Analysis of worldwide sequence mutations in Zika virus proteins E, NS1, NS3 and NS5 from a structural point of view

SUPPLEMENTARY INFORMATION

Supplementary Results

Validation test of the ZIKV structural models

Structural models for ZIKV proteins NS1, NS3 and NS5 were created and refined as explained on the methods section. After refinement, the quality of the models was assessed by means of the Ramachadran Plot, were 96.3% 96.6% and 97.7% of the residues were found in favored regions for the NS1, NS3 and NS5 proteins, respectively. The few outlier residues are located on flexible loops in the protein structures. The quality of the models was also validated with the Verify-3D server, finding 81.25%, 83,68% and 87.98% of the residues with an averaged 3D-1D score higher than 0.2, for the NS1, NS3 and NS5 proteins, respectively.

Supplementary Tables

Table S1: Mutations in protein C of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Table S2: Mutations in protein prM of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Table S3: Mutations in E protein of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Table S4: Mutations in NS1 protein of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Table S5: Mutations in NS2A protein of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Table S6: Mutations in NS2B protein of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Table S7: Mutations in NS3 protein of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Table S8: Mutations in NS4A protein of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Table S9: Mutations in NS4B protein of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Table S10: Mutations in NS5 protein of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Supplementary Figures

Figure S1. Molecular Phylogenetic analysis by the Maximum Likelihood method. The evolutionary history of 41 non-recombinant Zikavirus sequences available in GenBank database up to April,2016 was inferred by using the Maximum Likelihood method based on the Tamura-Nei model. Two major lineages, namely African and Asian, can be observed. Within the Asian lineage a new clade can be found, named American lineage.

Figure S2. ZIKV E protein (PDB 5IRE), showing the mutations found in zika patients. Mutations corresponding to substitutions between very similar aminoacids, namely V-L, S-T, R-K, D-E, are shown in blue. The other substitutions are shown in red. The different regions of the protein structure are highlighted. The figure has been created with The PyMOL Molecular Graphics System, Version 1.8 Schrödinger, LLC.

Figure S3. ZIKV NS1 model, showing the mutations found in zika patients. Same coloring scheme as Figure S1. One monomer is shown in white and the other in black. The different regions of the protein structure are highlighted. The figure has been created with The PyMOL Molecular Graphics System, Version 1.8 Schrödinger, LLC.

Figure S4. ZIKV NS3 model, showing the mutations found in zika patients. Same coloring scheme as Figure S1. The different regions of the protein structure are highlighted. The figure has been created with The PyMOL Molecular Graphics System, Version 1.8 Schrödinger, LLC.

Figure S5. ZIKV NS5 model. In a) mutations found in zika patients are shown, with the same coloring scheme as Figure S1. The different regions of the protein structure are highlighted. In b) the main protein domains are colored as follows: MTase (black), linker (white), Fingers (magenta), α-NLS (green), α ,β-NLS (cyan), Palm (yellow), Thumb (pale pink), priming loop (blue). The figure has been created with The PyMOL Molecular Graphics System, Version 1.8 Schrödinger, LLC.

Figure S6. Mutations found on Microcephaly samples: a) NS1 protein of the Microcephaly sample KU527068, b) From left to right, E and NS5 proteins of the Microcephaly sample KU497555, c) From left to right, E, NS1 and NS5 proteins of the Microcephaly sample KU729217. Mutated residues are shown as red spheres. The structures have the same orientation of figures S1-4.The figure has been created with The PyMOL Molecular Graphics System, Version 1.8 Schrödinger, LLC.

Table S1: Mutations in protein C of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Aminoacid location on the protein structure	Mutations	Geographical origin (Country)	Sequence accession number in Genbank	Host
	K6R	Africa	HQ234501; KF383117	Mosquitoes, cell culture
	K7R	Africa	KF383116	Mosquitoes
	G10R	Africa	KF383118	Mosquitoes
	S25N	Africa	DQ859059; AY632535; HQ234500; KF268948; LC002520; KU720415	Mosquitoes, cell culture, sentinel monkey
	F27L	Africa	DQ859059; AY632535; HQ234500; KF268948; LC002520; KU720415	Mosquitoes, cell culture, sentinel monkey
	S71T	Africa	DQ859059	Mosquitoes, cell culture
	E76D	Americas (Chi/Ven)	KU744693	ZIKV infection
	I80T	America (Puerto Rico)	KU501215	ZIKV infection
	K101R	Africa	DQ859059; AY632535; HQ234500; KF268948; KF383115; LC002520; KU720415	Mosquitoes/cell culture/ sentinel monkey
	G105S	America (Brazil)	KU729218	ZIKV infection
	A106T[1]	Asia (Thailand)	KU681081	Mosquitoes/cell culture
		Asia (Micronesia)	EU545988	ZIKV infection
		Asia (Cambodia)	JN860885	
			KF993678	
	D107E[1]	America (Mexico)	KU922923; KU922960	ZIKV infection
		America (Martinique)	KU647676	ZIKV infection
	T108A[1]	Africa	HQ234500	Cell culture
	S109N[1]	Asia (Chi/Samoa)	KU866423; KU820899	ZIKV infection
	V110I[1]	Africa	DQ859059; AY632535; HQ234500; KF268948; KF383115; LC002520; KU720415	Mosquitoes, cell culture, sentinel monkey
	V113I[1]	Africa	AY632535; KF268948; KF383115; KF383117; LC002520; KU720415	Mosquitoes, cell culture, sentinel monkey
	G114S[1]	Africa	HQ234500	Cell culture
	A120V[1]	Africa	HQ234500	Cell culture

[1]Mutations belonging to the propeptide.

Table S2: Mutations in protein prM of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Aminoacid location on the protein structure	Mutations	Geographical origin (Country)	Sequence accession number in Genbank	Host
	A123V	Asia (Philipines)	KU681082	ZIKV infection
		Asia (Micronesia)	EU545988	ZIKV infection
		Asia (Malaysia)	HQ234499	Cell culture
		Asia (Cambodia)	JN860885	ZIKV infection
	V125I	Africa	DQ859059; AY632535; HQ234500; KF268948; KF383115;LC002520; KU720415	Mosquitoes, cell culture, sentinel monkey
	S130N	Asia (Cambodia)	JN860885	ZIKV infection
	N139S	Asia (Thailand)	KU681081	ZIKV infection
		Asia (Philipines)	KU681082	ZIKV infection
		Asia (Micronesia)	EU545988	ZIKV infection
		Asia (Malaysia)	HQ234499	Cell culture
		Asia (Cambodia)	JN860885	ZIKV infection
		Africa	DQ859059; LC002520; KU720415	Mosquitoes, cell culture, sentinel monkey
	E143K	Africa	DQ859059; AY632535; HQ234500; KF268948; KF383115; LC002520; KU720415	Mosquitoes, cell culture, sentinel monkey
	P148A	Africa	DQ859059; AY632535; HQ234501; KF268948; KF383115; LC002520; KU720415	Mosquitoes, cell culture, sentinel monkey
	P148V	Africa	HQ234500	Cell culture
	T150N	Africa	KF268948; KF268949; KF268950	Mosquitoes
	L151M	Asia (Cambodia)	JN860885	ZIKV infection
	M153V	Asia (Malaysia)	HQ234499	Cell culture
		Africa	DQ859059; AY632535; KF268948; KF383115; LC002520; KU720415	Mosquitoes, cell culture, sentinel monkey

	Y157H	Africa	HQ234500; DQ859059; AY632535; KF268948; KF383115; LC002520; KU720415	Mosquitoes, cell culture, sentinel monkey
	I158V	Africa	HQ234500; DQ859059; AY632535; KF268948; KF383115; LC002520; KU720415	Mosquitoes, cell culture, sentinel monkey
	M166T	America (Suriname)	KU312312	ZIKV infection
	H204Q	Africa	KF383116	Mosquitoes
	A210T	Africa	KF383118	Mosquitoes
	T218S	Africa	KF383118	Mosquitoes
	P220R	Africa	KF383118	Mosquitoes
	S221Y	Africa	KF383118	Mosquitoes
	S223Y	Africa	KF383118	Mosquitoes
	T241K	Africa	KF383118	Mosquitoes
	R246M	Africa	KF383118	Mosquitoes
	R246K	Africa	DQ859059; AY632535; HQ234500; KF268948; KF383115; KF383119; LC002520; KU720415	Mosquitoes, cell culture, sentinel monkey
	A258T	Africa	DQ859059	Mosquitoes, cell culture
	L259I	Africa	KF383118	Mosquitoes
	A260V	Africa	DQ859059; AY632535; HQ234500; KF383116; KF383118; LC002520; KU720415	Mosquitoes, cell culture, sentinel monkey
	A261S	Africa	KF383118	Mosquitoes
	A262V	Africa	DQ859059; AY632535; HQ234500; KF268948; KF383115; LC002520; KU720415	Mosquitoes, cell culture, sentinel monkey
	A263V	Asia (Philipines)	KU681082	ZIKV infection
	A265T	Africa	KF383118	Mosquitoes
	L268M	Africa	KF383118	Mosquitoes
	S271L	Africa	KF383118	Mosquitoes
	V280I	Africa	KF383115	Mosquitoes, cell culture, sentinel monkey
	L283V	Africa	KF383118	Mosquitoes
	A286V	Africa	KF383118	Mosquitoes
	P287L	America (Mexico)	KU922923	ZIKV infection

