V YKE.T..... .....A.LM.
DEN-3   ..V..... PET...E.E. .....K.Q.I .G.......V QKE..... .....A.LT.
DEN-4   ..A..... ...K..... .......... .G..... .......... ..........

DEN-1   ETGRLEPSWA DVRNDMISYG GGWRLGDKWD KEEDVQVLAI EPRKNPKHVQ TKPGLFKTLT
DEN-2   KGK.I..... ..KK.L.... ...K.EGE.K EG.E.....L ..G...RA.. ........N.
DEN-3   NGK....N.. S.KK.L.... .....SAQ.Q .G.E...I.V ..F....NF. .M..I.Q.T.
DEN-4   .......... .......... .......... .......... .......... ...S......

DEN-1   GGIGAVTLDF KPSTSGSPII NRKGKVIGLY GNGVVTKSGD YVSAITQAER IGEPDYEVDE
DEN-2   .T....S... S.G......V D.....V... ......R..A .....A.T.K SI.DNP.IED
DEN-3   .E...IA... ..G..... ..E...V... .......N.G ...G.A.TNA EPDGPTPEL.
DEN-4   .E..... ..G..... .......... .......... .......... ..........

DEN-1   DI FRKKRLT IMDLHPGAGK TKRILPSIVR EALKRRLRNL ILAPTR  AA EMEEALRGLP
DEN-2   .. ..... .......... ...Y..A... ..I..G..T. ......VV.. ..........
DEN-3   EEM.K.RN.. .......S.. ..KY..A... ..I.....T. ......VV.. ....PMK...
DEN-4   .. ..... .......... .......... ........T. ......VV.. ..........

DEN-1   IRYQTPAVKS EHTGREIVDL MCHATFTTRL LSSTRVSNYN LIVMDEAHFT DPSSVAARGY
DEN-2   .......IRA .......... .......M.. ..PV..P... ..I..... ..A.I.....
DEN-3   .....T.T.. .......... .......M.. ..PV..P... ..I..... S.A.I.....
DEN-4   .......... .......... .......... ......P... .......... ..........

DEN-1   ISTRVEMGEA AAIFMTATPP GATDPFPQSN SPIEDIEREI PERSWDTGFD WITDYQGKTV
DEN-2   .......... .G........ .SR..... A..M.E.... .....NS.HE .V..FK....
DEN-3   .....G.... .......... .TA.A..... A..Q.E..D. .....NS.NE ....FV....
DEN-4   .......... .......... .......... .......... .......... ..........

DEN-1   WFVPSIKAGN DIANCLRKSG KKVIQLSRKT FDTEYPKTKL TDWDFVVTTD ISEMGANFRA
DEN-2   .......... ...A....N. .......... ..S..V..RA N......... ........K.
DEN-3   .......... V.......N. .......... .....Q.... N......... ........I.
DEN-4   .......... .......... .......... .......... .......... ..........
```

```
DEN-1     GRVIDPRRCL KPVILTCGPE RVILAGPIPV TPASAAQRRG RIGRNPAQED DQYVFSGDPL
DEN-2     E........M ......D.E. .......M.. .HS....... ......KN.N ...IYM.E..
DEN-3     D......... .......... .......M.. .V........ .V....QK.N ...I.M.Q..
DEN-4     .......... .....P.... .......... .......... .......... ..........

DEN-1     KNDEDHAHWT EAKMLLDNIY TPEGIIPTLF GPEREKTQAI DGEFRLRGEQ RKTFVELMRR
DEN-2     E....C...K .........N .......SM. E.....VD.. ...Y.....A .....D....
DEN-3     NK........ .........N .......A.. E.....SA.. ...Y..K.DS ..........
DEN-4     .......... .......... .......... .......... .......... ..........

DEN-1     GDLPVWLSYK VASAGISYKD REWCFTGERN NQILEENMEV EIWTREGEKK KL PRWLDAR
DEN-2     .......A.R ..AE..N.A. .R...D.IK. .......V.. ....K...R. ..K.......
DEN-3     .......AH. ...E..K.T. .K...D.... ........D. ....K..... ..R.......
DEN-4     .......... .......... .......... .......... .......... ..R.......

DEN-1     VYSCPLALKD FKEFASGRK
DEN-2     I..D.....E .....A...
DEN-3     T..D.....E ..D..A...
DEN-4     ..A..M.... .........
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COMPARISON OF THE DEDUCED NS4a AND NS4B AMINO ACID SEQUENCES OF DENGUE VIRUSES

```
          NS4a
DEN-1     SITLDILTEI ASLPTYLSSR AKLALDNIVM LHTTERGGRA YLHALNELPE SLETLMLVAL
DEN-2     .L..NLI..M GR...FMTQK .RD....ALV ...A.A.... .....S.... T....L.LT.
DEN-3     ..A..LV... GRV.SH.AH. TRN....L.. ...S.H.... .R..VE.... TM...L.LG.
DEN-4     .......... .......... .......... .......... .Q......T. ..........

DEN-1     LGAMTAGIFL FFMQGKGIGK LSMGLITIAV ASGLLWVAEI QPQWIAASII LEFFRMVLLI
DEN-2     .ATV.G.... .L.S...... MTL.MCC.IT ..I...Y.Q. ..H....... ....LI....
DEN-3     MILL.G.AM. .LIS...... T.I...CVIA S..M..M.DV PL....SA.V ....M.....
DEN-4     .......... .......... .......... .......... .......... ....L.....

DEN-1     PEPEKQRTPQ DNQLIYVILT ILTIIGLIAA NEMGLIEKTK TDFGFYQVKT    ETTILDV
DEN-2     .......... ....T...IA ...VVAATM. ..N.FL.... K.L.LGSIT. QESESN...I
DEN-3     .......... ....A..VIG ...LAAIV.. .....L.TTH R.L.MSKEPG VVSP.SY...
DEN-4     .......... .......... .......... .......... ..........    .......

DEN-1     DLRPASAWTL YAVATTILTP MLRHTIENTS ANLSLAAIAN QAAVLMGLGK GWPLHRMDLG
DEN-2     .......... ......FV.. ....S...S. V.V..T.... ..T....... ....SKIHI.
DEN-3     ..H....... ......V... ........ST ..V....... ..V.....D. ...ISK....
DEN-4     .......... .......... .......... .......... .......... ..........
                                                                 NS4B
DEN-1     VPLLAMGCYS QVNPTTLTAS LGMLLVHYAI IGPGLQAKAT REAQKRTAAG IMKNPTVDFI
DEN-2     .....I.... ....I....A .LL.VA.... .......... ......A... ........G.
DEN-3     .....L.... ....L..I.A VLL.VT.... .......... .......... ........G.
DEN-4     .......... .......A.. .V........ .......... .......... .....I..G.

DEN-1     TVIDLEPISY DPKFEKQLGQ VMLLVLCAGQ LLLMRTTWAF CEVLTLATGP ILTLWEGNPG
DEN-2     ........P. .......... ....I..VT. V.M......L ..A....... .S........
DEN-3     MT...D.VI. .S........ .......... ......S..L .......... .T.....S..
DEN-4     .......... .......... .......... .......... .......... ..........

DEN-1     RFWNTTIAVS YANIFRGSYL AGAGLAFSLI KNAQTPRR
DEN-2     .......... H......... .....L..IM ..TTNT..
DEN-3     K......... M......... ......L.IM .SVG.GK.
DEN-4     .......... T......... .......... ........
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COMPARISON OF THE DEDUCED NS5 AMINO ACID SEQUENCE OF DENGUE VIRUSES

NS5

```
DEN-1   GTGTTGETLG EKWKTQLNQL SKSEFNTYKR SGIMEVDRSE AKEGLKRGET TKHAVSRGTA
DEN-2   ...NI..... ....SR..A. GE...QI..K ...Q....TL ....I..... D.......S.
DEN-3   ...SQ..... ....KK.... .RK..DL..K ...T....T. .........I .H......S.
DEN-4   .......... ....R...S. DRK..EE... ...L....T. ..SA..D.SK M.......SS

DEN-1   KLRWFVERNL VKPEGKVIDL GCGRGGWSYY CAGLKKVTEV KGYTKGGPGH EEPIPMATYG
DEN-2   .........M .I.....VC. .......... .G...N.R.. ..L..... .....HS...
DEN-3   .........M .I...R.... .......... .......... R......... ...V..S...
DEN-4   .I..I...GM .K.K.E.V.. .......... M.TL.N.... .......... ..........

DEN-1   WNLVKLHSGK DVFFTPPEKC CTLLCDIGES SPNPTIEEGR TLRVLKMVEP WLRGN QFCI
DEN-2   ....R.Q..V C......... .I........ .......A.. I....NL..N ..NN.T....
DEN-3   .......... ...Y..... .......... ..S..V..S. .......... ..KN. ....
DEN-4   ...Y.....V .L.YK.T.QV D......... .S........ .......... ..SSKPE.W.

DEN-1   KILNPYMPSV VETLEQMQRK HGGMLVRNPL SRNSTHEMYW VSCGTGNIVS AVNMTSRMLL
DEN-2   .VS....... I.KM.TL... Y..A..... .......... ..NAS..... S..HI..H.I
DEN-3   .V......T. I.H..RL... .......... .......... I.N....... S...V..L..
DEN-4   .V......T. I.E..KL... ...N...C.. .......... ..GAS..... S..I..K...

DEN-1   NRFTMAHRKP TYERDVDLGA GRRHVAVEPE VANLDIIGQR IENIKNEHKS TWHYDEDNPY
DEN-2   .....K..KA ...T.....S .T.NIGI.S. IP....T.K. .....Q..ET S....Q....
DEN-3   ........R. .I.K...... .T...NA... TP.M.V..E. .KR..E..S. .....DE...
DEN-4   ....TR.... ...K...... .T.S.ST.TK KPDMIISGR. LQRLQE...E .....Q....

DEN-1   KTWAYHGSYE VKPSGSASSM VNGVVRLLTK PWDVIPMVTQ IAMTDTTPFG QQRVFKEKVD
DEN-2   .......... T.QT...... .......... ....V..... N.H....... ..........
DEN-3   .......... ..AT...... I....K.... ....V..... M......... ..........
DEN-4   R......... PPST..P... .....K.... ..C....... L.V..AIH.. ..........

DEN-1   TRTPRAKRGT AQIMEVTAKW LWGFLSRNKK PRICTREEFT RKVRSNAAIG AVFVDENQWN
DEN-2   ...QEP.E.. KKL.LI..E. ..KE.GKK.T ..M....... ........L. .I.I..NK.K
DEN-3   .....PMP.. RKV..I..E. ..RT.G...R ..L....... K...T...M. ...TE....D
DEN-4   ....QP.P.. RMV.TT..N. ..AL.GKK.N ..L......I S......... R..QE.QG.T
```

```
DEN-1     SAKEAVEDER FWDLVHRERE LHKQGKCATC VYNMMGKREK KLGEFGKAKG SRAIWYMWLG
DEN-2     ..R.....S. ..E..D...N ..LEC..... .......... .......... ......E...
DEN-3     ..RA.....E ..K..D.... ...L...GS. .......... .......... ..........
DEN-4     ..S.....S. ..E..DK..A ..QE...ES. .......... ......R... ..........

DEN-1     ARGLEFEALG FMNEDHWFSR ENSLSGVEGE GLHKLGYILR DISKIPGGNM YADDTAGWDT
DEN-2     ..F..P.... .L........ G.......V. .......... .V...E..A. ....I.....
DEN-3     .......... .L........ ...Y...... .......... ........A. ..........
DEN-4     ..F....... .L......G. ...W...... ...R.....E E.D.KD.DL. ..........

DEN-1     RITEDDLQNE AKITDIMEPE HALLATSIFK LTYQNKVVTL QRPAKNGTVM DVISRRDQRG
DEN-2     ..L.. .K.. EHV.NH..G. .KK..EA... ........RV ...TPR.... .I........
DEN-3     .......H.. E...QQ.D.. .RQ..NA... ........KV ...TPK.... .I...K....
DEN-4     .......... DL..EQ.A.H .KI..KA... ........FV L..TPR.A.. .I...KE...

DEN-1     SGQVGTYGLN TFTNMEVQLI RQMESEGVIT QDDMQNPKGL KERVEKWSKE CGVDRLKRMA
DEN-2     .......... .......... .G..G..IFK SIQHLTVTEE IAVQN .LAR V.KE..S...
DEN-3     .......... ......AG.. ....G...LS KA.LE..HP. EKKITQ.LET K..E......
DEN-4     .......... .........S ....A..... .......... .......L.. ..........