Table S3: Mutations in E protein of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Aminoacid location on the protein structure	Mutations[1]	Geographical origin (Country)	Sequence accession number in Genbank	Host
Domain 1 (DI)	**F11**(301)**L**	Africa	KF383118	Mosquitoes
	V23(413)**L**	America (Brazil)	KU321639	ZIKV infection
	V33(323)**A**	America (Chi/Ven)	KU744693	ZIKV infection
	V33(323)**E**	Africa	KF383118	Mosquitoes
	T40(330)**A**	Asia (Micronesia)	EU545988	ZIKV infection
	T47(337)**S**	America (Brazil)	KU729217	Microcephaly
	T48(338)**M**	Africa	KF383118	Mosquitoes
	S142(432)**P**	Africa	KF383118	Mosquitoes
	I152(442)**L**	America (Chi/Ven)	KU744693	ZIKV infection
	I152(442)**T**	Africa	LC002520	Sentinel monkey
	T156(-)**I**	Africa	LC002520; KF383119; KF383118; KF383116; HQ234500; HQ234498	Sentinel monkey, Mosquitoes, cell culture
	H158(444)**Y**	Africa	HQ234498; KU720415; LC002520; NC012532; AY632535	Sentinel monkey, Mosquitoes, cell culture
	N163(449)**D**	Africa	NC012532; AY632535;	Sentinel monkey
	K166(452)**E**	Africa	KF383115	Mosquitoes
	I169(455)V	Africa	All African sequences	Sentinel monkey, mosquitoes, cell culture
Domain 2 (DII)	**V56**(346)**I**	America (Guatemala)	KU501217; KU501216	ZIKV infection
	S64(354)**T**	America (Brazil)	KU729217	Microcephaly
	I65(355)**L**	Africa	KF383118	Mosquitoes
	M68(358)**T**	America (Brazil)	KU940227	Unknown
	M68(358)**I**	America (Brazil)	KU729217	Microcephaly
	D71(361)**A**	Africa	KF383118	Mosquitoes
	A80(370)**P**	Africa	KF383118	Mosquitoes
	Y81(371)**S**	Africa	KF383118	Mosquitoes
	Y90(380)**S**	Africa	KF383118	Mosquitoes
	V97(387)**G**	Africa	KF383118	Mosquitoes
	L107(397)**I**	Africa	KF383118	Mosquitoes
	A117(407)**S**	Africa	KF383118	Mosquitoes
	A120(410)**T**	Africa	All African sequences	Mosquitoes, sentinel monkey, cell culture

	S122(412)**C**	Africa	KF383118	Mosquitoes
	T126(416)**P**	Africa	KF383118	Mosquitoes
	W211(497)**R**	Africa	KF383117	Mosquitoes
	V213(499)**A**	America (Chi/Ven)	KU744693	ZIKV infection
	H214(500)**R**	Africa	KF383117	Mosquitoes
	A227(513)**S**	Africa	HQ234501	Mosquitoes
	A227(513)**T**	Asia (Thailand)	KU681081	ZIKV infection& cell culture
	D230(516)**A**	America (Chi/Ven)	KU744693	ZIKV infection
	G232(518)**E**	Africa	HQ234500	Cell culture
	V255(541)**A**	America (Brazil)	KU729217	Microcephaly
	S260(546)**T**	America (Brazil)	KU497555	Microcephaly
	R283(569)**K**	Africa	LC002520; HQ234498; KU720415	Cell culture, sentinel monkey
	S285(571)**E**	Africa	All African sequences	Mosquitoes, cell culture, sentinel monkey
Domain 3 (DIII)	**T309**(595)**N**	America (Brazil)	KU940227	Unknown
	A311(597)**V**	Africa	KF383116	Mosquitoes
	F312(598)**C**	Africa	KF383116	Mosquitoes
	F314(560)**A**	Africa	KF383116	Mosquitoes
	T315(601)**A**	Africa	KF383116	Mosquitoes
	I317(603)**V**	Africa	All African sequences	Mosquitoes, cell culture, sentinel monkey
	L322(608)**V**	America (Chi/Ven)	KU744693	ZIKV infection
	H323(609)**D**	America (Chi/Ven)	KU744693	ZIKV infection
	V330(616)**G**	America (Chi/Ven)	KU744693	ZIKV infection
	Y332(618)**S**	Africa	KF383118	Mosquitoes
	A333(619)**G**	America (Chi/Ven)	KU744693	ZIKV infection
	T335(621)**R**	America (Brazil)	KU926310	ZIKV infection
	T335(621)**A**	Africa	HQ234500	Mosquitoes
	V341(627)**F**	Africa	LC002520; HQ234498; NC012532; AY632535	Cell culture, sentinel monkey
	A343(629)**V**	Africa	LC002520; HQ234498; NC012532; AY632535	Cell culture, sentinel monkey
	M349(635)**T**	America (Brazil)	KU729217	Microcephaly
	S368(654)**G**	Asia (Thailand)	KU681081	ZIKV infection& cell culture
	H401(687)**L**	Africa	KF383117	Mosquitoes
	R402(688)**K**	Africa	KF383117	Mosquitoes
	S403(689)**K**	Africa	KF383117	Mosquitoes

Stem-anchor region	**T406**(692)**S**	Africa	KF383117	Mosquitoes
	T406(692)**I**	Africa	HQ234500	Cell culture
	K419(705)**R**	Asia (Chi/ Sam)	KU866423; KU820899	ZIKV infection
	A437(723)**V**	Asia (Thailand)	KU681081	ZIKV infection & cell culture
		Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	L438(724)**F**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	I445(731)**V**	Africa	KF383117; HQ234498; DQ859059; KF268950	Cell culture, mosquitoes
	F449(735)**I**	America (Chi/Ven)	KU744693	ZIKV infection
	M473(759)**V**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
		Asia (Malaysia)	HQ234499	Cell culture
		Asia (Philippines)	KU681082	ZIKV infection & cell culture
		Asia (Micronesia)	EU545988	ZIKV infection
		Asia (Cambodia)	JN860885	ZIKV infection
Transmembrane region	**T479**(765)**A**	America (Suriname)	KU312312	ZIKV infection
	M487(773)**T**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
		Asia (Malaysia)	HQ234499	Cell culture
		Asia (Philippines)	KU681082	ZIKV infection & cell culture
		Asia (Micronesia)	EU545988	ZIKV infection
	L495(781)**M**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	A504(790)**G**	America (Chi/Ven)	KU744693	ZIKV infection
	D505(791)**G**	America (Chi/Ven)	KU744693	ZIKV infection

[1]: Mutations according to the PBD numbering in bold letter, and polyprotein numbering in brackets (uniprot entry Q32ZE10).

Table S4: Mutations in NS1 protein of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Aminoacid location on the protein structure	Mutations[1]	Geographical origin (Country)	Sequence accession number in Genbank	Host
Membrane-binding region	**K11**(801)**R**	Africa	KF383119; KF383115; KF268950; KF268949; KF268948	Mosquitoes, cell culture
	E26(816)**D**	Asia (Micronesia)	EU545988	ZIKV infection
	K33(823)**R**	Africa	HQ234500	Cell culture
Dimerization region	**D1**(791)**G**	America (Chi/Ven)	KU744693	ZIKV infection
	V162(952)**I**	Africa	HQ234501; KF383117; KF383116	Mosquitoes, cell culture
	V188(978)**A**	Asia (Malaysia)	HQ234499	Cell culture
		Asia (Micronesia)	EU545988	ZIKV infection
		Asia (Cambodia)	JN860885	ZIKV infection
		Asia (Philippines)	KU681082	ZIKV infection
	G190(980)**E**	America (Brazil)	KU729217	Microcephaly
	K191(981)**R**	Africa	LC002520; KF383119; KF383118; HQ234500; HQ234498; AY632535; NC012532	Mosquitoes, cell culture, sentinel monkey
	V194(984)**A**	Africa	All African sequences	Mosquitoes, cell culture, sentinel monkey
	T233(1023)**A**	America (Brazil)	KU527068	Microcephaly
Hexameration region	**R69**(859)**K**	Africa	All African sequences	Mosquitoes, cell culture, sentinel monkey
	R211(1001)**W**	America (Chi/Ven)	KU744693	ZIKV infection
	K213(1003)**R**	Asia (Thailand)	KU681081	ZIKV infection& cell culture
		Africa	HQ234501; KF383117; KF383116	Mosquitoes, cell culture
	R324(1114)**Q**	Asia (Chi/Sam)	KU866423; KU820899	ZIKV infection
		Asia (Chi/Ven)	KU744693	ZIKV infection
	R324(1114)**W**	America (Mexico)	KU922960; KU922923	ZIKV infection
		America (Colombia)	KU820897	ZIKV infection
		America (Martinique)	KU647676	ZIKV infection
Loop region (not resolved in crystal structures)	**E110**(900)**G**	Africa	KF383116	Mosquitoes
	Y122(912)**H**	America (Brazil) America (Haiti)	KU321639 KU509998	ZIKV infection ZIKV infection

Solvent accesible surface both in dimer and hexamer forms	**V21**(811)**I**	Africa	LC002520; AY632535; NC012532;KU720415; HQ234498	Cell culture, sentinel monkey
	A45(835)**V**	Asia (Thailand)	KU681081	ZIKV infection& cell culture
	D52(842)**E**	Africa	All African sequences	Mosquitoes, cell culture, sentinel monkey
	G100(890)**A**	America (Guatemala)	KU501216; KU501217	ZIKV infection
	Q102(892)**R**	Africa	HQ234500	Cell culture
	S132(922)**R**	Africa	HQ234499	Cell culture
	K146(936)**E**	Africa	LC002520; AY632535; NC012532; KU720415; HQ234498	Mosquitoes, cell culture, sentinel monkey
		America (Brazil)	KU527068	Microcephaly
	S176(966)**W**	America (Chi/Ven)	KU744693	ZIKV infection
	G199(989)**C**	Africa	KF383117	Mosquitoes
	I236(1026)**V**	Africa	All African sequences	Mosquitoes, cell culture, sentinel monkey
		Asia (Philippines)	KU681082	ZIKV infection& cell culture
	T256(1046)**A**	America (Chi/Ven)	KU744693	ZIKV infection
	M264(1054)**V**	Asia (Malaysia)	HQ234499	Mosquitoes cell culture
		Africa	All African sequences	Mosquitoes, cell culture, sentinel monkey
	M264(1054)**A**	Africa	KF383115; KF268950; KF268949; KF268948	Mosquitoes
	M264(1054)**L**	Africa	HQ234501	Mosquitoes cell culture
	H286(1076)**Y**	Africa	LC002520; KF383117; AY632535; NC012532; KU720415	Mosquitoes, cell culture, sentinel monkey
	C313(1103)**S**	America (Chi/Ven)	KU744693	ZIKV infection
	M349(1139)**V**	America (Brazil)	KU729217; KU527068	Microcephaly
			KU926310	ZIKV infection
		America (Dom Rep)	KU853013; KU853012	ZIKV infection

[1]: Mutations according to the PBD numbering in bold letter, and polyprotein numbering in brackets (uniprot entry Q32ZE10).

Table S5: Mutations in NS2A protein of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Aminoacid location on the protein structure	Mutations	Geographical origin (Country)	Sequence accession number in Genbank	Host
	I1176M	Africa	KU720415; LC002520; KF383119; KF383118; KF383117; KF383116; HQ234501; HQ234500; HQ234498; NC012532; KF268950; KF268949; KF268948; AY632535; DQ859059	Mosquitoes, cell culture, sentinel monkey
	I1176V	Africa	KF383115	Sentinel monkey, Mosquitoes, cell culture
	V1182M	Africa	HQ234500	Cell culture
	A1185V	Africa	KU720415; LC002520; KF383119; KF383118; HQ234498; NC012532; AY632535;	Mosquitoes, cell culture, sentinel monkey
	I1187V	Africa	KF383117; KF383116; HQ234501; HQ234500	Mosquitoes, cell culture, sentinel monkey
	S1192L	Africa	KF268950; KF268948	Mosquitoes
	A1200V	Africa	KU720415; LC002520; KF383119; KF383118; KF383117; KF383116; KF383115; HQ234501; HQ234500; HQ234498; NC012532; KF268950; KF268949; KF268948; AY632535; DQ859059	Mosquitoes, cell culture, sentinel monkey
	I1222T	America (Mexico)	KU922923; KU922960	ZIKV infection
		America (Martinique)	KU647676	ZIKV infection
		Asia (Thailand)	KU681081	
	I1222V	Africa	KU720415; LC002520; KF383119; KF383118; KF383117; KF383116; KF383115; HQ234501; HQ234500; HQ234498; NC012532; KF268950; KF268949; KF268948; AY632535; DQ859059	Mosquitoes, cell culture, sentinel monkey
	F1237L	Africa	KF383119; KF383118	Mosquitoes
	L1255F	America (Brazil)	KU497555	Microcephaly
	D1266E	Africa	KF383117; KF383116; HQ234501; HQ234500	Mosquitoes, cell culture, sentinel monkey
	L1270P	Asia (Cambodia)	JN860885	ZIKV infection

I1271V	Africa	KF383119; KF383118; KF383117; KF383116; KF383115; HQ234501; HQ234500; KF268950; KF268949; KF268948; DQ859059	Mosquitoes, cell culture, sentinel monkey
I1281V	Asia (China)	KU820898; KU740184	ZIKV infection
V1285A	Asia (Malaysia)	HQ234499	Cell culture
	Africa	KU720415; LC002520; KF383119; KF383118; KF383117; KF383116; KF383115; HQ234501; HQ234500; HQ234498; NC012532; KF268950; KF268949; KF268948; AY632535; DQ859059	Mosquitoes, cell culture, sentinel monkey
T1293A	Africa	KU720415; LC002520; KF383119; KF383118; KF383117; KF383116; KF383115; HQ234501; HQ234500; HQ234498; NC012532; KF268950; KF268949; KF268948; AY632535; DQ859059	Mosquitoes, cell culture, sentinel monkey
A1295P	Africa	KU720415; LC002520; HQ234498; NC012532; AY632535	Mosquitoes, cell culture, sentinel monkey
I1296T	Africa	KF383117	Mosquitoes
I1296V	Africa	KF268949	Mosquitoes
A1298T	Asia (Micronesia)	EU545988	ZIKV infection
V1310M	America (Brazil)	KU940227	Unknown
F1322I	Africa	KU720415; LC002520; HQ234498; NC012532; AY632535	Mosquitoes, cell culture, sentinel monkey
L1325I	Africa	HQ234500	Cell culture
M1341A	Africa	DQ859059	Mosquitoes, cell culture
L1345M	Africa	KF383115	Mosquitoes
T1346A	Africa	KF383117	Mosquitoes
L1350V	Africa	KU720415; LC002520; KF383119; KF383118; HQ234498; NC012532; AY632535	Mosquitoes, cell culture, sentinel monkey
L1350I	Africa	KF383117; KF383116; KF383115; HQ234501; HQ234500; KF268950; KF268949; KF268948; DQ859059	Mosquitoes, cell culture, sentinel monkey

Table S6: Mutations in NS2B protein of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Aminoacid location on the protein structure	Mutations	Geographical origin (Country)	Sequence accession number in Genbank	Host
	M1400I	America (Brazil)	KU926309	ZIKV infection
			KU729217	Microcephaly
	S1413T	Africa	HQ234500	Cell Culture
	V1435I	Asia (Philipines)	KU681082	ZIKV infection
	D1457E	Africa	KU720415; LC002520; KF383119; KF383118; KF383117; KF383116; KF383115; HQ234501; HQ234500; HQ234498; NC012532; KF268950; KF268949; KF268948; AY632535; DQ859059	Mosquitoes, cell culture, sentinel monkeys
	T1473A	Africa	KU720415; LC002520; KF383119; KF383118; KF383117; KF383116; KF383115; HQ234501; HQ234500; HQ234498; NC012532; KF268950; KF268949; KF268948; AY632535; DQ859059	Mosquitoes, cell culture, sentinel monkeys