DEN-1     ISADDCVVKP LDERFGTSLL FLNDMGKVRK DIPQWEPSKG WNDWQQVPFC SHHFHQLIMK
DEN-2     ..G....... ..D..ASA.T A......... ..Q.....R. ....T..... ..I..E.V..
DEN-3     .......... I.D..ANA.. A......... .....Q.... .H........ .....E....
DEN-4     ..G....... .......... .......... .......... .K...E.... A..L.KTF..

DEN-1     DGREIVVPCR NQDELVARAR VSQGAGWSLR ETACLGKSYA QMWQLMYFNR RDLRLAANAI
DEN-2     .C.VL..... .....IG... I........K .......... ...T....H. ..........
DEN-3     ...KL....Q P....IG... I......... .......... ...T....H. ......S...
DEN-4     ...SL..... .....IG... I......... .......A.. ...S....H. .......M..

DEN-1     CSAVPVDWVP TSRTTWSIHA HHQWMTTEDM LSVWNRVWIE ENPWMEDKTP VHSWEEVPYL
DEN-2     .....SH... I......... K.E.N..... .A...K...Q .......... .E........
DEN-3     ......H... .......... .......... .T........ D......... .TT..D....
DEN-4     .....TE.F. .......... .......... .K........ D..N.T.... .....DI...