Table S7: Mutations in NS3 protein of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Aminoacid location on the protein structure	Mutations[1]	Geographical origin (Country)	Sequence accession number in Genbank	Host
NS3pro	**A56**(1554)**S**	Africa	All African sequences	Mosquitoes, cell culture, sentinel monkey
	A88(1586)**T**	Africa	KF383117	Mosquitoes, cell culture
	L92(1590)**H**	Africa	All African sequences, except for: NC012532;DQ859059	Mosquitoes, cell culture, sentinel monkey
	L92(1590)**V**	Africa	DQ859059	Mosquitoes, cell culture
	A106(1604)**E**	America (Mexico)	KU922960;KU922923	ZIKV infection
	R107(1605)**K**	Africa	HQ234500	Cell culture
	L112(1610)**P**	Asia (Micronesia)	EU545988	ZIKV infection
	I115(1613)**T**	Asia (Philippines)	KU681082	ZIKV infection
	D120(1618)**G**	America (Brazil)	KU940224; KU940228	Unknown
	K169(1667)**R**	Africa	All African sequences	Mosquitoes, cell culture, sentinel monkey
Linker	**T174**(1672)**A**	Africa	KF383117; KF383116; HQ234501	Mosquitoes, cell culture
	K185(1683)**R**	Africa	KF383117; KF383116; HQ234501; HQ234500	Mosquitoes, cell culture
NS3hel	**K215**(1713)**T**	Africa	All African sequences	Mosquitoes, cell culture, sentinel monkey
	V220(1718)**L**	Africa	KF383116	Mosquitoes
	N249(1747)**K**	Africa	DQ859059	Cell culture
	N282(1780)**Y**	Africa	KF383119; KF383118; KF383117; KF383116; KF383115; AY632535;NC012532;	Mosquitoes, sentinel monkey
	M334(1832)**T**	America (Brazil)	KU729218	Fatal ZIKV infection
	S347(1845)**T**	Asia (Philippines)	KU681082	ZIKV infection& cell culture
	D354(1852)**E**	America (Chi/ Ven)	KU744693	ZIKV infection
	H355(1853)**Y**	America (Chi/Ven)	KU744693	ZIKV infection
	V360(1858)**I**	Africa	KF383117; KF383116; HQ234501; HQ234500	Mosquitoes
	S365(1863)**R**	America (Chi/Ven)	KU744693	ZIKV infection
	N398(1866)**S**	Africa	KF383118; KF383116	Mosquitoes
	N370(1868)**E**	Africa	KF383118; KF383116	Mosquitoes

I372(1870)**S**	Africa	KF383118; KF383116	Mosquitoes
A373(1871)**T**	Africa	KF383115	Mosquitoes
Q396(1894)**L**	Asia (Micronesia)	EU545988	ZIKV infection
H400(1898)**N**	Asia (Malaysia)	HQ234499	Cell culture
	Asia (Philippines)	KU681082	ZIKV infection& cell culture
	Asia (Micronesia)	EU545988	ZIKV infection
	Africa	All African sequences	Mosquitoes, sentinel monkey, cell culture
V407(1905)**I**	Africa	All African sequences	Mosquitoes, sentinel monkey, cell culture
D436(1934)**G**	America (Chi/ Ven)	KU744693	ZIKV infection
I460(1958)**V**	Africa	HQ234501	Mosquitoes
M472(1970)**L**	Asia (Malaysia)	HQ234499	Cell culture
	Africa	All African sequences	Mosquitoes, cell culture, sentinel monkey
D483(1981)**G**	Africa	KU720415; LC002520 KF383119; KF268948 AY632535; NC012532	Mosquitoes, sentinel monkey
R525(2023)**K**	Asia (Chi/Sam)	KU866423	ZIKV infection
K537(2035)**R**	America (Brazil)	KU926309	ZIKV infection
R560(2058)**K**	Asia (Micronesia)	EU545988	ZIKV infection
T567(2065)**M**	Asia (Thailand)	KU681081	Cell culture
	Asia (Philippines)	KU681082	ZIKV infection
M572(2070)**L**	America (Guatemala)	KU501216; KU501217	ZIKV infection
R583(2081)**K**	Africa	All African sequences	Mosquitoes, sentinel monkey, cell culture
Y584(2082)**H**	Asia (Malaysia)	HQ234499	Cell culture
	Asia (Philippines)	KU681082	ZIKV infection
	Asia (Micronesia)	EU545988	ZIKV infection
	Africa	All African sequences	Mosquitoes, sentinel monkey, cell culture

[1]: Mutations according to the PBD numbering in bold letter, and polyprotein numbering in brackets (uniprot entry Q32ZE10).

Table S8: Mutations in NS4A protein of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Aminoacid location on the protein structure	Mutations	Geographical origin (Country)	Sequence accession number in Genbank	Host
	A2117V	Africa	KF268950; KF268948	Mosquitoes
	A2118T	America (Brazil)	KU926310	ZIKV infection
	F2119L	America (Brazil)	KU940228; KU940224	ZIKV infection
		Africa	KU720415; LC002520; KF383119; KF383118; KF383117; KF383116; KF383115; HQ234501; HQ234500; HQ234498; NC012532; KF268950; KF268949; KF268948; AY632535; DQ859059	Mosquitoes, cell culture, sentinel monkey
	M2122I	Asia (Philipines)	KU681082	ZIKV infection
	E2123D	Africa	KF383117; KF383116; HQ234501; HQ234500	Mosquitoes, cell culture, sentinel monkey
	K2157E	Asia (Micronesia)	EU545988	ZIKV infection
	Q2162P	Africa	KF383115	Mosquitoes
	L2163M	America (Brazil)	KU940228; KU940227; KU940224	Unkown
	I2193M	Asia (Philipines)	KU681082	ZIKV infection
	G2199E	Africa	DQ859059	Cell culture

Table S9: Mutations in NS4B protein of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Aminoacid location on the protein structure	Mutations	Geographical origin (Country)	Sequence accession number in Genbank	Host
	V2255I[1]	Asia (Micronesia)	EU545988	ZIKV infection
	S2276N	Africa	KU720415; LC002520 KF383119; KF383118; KF383115; HQ234498; NC012532; KF268950; KF268949; KF268948; AY632535; DQ859059	Mosquitoes, cell culture, sentinel monkey
	L2278I	Africa	KU720415; LC002520; KF383119; KF383118; KF383117; KF383116; KF383115; HQ234501; HQ234500; HQ234498; NC012532; KF268950; KF268949; KF268948; AY632535; DQ859059	Mosquitoes, cell culture, sentinel monkey
	S2279G	Asia (Malaysia)	HQ234499	Cell culture
	S2279A	Africa	KU720415; LC002520; KF383119; KF383118; KF383117; KF383116; KF383115; HQ234501; HQ234500; HQ234498; NC012532; KF268950; KF268949; KF268948; AY632535; DQ859059	Mosquitoes, cell culture, sentinel monkey
	H2280Y	Africa	KF383117	Mosquitoes
	R2284K	Africa	DQ859059	Mosquitoes, cell culture
	R2285K	Africa	KF383117; KF383116 HQ234501; HQ23450	Mosquitoes, cell culture, sentinel monkey
	A2289T	Africa	KF383117; KF383116; HQ234501; HQ234500; AY632535	Mosquitoes, cell culture, sentinel monkey
	A2289V	Africa	KF383115; KF268950; KF268949; KF268948	Mosquitoes, cell culture, sentinel monkey
	I2291M	America (Brazil)	KU321639	ZIKV infection
		America (Haiti)	KU509998	ZIKV infection
		America (Chi/Ven)	KU744693	ZIKV infection
		Asia (Malaysia)	HQ234499	Cell culture
		Africa	KU720415; LC002520; KF383119; KF383118; KF383115; HQ234501; HQ234498; NC012532; KF268950; KF268949; KF268948; AY632535	Mosquitoes, cell culture, sentinel monkey