DEN-1     GKREDLWCGS LIGL SSRAT WDENIHTAIT QVRNLIGKEE YVDYMPVMKR YSAPSESEGVL
DEN-2     .....Q.... ....T. ... .AK..Q...N ...S...H.. .T....S... FRREE.EA...W
DEN-3     .....Q.... ....T. ... .AQ..L...Q ...S...N.. FL....R... FRKEE....AIW
DEN-4     .......... ....T..... .AK....... .......... .......... ..........
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```
DEN-1   GGU GUC GAC AGG CUG AAA AGA AUG GCA AUU AGC GGA GAU GAU UGU GUG GUG AAA CCA AUU AGU
DEN-2   ..G CGU ..A ... ..A UC. ... ... ..C ..C ..U ... ... ... ... ..U ..A ... ..U U.A GA.
DEN-3   ..A ..G ..G ... U.A ... ... ... ..C ..C ... ..G ... ... ..C ..A ... ... ... ..C GAC
DEN-4   ... ... ... ... U.A ..G ..G ... ... ..C ..U ... ..C ... ..C ... ... ..G ..C C.A GA.
        9577
DEN-1   GAC AGG UUC GCA ACA GCC UUA AUA GCU CUG AAU GAC AUG GGA AAA GUA AGA AAA GAC AUA CCG
DEN-2   ... ..A ..U ... .GU ..U ... .C. ... ..A ... ... ... ... ... ..U ..G ... ..U ... .AA
DEN-3   ... ..A ... ..C .AU ... C.G C.U ..C ... ..C ..U ... ... ..G ..U ..G ..G ... ... ..U
DEN-4   ... ... ..U .GC ..U U.. C.C C.C UUC U.. ..C C.G ... ... ..G ..G ..G ... ... ..U ...
        9640
DEN-1   CAG UGG GAA CCU UCA AAA GGA UGG AAU GAC UGG CAG CAA GUG CCU UUC UGU UCA CAC CAU UUC
DEN-2   ..A ... ... ... ... .G. ... ... ..C ..U ... ACA ... ... ... ... ... ... ... ... ..U
DEN-3   ..A ... C.G ..A ... ..G ... ... C.. ..U ... ..A ..G ..C ... ... ..C ..C ... ..C ..U
DEN-4   ... ... ... ..A ..U ..G ... ... ..A A.. ... ..A G.G ..U ... ..U ..C G.C ... ..C C.U
        9703
DEN-1   CAC CAG CUG AUC AUG AAG GAU GGG AGG GAA AUA GUG GUG CCA UGC CGC AAC CAA GAU GAA CUU
DEN-2   ..U G.. U.A G.. ... ..A ... ..U C.C .UG C.C ..A ..C ... ... A.A ... ... ... ... ..G
DEN-3   ..U G.A U.. ... ... ..A ... ..A ..A A.G U.G ..A ..U ..C ... A.A CC. ..G ..C ... ..A
DEN-4   ... A.. ACC U.U ... ... ... ..C C.C UC. C.. ..U ..U ... ..U A.A ... ..G ... ... ..G
        9766
DEN-1   GUG GCA AGG GCU AGA GUA UCA CAA GGC GCC GGA UGG AGC CUG AGA GAA ACU GCU UGC CUA GGC
DEN-2   A.U .GU ..A ..C C.. A.U ..C ..G ..A ... ..G ... UCU U.. .AG ..G ..G ..C ..U U.G ..G
DEN-3   A.A .G. ..A ..G ... A.C ..U ... ..A ..A .A. ... ... ..U ... ... ... ..A ..U ... ..G
DEN-4   A.A .G. ..A ..C ... A.C ..G ..G ..A ..U ... ... ... U.A ... ... ..A ..C ... ..G ...
        9829
DEN-1   AAG UCA UAU GCA CAA AUG UGG CAG CUG AUG UAC UUC CAC AGG AGA GAC CUG AGA CUA GCG GCU
DEN-2   ... ..U ..C ..C ... ... ... ACC ... ... ... ... ... ..A C.. ... ..C ... ..G ... ..A
DEN-3   ..A G.C ..C ..U ... ... ... ACU ..C ... ..U ..U ... ..A ... ..U ..U ... ... ..A U.C
DEN-4   ..A G.U ..C ..C ..G ... ... UCG ..U ... ... ... ... ..A .AG ..U ... C.U U.. ..C U.C
        9892
DEN-1   AAU GCU AUC UGU UCA GCC GUC CCA GUU GAU UGG GUC CCA ACC AGC CGC ACA ACC UGG UCA AUC
DEN-2   ... ... ..U ..C ..G ..A ... ..G UCA C.. ... ..U ... ..A ..U ..A ... ... ... ..C ..A
DEN-3   ..C ..C ..A ... ... ..A ..A ... ..C C.. ... ... ..C ..G ... A.A ..G ..A ... ..U ..U
DEN-4   .UG ..C ..A ..C ... ..A ..U ... ACG ..A ... U.U ... ..A ... A.A ... ..A ... ... ...
        9955
DEN-1   CAU GCC CAC CAC CAA UGG AUG ACA ACA GAA GAC AUG UUA UCA GUG UGG AAU AGG GUU UGG AUA
DEN-2   ..C ..U A.G ..U G.. ... ... ..G ..G ... ... ... C.G G.. ... ... ... ... ..C ... ..C
DEN-3   ... ..U ... ..U ..G ... ... ..U ... ... ... ... C.U A.U ..C ... ..C ... ..G ... ...
DEN-4   ..C ..U ..U ... ..G ... ... ..C ..U ... ..U ... C.C AA. ... ... ..C ..A ..G ... ...
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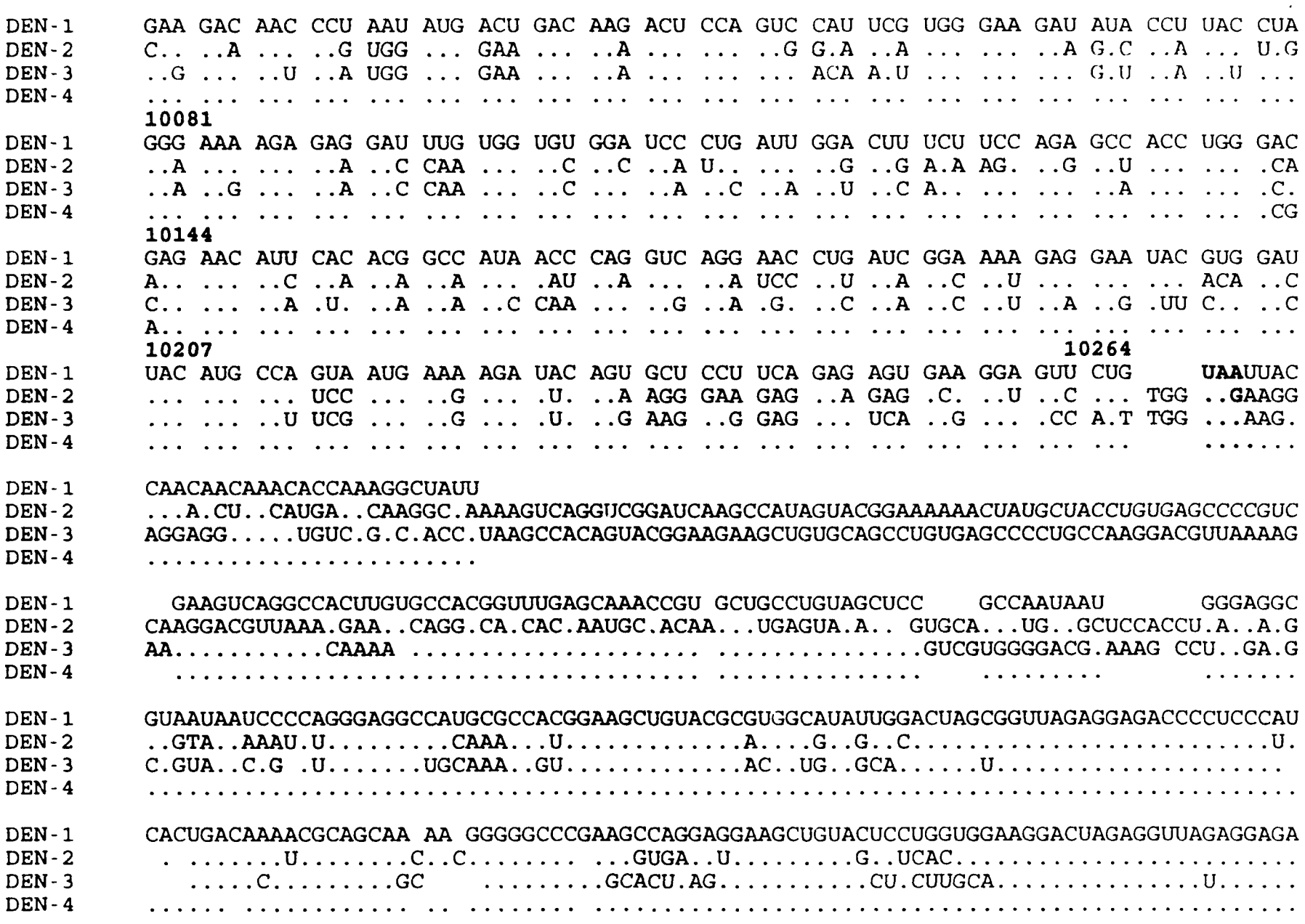
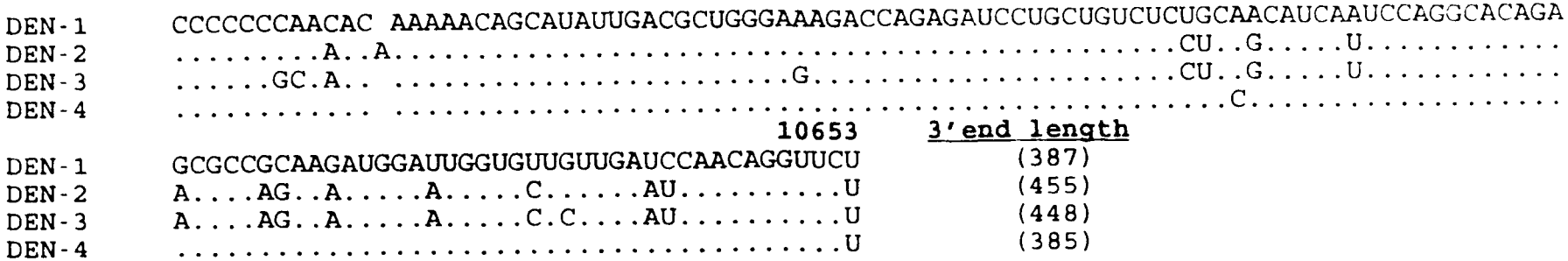