	I2291T	Asia (Philipines)	KU681082	ZIKV infection
	I2291V	Africa	HQ234500; DQ859059	Mosquitoes, cell culture
	A2309P	America (Chi/Ven)	KU744693	ZIKV infection
	T2313S	America (Chi/Ven)	KU744693	ZIKV infection
	F2314L	Asia (Malaysia)	HQ234499	Cell culture
		Africa	KU720415; LC002520; KF383119; KF383118; KF383117; KF383116; KF383115; HQ234501; HQ234500; HQ234498; NC012532; KF268950; KF268949; KF268948; AY632535; DQ859059	Mosquitoes, cell culture, sentinel monkey
	F2356L	Africa	KU720415; LC002520; KF383118; HQ234498; NC012532; AY632535; DQ859059	Mosquitoes, cell culture, sentinel monkey
	I2363M	Asia (Malaysia)	HQ234499	Cell culture
		Asia (Philipines)	KU681082	ZIKV infection
		Asia (Micronesia)	EU545988	ZIKV infection
		Africa	KU720415; LC002520; KF383119; KF383118; KF383116; KF383115; HQ234501; HQ234500; HQ234498; NC012532; KF268950; KF268948; AY632535; DQ859059	Mosquitoes, cell culture, sentinel monkey
	I2363V	Africa	KF268949	Mosquitoes
	D2415E	America (Chi/Ven)	KU744693	ZIKV infection
	P2429H	Asia (Micronesia)	EU545988	ZIKV infection
	Q2430R	Asia (Micronesia)	EU545988	ZIKV infection
	I2441M	America (Haiti)	KU509998	ZIKV infection
		America (Brazil)	KU321639	ZIKV infection
		America (Chi/Ven)	KU744693	ZIKV infection
	V2445I	Asia (Malaysia)	HQ234499	Cell culture
		Africa	KU720415; LC002520; KF383119; KF383118; KF383115; HQ234498; NC012532; KF268950; KF268949; KF268948; AY632535	Mosquitoes, cell culture, sentinel monkey
	V2445A	Africa	HQ234500	Cell culture
	I2449V	Asia (Malaysia)	HQ234499	Cell culture

		Africa	KU720415; LC002520; KF383119; KF383118; KF383117; KF383116; KF383115; HQ234501; HQ234500; HQ234498; NC012532; KF268950; KF268949; KF268948; AY632535; DQ859059	Mosquitoes, cell culture, sentinel monkey
	S2451L	Asia (Malaysia)	HQ234499	Cell culture
		Africa	KU720415; LC002520; KF383119; KF383118; KF383117; KF383116; KF383115; HQ234501; HQ234500; HQ234498; NC012532; KF268950; KF268949; KF268948; AY632535; DQ859059	Mosquitoes, cell culture, sentinel monkey
	W2455G	Africa	KF383117	Mosquitoes
	T2505I	America (Brazil)	KU527068	Microcephaly

[1] Mutation belonging to the peptide 2K.

Table S10: Mutations in NS5 protein of ZIKV, according to protein structural regions, geographical origin, sequence accession number in Genbank and clinical data, when available.

Aminoacid location on the protein structure	Mutations[1]	Geographical origin (Country)	Sequence accession number in Genbank	Host
MTase Domain	**D46**(2562)**N**	Africa	KF268949	Mosquitoes
	L62(2578)**I**	Africa	AY632535; NC012532	Sentinel monkey, cell culture, mosquitoes
	V66(2582)**E**	Africa	AY632535; NC012532	Sentinel monkey, cell culture, mosquitoes
	Y74(2590)**H**	America (Brazil)	KU940228; KU940227 KU940224;	Unknown
		Africa	KF383119; KF383118 KF383117; KF383116 KF383115; HQ234500 HQ234501; KF268950 KF268949; KF268948	Cell culture, mosquitoes
	V78(2594)**I**	Africa	All African sequences, except for: HQ234501; HQ234500	Sentinel monkey, cell culture, mosquitoes
	A91(2607)**V**	America (Puerto Rico)	KU501215	ZIKV infection
	K101(2617)**R**	Africa	All African sequences, except for: KF268950 KF268949; KF268948	Sentinel monkey, cell culture, mosquitoes
	M114(2630)**V**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
		Asia (Thailand)	KU681081	Cell culture
		Asia (Chi/Sam)	KU866423	ZIKV infection
		Asia (Philippines)	KU681082	ZIKV infection & cell culture
		Asia (Can/Thai)	KF993678	ZIKV infection
		Asia (French Pol)	KJ776791	ZIKV infection
		Asia (Cambodia)	JN860885	ZIKV infection
		Asia (Micronesia)	EU545988	ZIKV infection
		Asia (China)	KU820899	ZIKV infection
	M114(2630)**T**	Asia (Malaysia)	HQ234499	Cell culture

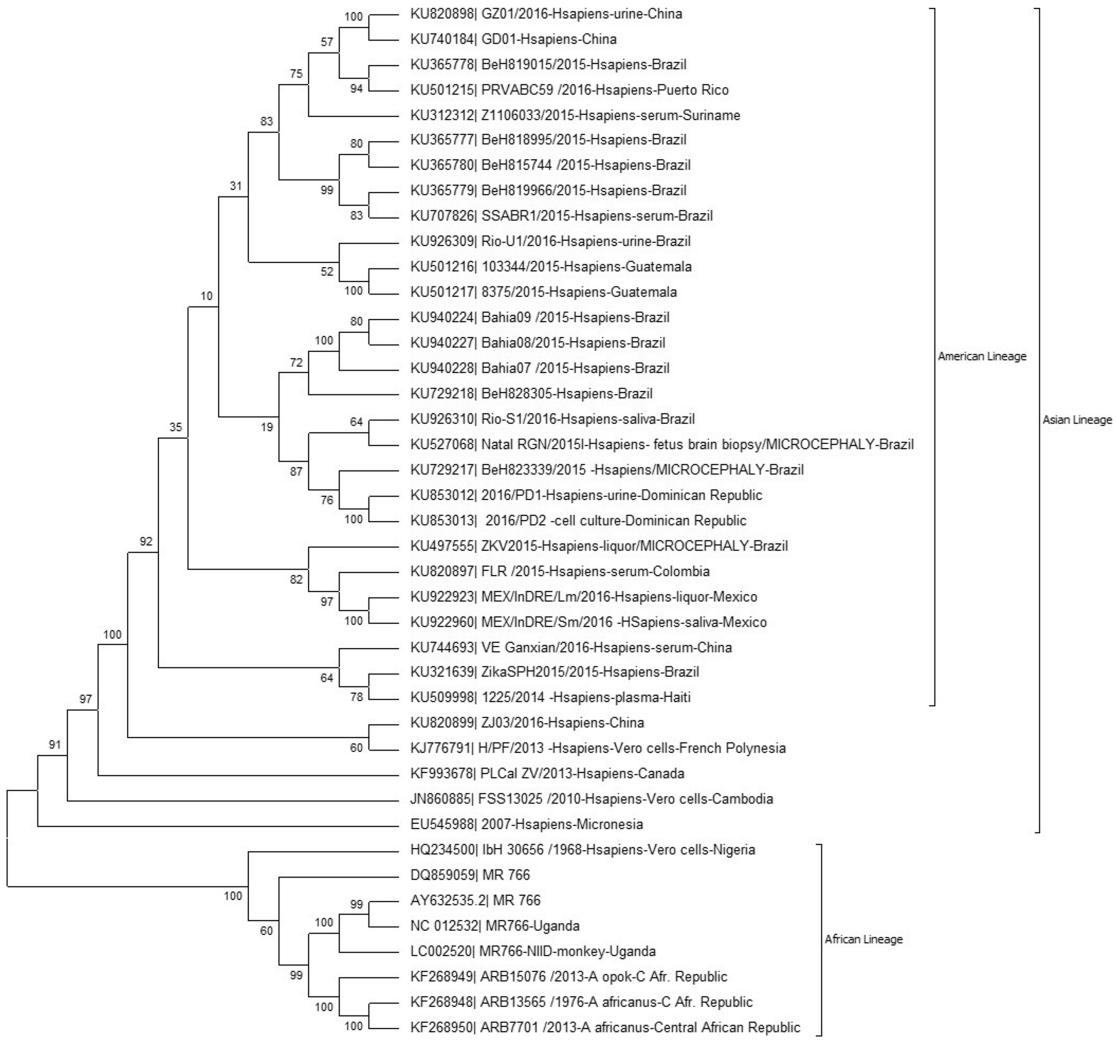
	V124(2640)**I**	Asia (Chi/Sam)	KU866423	ZIKV infection
		Africa	DQ859059	Cell culture
	P139(2655)**S**	Asia (Malaysia)	HQ234499	Cell culture
		Africa	DQ859059	Cell culture
	A159(2675)**T**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	V168(2684)**A**	America (Brazil)	KU926310	ZIKV infection
	G169(2685)**E**	Africa	KF383117	Mosquitoes
	K174(2690)**R**	America (Guatemala)	KU501216; KU501217	ZIKV infection
	I181(2697)**V**	Asia (Thailand)	KU681081	ZIKV infection & cell culture
	L195(2711)**M**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	Y202(2718)**H**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	C212(2728)**S**	Africa	AY632535; NC012532	Sentinel monkey
	T229(2745)**I**	Asia (China)	KU820898; KU740184	ZIKV infection
		Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
		Asia (Malaysia)	HQ234499	Cell culture
	T229(2745)**V**	Africa	KF268950; KF268948	Mosquitoes
	D245(2761)**E**	Africa	HQ234501	Cell culture
Linker	**N259**(2775)**D**	America (Brazil)	KU365777; KU365780	ZIKV infection
	V267(2783)**A**	Asia (China)	KU820898; KU740184	ZIKV infection
		Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
		Asia (Malaysia)	HQ234499	Cell culture
RdRp domain (Fingers)	**M275**(2791)**L**	Asia (Malaysia)	HQ234499	Cell culture
	I277(2793)**V**	Africa	KF268950; KF268948; DQ859059	Mosquitoes, cell culture

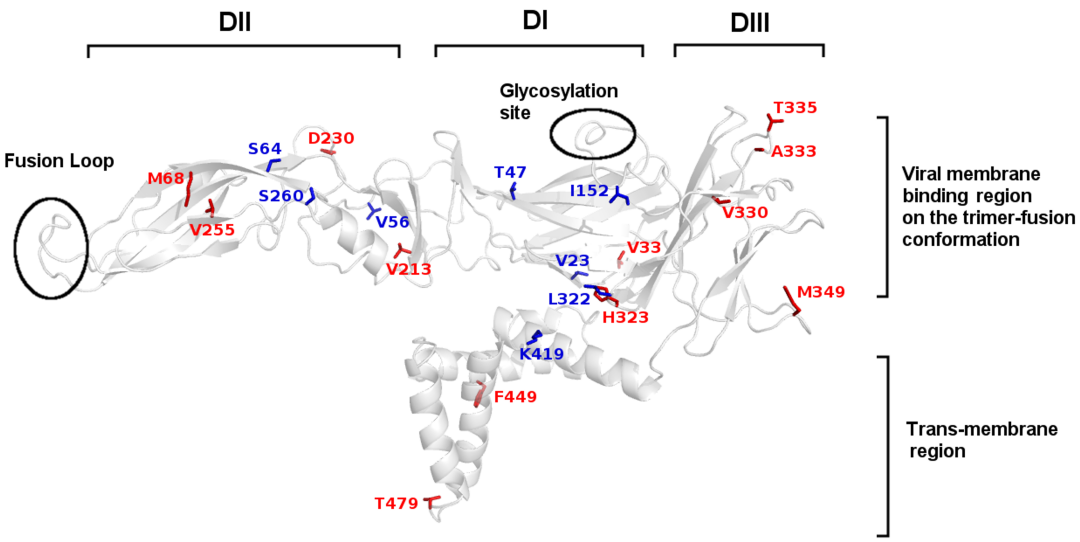
	N280(2796)**R**	Africa	KU720415; LC002520 KF383119; KF383118 KF383117; KF383116 HQ234501; HQ234500 HQ234498; NC012532 AY632535; DQ859059	Sentinel monkey, cell culture, mosquitoes
	N280(2796)**D**	America (Brazil)	KU729217	Microcephaly
	N280(2796)**K**	Africa	KF383115; KF268950 KF268949; KF268948	Mosquitoes
	I282(2798)**V**	Asia (Malaysia)	HQ234499	Cell culture
	S287(2803)**N**	America (Chi/Ven)	KU744693	ZIKV infection
	S287(2803)**A**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	H289(2805)**Q**	America (Mexico)	KU922960; KU922923	ZIKV infection
	H289(2805)**K**	America (Chi/Ven)	KU744693	ZIKV infection
	F295(2811)**L**	Africa	KU720415; LC002520 KF383119; KF383118 HQ234498; NC012532 AY632535	Sentinel monkey, mosquitoes
	E311(2827)**D**	America (Chi/Ven)	KU744693	ZIKV infection
	E311(2827)**V**	America (Brazil)	KU497555	Microcephaly
	P313(2829)**A**	America (Chi/Ven)	KU744693	ZIKV infection
	K438(2954)**R**	Africa	KU720415; LC002520 KF383119; KF383118 HQ234498; AY632535 NC012532	Sentinel monkey, cell culture, mosquitoes
	Q449(2965)**H**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	N454(2970)**I**	America (Chi/Ven)	KU744693	ZIKV infection
	M455(2971)**T**	America (Chi/Ven)	KU744693	ZIKV infection
	A489(3005)**S**	Africa	KF383118; KF383115	Mosquitoes
	R545(3061)**K**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	E559(3075)**D**	Africa	DQ859059	Cell culture
	K560(3076)**E**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	A564(3080)**T**	Africa	KU720415; LC002520 KF383119; KF383118 HQ234498; AY632535 NC012532; DQ859059	Sentinel monkey, cell culture, mosquitoes
	I569(3085)**V**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	K587(3103)**R**	Asia (Malaysia)	HQ234499	Cell culture
	K587(3103)**G**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
RdRp domain (α-NLS)	**V322**(2838)**I**	America (Brazil)	KU940228; KU940227 KU940224	Unknown
		America (Dom Rep)	KU853012; KU853013	ZIKV infection
		Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes

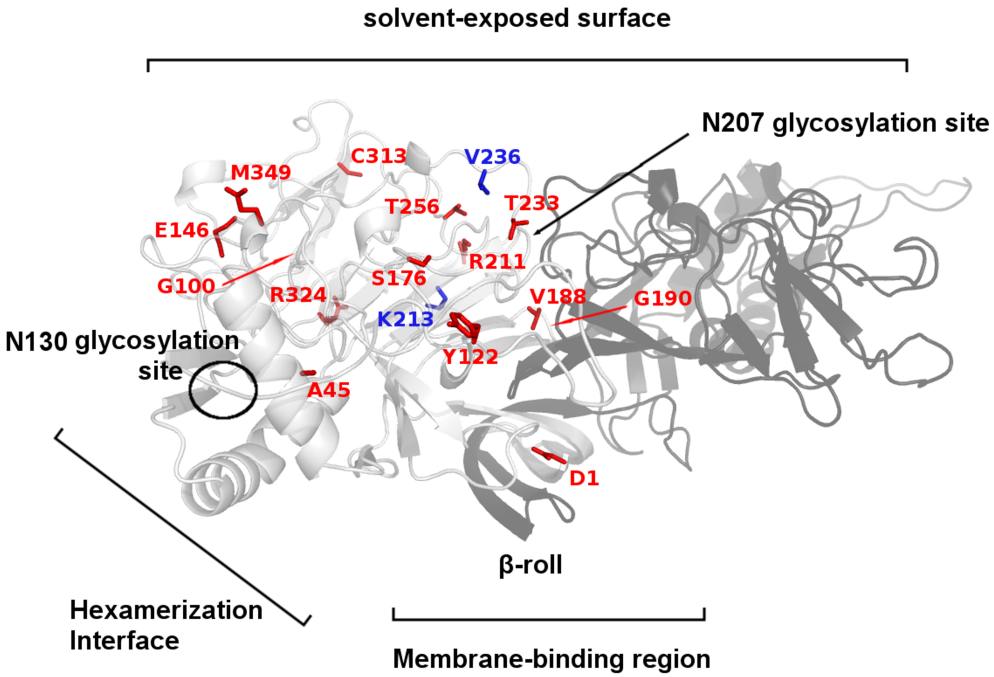
RdRp domain (α,β-NLS)	**Q373**(2889)**R**	Africa	HQ234500	Mosquitoes
	V374(2890)**I**	Asia (Can/ Thai)	KF993678	ZIKV infection
	V374(2890)**T**	Africa	KF268949	Mosquitoes
	V374(2890)**A**	Africa	KF268950; KF268948	Mosquitoes
	S376(2892)**N**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
		Asia (Malaysia)	HQ234499	Cell culture
	M377(2893)**I**	Africa	KU720415; LC002520 KF383117; HQ234498 AY632535; NC012532	Sentinel monkey, cell culture, mosquitoes
	S379(2895)**A**	Africa	DQ859059	Cell culture
	H389(2905)**R**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
RdRp domain (Palm)	**G510**(3026)**V**	America (Mexico)	KU922960; KU922923	ZIKV infection
	V519(3035)**I**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	S524(3040)**N**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	R525(3041)**Q**	Africa	KF383119; KF383118	Mosquitoes
	R525(3041)**C**	America (Guatemala)	KU501216; KU501217	ZIKV infection
	I526(3042)**A**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	I526(3042)**T**	Asia (Malaysia)	HQ234499	Cell culture
	R530(3046)**K**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
		Asia (Malaysia)	HQ234499	Cell culture
	N624(3140)**S**	Asia (China)	KU820899	ZIKV infection
	D634(3150)**Q**	Africa	HQ234501; HQ234500 KF383117; KF383116	Mosquitoes
	R641(3157)**K**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	S642(3158)**P**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	N647(3163)**R**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	S651(3167)**C**	Africa	KF268950; KF268949; KF268948	Mosquitoes
	N652(3168)**S**	Africa	DQ859059	Cell culture
	R656(3172)**G**	Africa	KF383119	Mosquitoes
	K670(3186)**R**	Asia (Chi/Sam)	KU866423; KU820899	ZIKV infection
	H678(3194)**C**	Africa	KF383115	Mosquitoes
	A679(3195)**C**	Africa	KF383115	Mosquitoes
	S651(3167)**C**	Africa	KF268950; KF268949; KF268948	Mosquitoes
	N652(3168)**S**	Africa	DQ859059	Cell culture
	R656(3172)**G**	Africa	KF383119	Mosquitoes