DEN-1 GAA GAC AAC CCU AAU AUG ACU GAC AAG ACU CCA GUC CAU UCG UGG GAA GAU AUA CCU UAC CUA
DEN-2 C.. ..A ... ..G UGG ... GAA ... ..A ... .G G.A ..A ... .A G.C ..A ... U.G
DEN-3 ..G ... ..U ..A UGG ... GAA ... ..A ... ... ACA A.U ... ... G.U ..A ..U ...
DEN-4 ... ...
10081
DEN-1 GGG AAA AGA GAG GAU UUG UGG UGU GGA UCC CUG AUU GGA CUU UCU UCC AGA GCC ACC UGG GAC
DEN-2 ..A ... .A ..C CAA ... ..C ..C ..A U.. ... ..G ..G A.A AG. ..G ..U ... ... .CA
DEN-3 ..A ..G ... ..A ..C CAA ... ..C ... ..A ..C ..A ..U ..C A.. ... .A ... ... .C.
DEN-4 ... ... .CG
10144
DEN-1 GAG AAC AUU CAC ACG GCC AUA ACC CAG GUC AGG AAC CUG AUC GGA AAA GAG GAA UAC GUG GAU
DEN-2 A.. ... ..C ..A ..A ..A ... .AU ..A ... ..A UCC ..U ..A ..C ..U ... ... ACA ..C
DEN-3 C.. ... ..A .U. ..A ..A ..C CAA ... ..G ..A .G. ..C ..A ..C ..U ..A ..G .UU C.. ..C
DEN-4 A.. ... ...
10207 10264
DEN-1 UAC AUG CCA GUA AUG AAA AGA UAC AGU GCU CCU UCA GAG AGU GAA GGA GUU CUG UAAUUAC
DEN-2 ... ... UCC ... ..G ... .U. ..A AGG GAA GAG ..A GAG .C. ..U ..C ... TGG ..GAAGG
DEN-3 ... .U UCG ... ..G ... .U. ..G AAG ..G GAG ... UCA ..G ... .CC A.T TGG ...AAG.
DEN-4 ... ...
DEN-1 CAACAACAAACACCAAAGGCUAUU
DEN-2 ...A.CU..CAUGA..CAAGGC.AAAAGUCAGGUCGGAUCAAGCCAUAGUACGGAAAAAACUAUGCUACCUGUGAGCCCCGUC
DEN-3 AGGAGG.....UGUC.G.C.ACC.UAAGCCACAGUACGGAAGAAGCUGUGCAGCCUGUGAGCCCCUGCCAAGGACGUUAAAAG
DEN-4 .....
DEN-1 GAAGUCAGGCCACUUGUGCCACGGUUUGAGCAAACCGU GCUGCCUGUAGCUCC GCCAAUAAU GGGAGGC
DEN-2 CAAGGACGUUAAA.GAA..CAGG.CA.CAC.AAUGC.ACAA...UGAGUA.A.. GUGCA...UG..GCUCCACCU.A..A.G
DEN-3 AA.....CAAAA ....GUCGUGGGGACG.AAAG CCU..GA.G
DEN-4 ....
DEN-1 GUAAUAAUCCCCAGGGAGGCCAUGCGCCACGGAAGCUGUACGCGUGGCAUAUUGGACUAGCGGUUAGAGGAGACCCCUCCCAU
DEN-2 ..GTA..AAAU.U.....CAAA...U.....A....G..G..C.....U.
DEN-3 C.GUA..C.G .U.....UGCAAA..GU.....AC..UG..GCA.....U.....
DEN-4 .....
DEN-1 CACUGACAAAACGCAGCAA AA GGGGGCCCGAAGCCAGGAGGAAGCUGUACUCCUGGUGGAAGGACUAGAGGUUAGAGGAGA
DEN-2 . .....U.....C..C..... ...GUGA..U.....G..UCAC.....
DEN-3 .....C.....GC .....GCACU.AG.....CU.CUUGCA.....U.....
DEN-4 ....


DEN-1 CCCCCCCAACAC AAAAACAGCAUAUUGACGCUGGGAAAGACCAGAGAUCCUGCUGUCUCUGCAACAUCAAUCCAGGCACAGA
DEN-2 .....A..A.....CU..G.....U.....
DEN-3 .....GC.A.. .....G.....CU..G.....U.....
DEN-4 ....C.....
10653
3'end length
DEN-1 GCGCCGCAAGAUGGAUUGGUGUUGUUGAUCCAACAGGUUCU (387)
DEN-2 A....AG..A.....A.....C.....AU.....U (455)
DEN-3 A....AG..A.....A.....C.C....AU.....U (448)
DEN-4 .....U (385)

COMPARISON OF THE DEDUCED NS1 AMINO ACID SEQUENCES OF DENGUE VIRUSES

NS1

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DEN-1     DSGCVINWKG KELKCGSGIF VTNEVHTWTE QYKFQADSPK RLSAAIGKAW EEGVCGIRST
DEN-2     .....VS..N .......... I.DN...... .....PE..S K.AS..Q..H ...I.....V
DEN-3     .M........ .......... .......... .......... .VAT..AG.. .N........
DEN-4     .M...VS.S. .......... .VDN...... .....PE..A ..AS..LN.H KD........

DEN-1     TRLENVMWKQ ITNELNYVLW EGGHDLTVVA GDVKGVLTKG KRALTPPVSD LKYSWKTWGK
DEN-2     .......... ..P...HI.S .NEVK..IMT .CI..IMQA. ..S.R.QPTE ..........
DEN-3     ..M..LL... .A.....I.. .NDIK....V .CIT...EQ. ..T...QPME .........L
DEN-4     .......... .......... .......... .......... .......... ..........

DEN-1     AKIFTPEARN STFLIDGPDT SECPNERRAW NSLEVEDYGF GMFTTNIWMK FREGSSEVCD
DEN-2     ..MLST.SH. Q.......E. A.....N... .......... .V....I.L. L..KQDVF..
DEN-3     ...V.A.TQ. .S.I....S. P...SAS... .VW....... .V......L. L..VYTQL..
DEN-4     .......... .......... .......... .......... .......... ..........

DEN-1     HRLMSAAIKD QKAVHADMGY WIESSKNQTW QIEKASLIEV KTCLWPKTHT LWSNGVLESQ
DEN-2     SK........ NR........ ....AL.D.. KM....F... .S.H...S.. .........E
DEN-3     .......V.. ER........ ....Q..GS. KL........ ...T...S.. .........D
DEN-4     .......... .......... .......... .......... .......... ..........