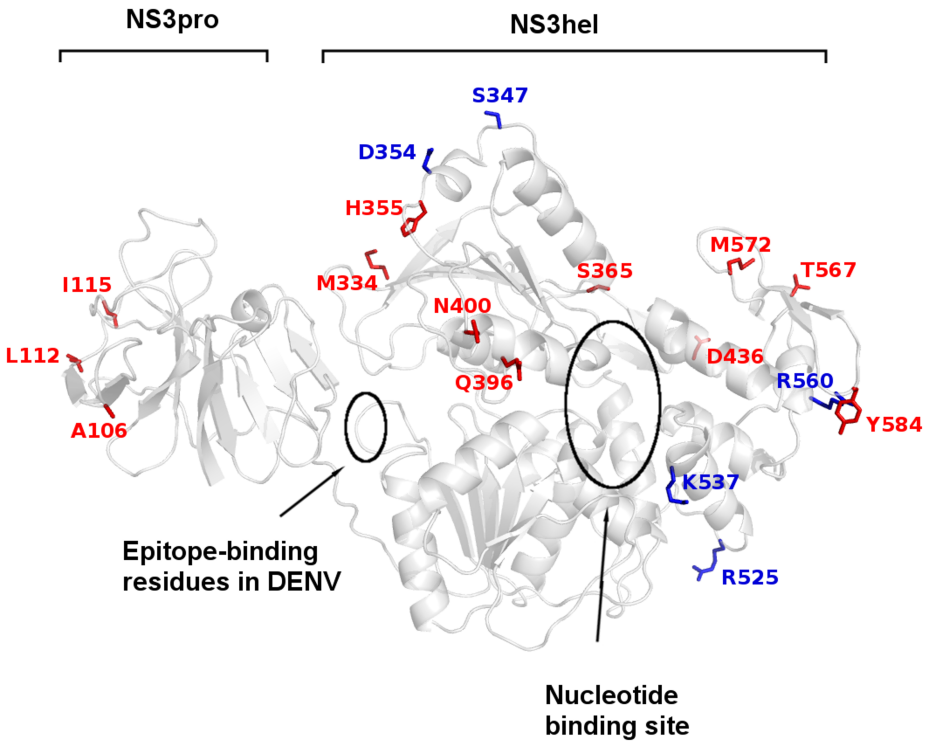
	K670(3186)**R**	Asia (Chi/Sam)	KU866423; KU820899	ZIKV infection
	H678(3194)**C**	Africa	KF383115	Mosquitoes
	A679(3195)**C**	Africa	KF383115	Mosquitoes
RdRp domain (Thumb)	**D703**(3219)**S**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	H719(3235)**Y**	Africa	KU720415; LC002520 KF383119; KF383118 HQ234498; AY632535 NC012532; HQ234498	Sentinel monkey, cell culture, mosquitoes
		Asia (Malaysia)	HQ234499	Cell culture
	R771(3287)**K**	Africa	KF383116	Mosquitoes
	T808(3324)**N**	Africa	HQ234500	Mosquitoes
	M813(3329)**V**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	V814(3330)**A**	America (Chi/Ven)	KU744693	ZIKV infection
	E827(3343)**G**	Africa	HQ234500	Mosquitoes
	T833(3349)**P**	America (Martinique	KU647676	ZIKV infection
		Africa	KF383117	Mosquitoes
	T833(3349)**A**	America (Colombia)	KU820897	ZIKV infection
	D837(3353)**E**	Africa	KF383117	Mosquitoes
	D846(3362)**S**	Africa	KF383117	Mosquitoes
	S851(3367)**Y**	Africa	KF383117	Mosquitoes
	L852(3368)**I**	Africa	KF383117	Mosquitoes
	D867(3383)**N**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	N870(3386)**S**	Africa	DQ859059	Cell culture
	V872(3388)**M**	Asia (Micronesia)	EU545988	ZIKV infection
		Asia (Philippines)	KU681082	ZIKV infection & cell culture
		Asia (Cambodia)	JN860885	ZIKV infection
		Asia (Chi/Sam)	KU866423	ZIKV infection
	R873(3389)**L**	Africa	KF383117	Mosquitoes
	I875(3391)**L**	Africa	KF383117	Mosquitoes
	D878(3394)**E**	America (Dom Rep)	KU853012; KU853013	ZIKV infection
	K881(3397)**R**	Africa	HQ234500	Mosquitoes
	M883(3399)**V**	Asia (Chi/Sam)	KU866423	ZIKV infection
		Asia (Cambodia)	JN860885	ZIKV infection
RdRp domain (Priming Loop)	**A784**(3300)**S**	Africa	All African sequences	Sentinel monkey, cell culture, mosquitoes
	V787(3303)**A**	Africa	HQ234500	Mosquitoes

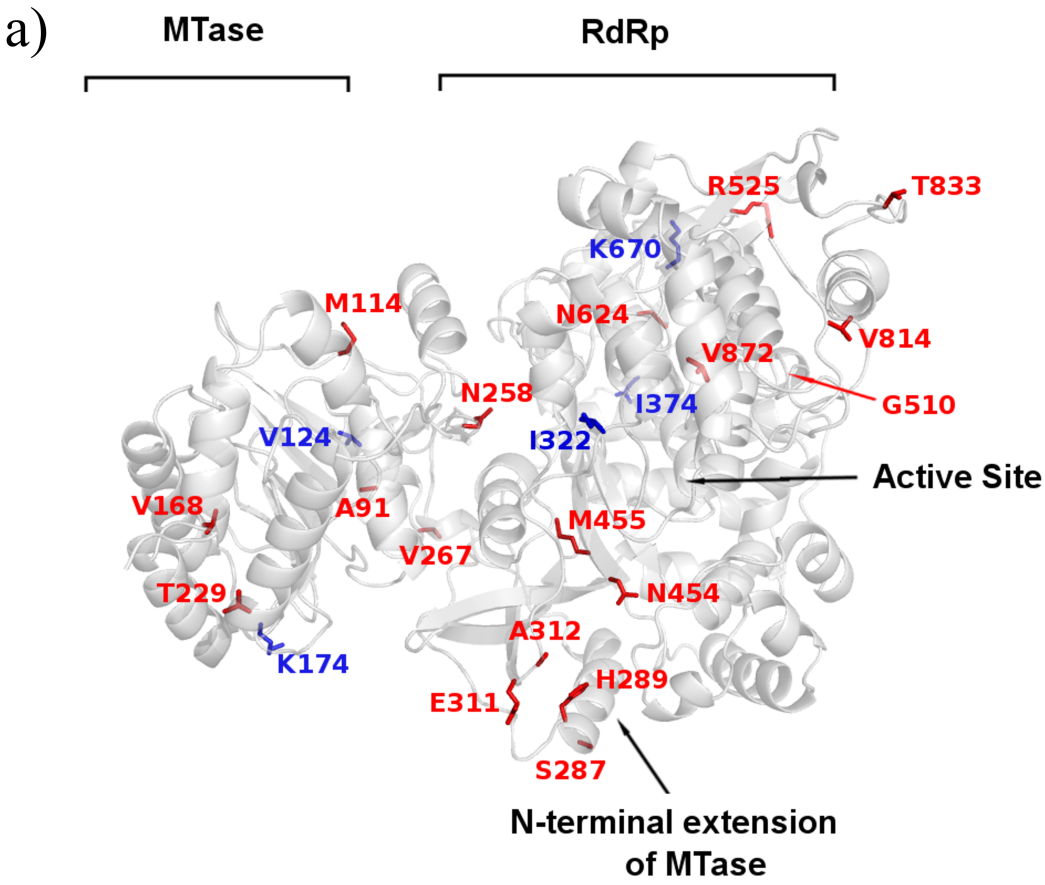
[1]: Mutations according to the PBD numbering in bold letter, and polyprotein numbering in brackets (uniprot entry Q32ZE10).