DEN-1     MLIPKEYAGP FSQHNYRQGY ATQTVGPWHL GKLEIDFGEC PGTTVTIQED CDHRGPSLRT
DEN-2     .I...NF... V......P.. H...A..... ....M..DF. E....VVT.. .GN.......
DEN-3     .....SL... I......P.. H...A..... ....L..NY. E....V.S.N .GT.......
DEN-4     .....S.... .......... .......... .......... .......... ..........

DEN-1     TTASGKLVTQ WCCRSCTMPP LRFLGEDGCW YGMEIRPLSE KEENMVKSQV TA
DEN-2     .......I.E .......L.. ..YR...... ........K. ....L.N.L. ..
DEN-3     .TV....IHE .......L.. ..YM...... .......IN. ........LA S.
DEN-4     .........A MV.T...... .......... .......... .......... ..
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COMAPRISON OF THE DEDUCED NS2a AND NS2B AMINO ACID SEQUENCES OF DENGUE VIRUSES

```
          NS2a
DEN-1     GQGTSETFSM GLLCLTLFVE ECLRRRVTRK HMILVVVITL CAIILGGLTW MDLLRALIML
DEN-2     .H.QIDN..L ...GMA..L. .M..T..GT. .A..L.AVSF VTL.T.NMSF R..G.VMV.V
DEN-3     ...KVDN.T. .V...AILF. .VM.GKFGK. ...AG.LF.F VLLLS.QI.. RGMAHT...I
DEN-4     .......... S......... .......... .......... .......... ..........

DEN-1     GDTMSGRIGG QIH LAIMAV FKMSPGYVLG VFLRKLTSRE TALMVIGMAM TTVLSIPHDL
DEN-2     .A..TDD..M GVTY..LL.A ..VR.TFAA. LL......K. LMMAT..I.L LSQST..ETI
DEN-3     .SNA.D.M.M GLTY..LI.T ..IQ.FLA.. F......... NL.LGV.L.. AAT.RL.E.I
DEN-4     .......... ... ...... .....R.... .......... .......... ..........

DEN-1     MELIDGISLG LILLKIVTQF DNTQVGTLAL SLTFIRSTMP LVMAWRTIMA VLFVVTLIPL
DEN-2     L..T.ALA.. MMV....RNM EKY.LAVTIM AILCVPNAVI .QN..KVSCT I.AA.SVS..
DEN-3     EQMAN..A.. .MA..LI... ETY.LW.ALV ...CSNTIFT .TV....ATL I.AGIS.L.V
DEN-4     ....S..... .......... .......... .......... .......... ....D.....
                                                      NS2B
DEN-1     CRTSCLQKQS HWVEITALIL GAQALPVYLM TLMKGASRRS WLLNEGIMAV GLVSLLGSAL
DEN-2     LL..SQ..AD  .IPLALTIK .LNPTAIF.T ...RTSKK.. .P...A.... .M..I.A.S.
DEN-3     .QS.SMR.TD  .LPM.VAAM .VPP..LFIF S.KDTLK... .P....V... ....I.A.S.
DEN-4     .......... ..A....... .......... .......... .P........ ..........

DEN-1     LKNDLPLASP MVAGGLLLAA YVMSGSSADL SLEKAANVQW DEMADITGSS PIIEVKQDED
DEN-2     ....I.MTG. L......TVC ..LT.R.... E..R..D.K. EDQ.EIS... ..LSITIS..
DEN-3     ....V.M.G. L......I.C ..IT.T.... TV....D.T. E.E.EQ..V. HNLMITV.D.
DEN-4     ...CV...G. .......... .M........ .......... .......... ..........

DEN-1     GSFSIRDVEE TSMITLLVKL DLITVSGLYP LAIPVTMTLW YMWQVKTQR
DEN-2     ..M..KNE.. EQTL.I.IRT G.LVI..VF. VS..I.AAA. .L.E..K..
DEN-3     .TMR.K.D.T ENIL.V.L.T A.LI...IF. YS..A..LV. HT..KQ...
DEN-4     .......... .N........ A......... .......... .........
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COMPARISON OF THE DEDUCED NS3 AMINO ACID SEQUENCE OF DENGUE VIRUSES

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          NS3
DEN-1     SGSLWDVPSP AATQKAALSE GVYRIMQRGL FRKTQVGVGI HMEGVFHTMW HVTRGSVICH
DEN-2     A.V..... PPVG..E.ED .A...K...I LGYS.I.A.V YKE.T..... .....A.LM.
DEN-3     ..V..... PET...E.E. .....K.Q.I .G.......V QKE..... .....A.LT.
DEN-4     ..A..... ...K..... .......... .G..... .......... ..........

DEN-1     ETGRLEPSWA DVRNDMISYG GGWRLGDKWD KEEDVQVLAI EPRKNPKHVQ TKPGLFKTLT
DEN-2     KGK.I..... ..KK.L.... ...K.EGE.K EG.E.....L ..G...RA.. ........N.
DEN-3     NGK....N.. S.KK.L.... .....SAQ.Q .G.E...I.V ..F....NF. .M..I.Q.T.
DEN-4     .......... .......... .......... .......... .......... ...S......

DEN-1     GGIGAVTLDF KPSTSGSPII NRKGKVIGLY GNGVVTKSGD YVSAITQAER IGEPDYEVDE
DEN-2     .T....S... S.G......V D.....V... ......R..A .....A.T.K SI.DNP.IED
DEN-3     .E...IA... ..G....... ..E...V... .......N.G ...G.A.TNA EPDGPTPEL.
DEN-4     .E........ ..G....... .......... .......... .......... ..........

DEN-1     DI FRKKRLT IMDLHPGAGK TKRILPSIVR EALKRRLRNL ILAPTR  AA EMEEALRGLP
DEN-2     .. ....... .......... ...Y..A... ..I..G..T. ......VV.. ..........
DEN-3     EEM.K.RN.. .......S.. ..KY..A... ..I.....T. ......VV.. ....PMK...
DEN-4     .. ....... .......... .......... ........T. ......VV.. ..........

DEN-1     IRYQTPAVKS EHTGREIVDL MCHATFTTRL LSSTRVSNYN LIVMDEAHFT DPSSVAARGY
DEN-2     .......IRA .......... .......M.. ..PV..P... ..I....... ..A.I.....
DEN-3     .....T.T.. .......... .......M.. ..PV..P... ..I....... S.A.I.....
DEN-4     .......... .......... .......... ......P... .......... ..........

DEN-1     ISTRVEMGEA AAIFMTATPP GATDPFPQSN SPIEDIEREI PERSWDTGFD WITDYQGKTV
DEN-2     .......... .G........ .SR....... A..M.E.... .....NS.HE .V..FK....
DEN-3     .....G.... .......... .TA.A..... A..Q.E..D. .....NS.NE ....FV....
DEN-4     .......... .......... .......... .......... .......... ..........

DEN-1     WFVPSIKAGN DIANCLRKSG KKVIQLSRKT FDTEYPKTKL TDWDFVVTTD ISEMGANFRA
DEN-2     .......... ...A....N. .......... ..S..V..RA N......... ........K.
DEN-3     .......... V.......N. .......... .....Q.... N......... ........I.
DEN-4     .......... .......... .......... .......... .......... ..........
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DEN-1     GRVIDPRRCL KPVILTCGPE RVILAGPIPV TPASAAQRRG RIGRNPAQED DQYVFSGDPL
DEN-2     E........M ......D.E. .......M.. .HS....... ......KN.N ...IYM.E..
DEN-3     D......... .......... .......M.. .V........ .V....QK.N ...I.M.Q..
DEN-4     .......... .....P.... .......... .......... .......... ..........

DEN-1     KNDEDHAHWT EAKMLLDNIY TPEGIIPTLF GPEREKTQAI DGEFRLRGEQ RKTFVELMRR
DEN-2     E....C...K .........N .......SM. E.....VD.. ...Y.....A .....D....
DEN-3     NK........ .........N .......A.. E.....SA.. ...Y..K.DS ..........
DEN-4     .......... .......... .......... .......... .......... ..........

DEN-1     GDLPVWLSYK VASAGISYKD REWCFTGERN NQILEENMEV EIWTREGEKK KL PRWLDAR
DEN-2     .......A.R ..AE..N.A. .R...D.IK. .......V.. ....K...R. ..K.......
DEN-3     .......AH. ...E..K.T. .K...D.... ........D. ....K..... ..R.......
DEN-4     .......... .......... .......... .......... .......... ..R.......

DEN-1     VYSCPLALKD FKEFASGRK
DEN-2     I..D.....E .....A...
DEN-3     T..D.....E ..D..A...
DEN-4     ..A..M.... .........
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COMPARISON OF THE DEDUCED NS4a AND NS4B AMINO ACID SEQUENCES OF DENGUE VIRUSES

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          NS4a
DEN-1     SITLDILTEI ASLPTYLSSR AKLALDNIVM LHTTERGGRA YLHALNELPE SLETLMLVAL
DEN-2     .L..NLI..M GR...FMTQK .RD....ALV ...A.A.... .....S.... T....L.LT.
DEN-3     ..A..LV... GRV.SH.AH. TRN....L.. ...S.H.... .R..VE.... TM...L.LG.
DEN-4     .......... .......... .......... .......... .Q......T. ..........

DEN-1     LGAMTAGIFL FFMQGKGIGK LSMGLITIAV ASGLLWVAEI QPQWIAASII LEFFRMVLLI
DEN-2     .ATV.G.... .L.S...... MTL.MCC.IT ..I...Y.Q. ..H....... ....LI....
DEN-3     MILL.G.AM. .LIS...... T.I...CVIA S..M..M.DV PL....SA.V ....M.....
DEN-4     .......... .......... .......... .......... .......... ....L.....

DEN-1     PEPEKQRTPQ DNQLIYVILT ILTIIGLIAA NEMGLIEKTK TDFGFYQVKT    ETTILDV
DEN-2     .......... ....T...IA ...VVAATM. ..N.FL.... K.L.LGSIT. QESESN...I
DEN-3     .......... ....A..VIG ...LAAIV.. .....L.TTH R.L.MSKEPG VVSP.SY...
DEN-4     .......... .......... .......... .......... ..........    .......

DEN-1     DLRPASAWTL YAVATTILTP MLRHTIENTS ANLSLAAIAN QAAVLMGLGK GWPLHRMDLG
DEN-2     .......... ......FV.. ....S...S. V.V..T.... ..T....... ....SKIHI.
DEN-3     ..H....... ......V... ........ST ..V....... ..V.....D. ...ISK....
DEN-4     .......... .......... .......... .......... .......... ..........
                                                                 NS4B
DEN-1     VPLLAMGCYS QVNPTTLTAS LGMLLVHYAI IGPGLQAKAT REAQKRTAAG IMKNPTVDFI
DEN-2     .....I.... ....I....A .LL.VA.... .......... ......A... ........G.
DEN-3     .....L.... ....L..I.A VLL.VT.... .......... .......... ........G.
DEN-4     .......... .......A.. .V........ .......... .......... .....I..G.

DEN-1     TVIDLEPISY DPKFEKQLGQ VMLLVLCAGQ LLLMRTTWAF CEVLTLATGP ILTLWEGNPG
DEN-2     ........P. .......... ....I..VT. V.M......L ..A....... .S........
DEN-3     MT...D.VI. .S........ .......... ......S..L .......... .T.....S..
DEN-4     .......... .......... .......... .......... .......... ..........

DEN-1     RFWNTTIAVS YANIFRGSYL AGAGLAFSLI KNAQTPRR
DEN-2     .......... H......... .....L..IM ..TTNT..
DEN-3     K......... M......... ......L.IM .SVG.GK.
DEN-4     .......... T......... .......... ........
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COMPARISON OF THE DEDUCED NS5 AMINO ACID SEQUENCE OF DENGUE VIRUSES

NS5

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DEN-1   GTGTTGETLG EKWKTQLNQL SKSEFNTYKR SGIMEVDRSE AKEGLKRGET TKHAVSRGTA
DEN-2   ...NI..... ....SR..A. GE...QI..K ...Q....TL ....I..... D.......S.
DEN-3   ...SQ..... ....KK.... .RK..DL..K ...T....T. .........I .H......S.
DEN-4   .......... ....R...S. DRK..EE... ...L....T. ..SA..D.SK M.......SS