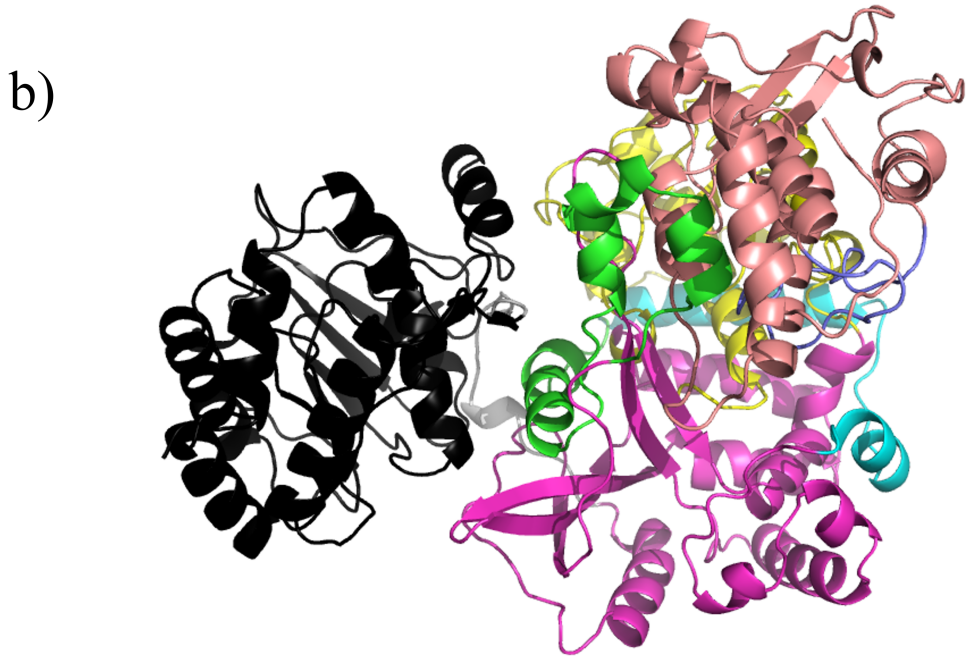

KU820898| GZ01/2016-Hsapiens-urine-China
KU740184| GD01-Hsapiens-China
KU365778| BeH819015/2015-Hsapiens-Brazil
KU501215| PRVABC59 /2016-Hsapiens-Puerto Rico
KU312312| Z1106033/2015-Hsapiens-serum-Suriname
KU365777| BeH818995/2015-Hsapiens-Brazil
KU365780| BeH815744 /2015-Hsapiens-Brazil
KU365779| BeH819966/2015-Hsapiens-Brazil
KU707826| SSABR1/2015-Hsapiens-serum-Brazil
KU926309| Rio-U1/2016-Hsapiens-urine-Brazil
KU501216| 103344/2015-Hsapiens-Guatemala
KU501217| 8375/2015-Hsapiens-Guatemala
KU940224| Bahia09 /2015-Hsapiens-Brazil
KU940227| Bahia08/2015-Hsapiens-Brazil
KU940228| Bahia07 /2015-Hsapiens-Brazil
KU729218| BeH828305-Hsapiens-Brazil
KU926310| Rio-S1/2016-Hsapiens-saliva-Brazil
KU527068| Natal RGN/2015l-Hsapiens- fetus brain biopsy/MICROCEPHALY-Brazil
KU729217| BeH823339/2015 -Hsapiens/MICROCEPHALY-Brazil
KU853012| 2016/PD1-Hsapiens-urine-Dominican Republic
KU853013| 2016/PD2 -cell culture-Dominican Republic
KU497555| ZKV2015-Hsapiens-liquor/MICROCEPHALY-Brazil
KU820897| FLR /2015-Hsapiens-serum-Colombia
KU922923| MEX/InDRE/Lm/2016-Hsapiens-liquor-Mexico
KU922960| MEX/InDRE/Sm/2016 -HSapiens-saliva-Mexico
KU744693| VE Ganxian/2016-Hsapiens-serum-China
KU321639| ZikaSPH2015/2015-Hsapiens-Brazil
KU509998| 1225/2014 -Hsapiens-plasma-Haiti
KU820899| ZJ03/2016-Hsapiens-China
KJ776791| H/PF/2013 -Hsapiens-Vero cells-French Polynesia
KF993678| PLCal ZV/2013-Hsapiens-Canada
JN860885| FSS13025 /2010-Hsapiens-Vero cells-Cambodia
EU545988| 2007-Hsapiens-Micronesia
HQ234500| IbH 30656 /1968-Hsapiens-Vero cells-Nigeria
DQ859059| MR 766
AY632535.2| MR 766
NC 012532| MR766-Uganda
LC002520| MR766-NIID-monkey-Uganda
KF268949| ARB15076 /2013-A opok-C Afr. Republic
KF268948| ARB13565 /1976-A africanus-C Afr. Republic
KF268950| ARB7701 /2013-A africanus-Central African Republic
American Lineage
Asian Lineage
African Lineage

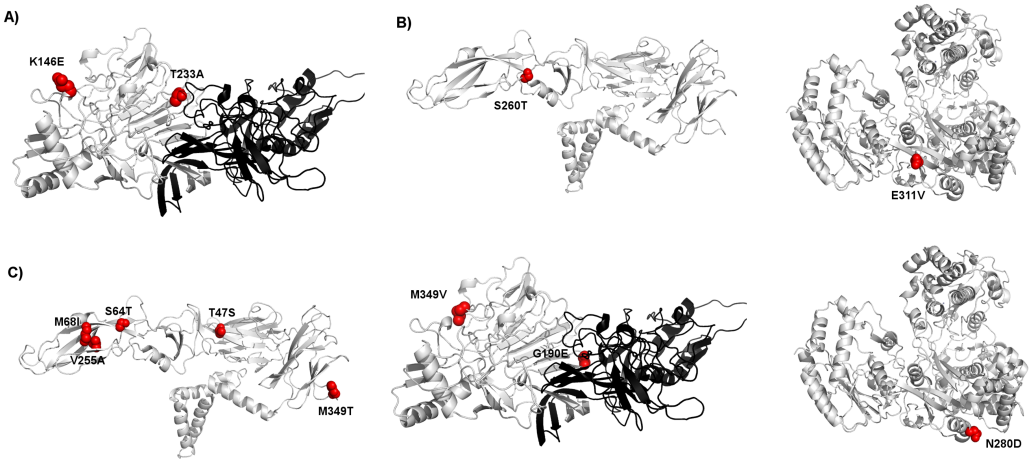

DII
DI
DIII
Glycosylation site
Fusion Loop
T335
A333
S64
D230
M68
T47
I152
S260
V56
V330
V255
V213
V33
V23
L322
H323
M349
K419
F449
T479
Viral membrane binding region on the trimer-fusion conformation
Trans-membrane region


solvent-exposed surface
N207 glycosylation site
C313
V236
M349
T256
T233
E146
R211
G100
S176
R324
V188
G190
K213
N130 glycosylation
site
Y122
A45
D1
β-roll
Hexamerization
Interface
Membrane-binding region


NS3pro
NS3hel
S347
D354
H355
M334
I115
L112
A106
N400
Q396
S365
M572
T567
D436
R560
Y584
K537
R525
Epitope-binding
residues in DENV
Nucleotide
binding site


a)
MTase
RdRp
R525
T833
K670
M114
N624
V814
V872
N258
I374
G510
V124
I322
Active Site
V168
A91
M455
V267
T229
N454
A312
K174
H289
E311
S287
N-terminal extension
of MTase


b)


A)
K146E
T233A
B)
S260T
E311V
C)
M68I
S64T
T47S
V255A
M349T
M349V
G190E
N280D