DEN-1   KLRWFVERNL VKPEGKVIDL GCGRGGWSYY CAGLKKVTEV KGYTKGGPGH EEPIPMATYG
DEN-2   .........M .I.....VC. .......... .G...N.R.. ..L..... .....HS...
DEN-3   .........M .I...R.... .......... .......... R......... ...V..S...
DEN-4   .I..I...GM .K.K.E.V.. .......... M.TL.N.... .......... ..........

DEN-1   WNLVKLHSGK DVFFTPPEKC CTLLCDIGES SPNPTIEEGR TLRVLKMVEP WLRGN QFCI
DEN-2   ....R.Q..V C......... .I........ .......A.. I....NL..N ..NN.T....
DEN-3   .......... ...Y...... .......... ..S..V..S. .......... ..KN. ....
DEN-4   ...Y.....V .L.YK.T.QV D......... .S........ .......... ..SSKPE.W.

DEN-1   KILNPYMPSV VETLEQMQRK HGGMLVRNPL SRNSTHEMYW VSCGTGNIVS AVNMTSRMLL
DEN-2   .VS....... I.KM.TL... Y..A...... .......... ..NAS..... S..HI..H.I
DEN-3   .V......T. I.H..RL... .......... .......... I.N....... S...V..L..
DEN-4   .V......T. I.E..KL... ...N...C.. .......... ..GAS..... S..I..K...

DEN-1   NRFTMAHRKP TYERDVDLGA GRRHVAVEPE VANLDIIGQR IENIKNEHKS TWHYDEDNPY
DEN-2   .....K..KA ...T.....S .T.NIGI.S. IP....T.K. .....Q..ET S....Q....
DEN-3   ........R. .I.K...... .T...NA... TP.M.V..E. .KR..E..S. .....DE...
DEN-4   ....TR.... ...K...... .T.S.ST.TK KPDMIISGR. LQRLQE...E .....Q....

DEN-1   KTWAYHGSYE VKPSGSASSM VNGVVRLLTK PWDVIPMVTQ IAMTDTTPFG QQRVFKEKVD
DEN-2   .......... T.QT...... .......... ....V..... N.H....... ..........
DEN-3   .......... ..AT...... I....K.... ....V..... M......... ..........
DEN-4   R......... PPST..P... .....K.... ..C....... L.V..AIH.. ..........

DEN-1   TRTPRAKRGT AQIMEVTAKW LWGFLSRNKK PRICTREEFT RKVRSNAAIG AVFVDENQWN
DEN-2   ...QEP.E.. KKL.LI..E. ..KE.GKK.T ..M....... ........L. .I.I..NK.K
DEN-3   .....PMP.. RKV..I..E. ..RT.G...R ..L....... K...T...M. ...TE....D
DEN-4   ....QP.P.. RMV.TT..N. ..AL.GKK.N ..L......I S......... R..QE.QG.T
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DEN-1     SAKEAVEDER FWDLVHRERE LHKQGKCATC VYNMMGKREK KLGEFGKAKG SRAIWYMWLG
DEN-2     ..R....S. ..E..D...N ..LEC..... .......... .......... ......E...
DEN-3     ..RA.....E ..K..D.... ...L...GS. .......... .......... ..........
DEN-4     ..S.....S. ..E..DK..A ..QE...ES. .......... ......R... ..........

DEN-1     ARGLEFEALG FMNEDHWFSR ENSLSGVEGE GLHKLGYILR DISKIPGGNM YADDTAGWDT
DEN-2     ..F..P.... .L........ G.......V. .......... .V...E..A. ....I.....
DEN-3     .......... .L........ ...Y...... .......... ........A. ..........
DEN-4     ..F....... .L......G. ...W...... ...R.....E E.D.KD.DL. ..........

DEN-1     RITEDDLQNE AKITDIMEPE HALLATSIFK LTYQNKVVTL QRPAKNGTVM DVISRRDQRG
DEN-2     ..L.. .K.. EHV.NH..G. .KK..EA... ........RV ...TPR.... .I........
DEN-3     .......H.. E...QQ.D.. .RQ..NA... ........KV ...TPK.... .I...K....
DEN-4     .......... DL..EQ.A.H .KI..KA... ........FV L..TPR.A.. .I...KE...

DEN-1     SGQVGTYGLN TFTNMEVQLI RQMESEGVIT QDDMQNPKGL KERVEKWSKE CGVDRLKRMA
DEN-2     .......... .......... .G..G..IFK SIQHLTVTEE IAVQN .LAR V.KE..S...
DEN-3     .......... ......AG.. ....G...LS KA.LE..HP. EKKITQ.LET K..E......
DEN-4     .......... .........S ....A..... .......... .......L.. ..........

DEN-1     ISADDCVVKP LDERFGTSLL FLNDMGKVRK DIPQWEPSKG WNDWQQVPFC SHHFHQLIMK
DEN-2     ..G....... ..D..ASA.T A......... ..Q.....R. ....T..... ..I..E.V..
DEN-3     .......... I.D..ANA.. A......... .....Q.... .H........ .....E....
DEN-4     ..G....... .......... .......... .......... .K...E.... A..L.KTF..

DEN-1     DGREIVVPCR NQDELVARAR VSQGAGWSLR ETACLGKSYA QMWQLMYFNR RDLRLAANAI
DEN-2     .C.VL..... .....IG... I........K .......... ...T....H. ..........
DEN-3     ...KL....Q P....IG... I......... .......... . .T....H. ......S...
DEN-4     ...SL..... .....IG... I......... .......A.. ...S....H. .......M..

DEN-1     CSAVPVDWVP TSRTTWSIHA HHQWMTTEDM LSVWNRVWIE ENPWMEDKTP VHSWEEVPYL
DEN-2     .....SH... I......... K.E.N..... .A...K...Q .......... .E........
DEN-3     ......H... .......... .......... .T........ D......... .TT..D....
DEN-4     .....TE.F. .......... .......... .K........ D..N.T.... .....DI...

DEN-1     GKREDLWCGS LIGL SSRAT WDENIHTAIT QVRNLIGKEE YVDYMPVMKR YSAPSESEGVL
DEN-2     .....Q.... ....T. ... .AK..Q...N ...S...H.. .T....S... FRREE.EA...W
DEN-3     .....Q.... ....T. ... .AQ..L...Q ...S...N.. FL....R... FRKEE....AIW
DEN-4     .......... ....T..... .AK....... .......... .......... ..........
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