S7 Fig.

```
DENV1 NS5    1 ---------- -GTGAQGETL GEKWKRQLNQ LSKSEFNTYK RSGIIEVDRS EAKEGLKRGE PTKHAVSRGT AKLRWFVERN
DENV2 NS5    1 ---------- -GTGNIGETL GEKWKSRLNA LGKSEFQIYK KSGIQEVDRT LAKEGIKRGE TDHHAVSRGS AKLRWFVERN
DENV3 NS5    1 ---------- -GTGSQGETL GEKWKKRLNQ LSRKEFDLYK KSGITEVDRT EAKEGLKRGE ITHHAVSRGS AKLQWFVERN
DENV4 NS5  -11 SLIKNAQTPR RGTGTTGETL GEKWKRQLNS LDRKEFEEYK RSGILEVDRT EAKSALKDGS KIKYAVSRGT SKIRWIVERG

DENV1 NS5      LVKPEGKVID LGCGRGGWSY YCAGLKKVTE VKGYTKGGPG HEEPIPMATY GWNLVKLYSG KDVFFTPPEK CDTLLCDIGE
DENV2 NS5      MVTPEGKVVD LGCGRGGWSY YCGGLKNVRE VKGLTKGGPG HEEPIPMSTY GWNLVRLQSG VDVFFTPPEK CDTLLCDIGE
DENV3 NS5      MVIPEGRVID LGCGRGGWSY YCAGLKKVTE VRGYTKGGPG HEEPVPMSTY GWNIVKLMSG KDVFYLPPEK CDTLLCDIGE
DENV4 NS5      MVKPKGKVVD LGCGRGGWSY YMATLKNVTE VKGYTKGGPG HEEPIPMATY GWNLVKLHSG VDVFYKPTEQ VDTLLCDIGE

DENV1 NS5      SSPNPTIEEG RTLRVLKMVE PWLRGN-QFC IKILNPYMPS VVETLEQMQR KHGGMLVRNP LSRNSTHEMY WVSCGTGNIV
DENV2 NS5      SSPNPTVEAG RTLRVLNLVE NWLNNNTQFC IKVLNPYMPS VIEKMEALQR KYGGALVRNP LSRNSTHEMY WLSNASGNIV
DENV3 NS5      SSPSPTVEES RTIRVLKMVE PWLKNN-QFC IKVLNPYMPT VIEHLERLQR KHGGMLVRNP LSRNSTHEMY WISNGTGNIV
DENV4 NS5      SSSNPTIEEG RTLRVLKMVE PWLSSKPEFC IKVLNPYMPT VIEELEKLQR KHGGSLVRCP LSRNSTHEMY WVSGVSGNIV

DENV1 NS5      SAVNMTSRML LNRFTMAHRK PTYERDVDLG AGTRHVAVEP EVANLDIIGQ RIENIKNGHK STWHYDEDNP YKTWAYHGSY
DENV2 NS5      SSVNMISRML INRFTMRHKK ATYEPDVDLG SGTRNIGIES EIPNLDIIGK RIEKIKQEHE TSWHYDQDHP YKTWAYHGSY
DENV3 NS5      SSVNMVSRLL LNRFTMTYRR PTIEKDVDLG AGTRHVNAEP ETPNMDVIGE RIRRIKEEHS STWHYDDENP YKTWAYHGSY
DENV4 NS5      SSVNTTSKML LNRFTTRHRK PTYEKDADLG AGTRSVSTET EKPDMTIIGR RLQRLQEEHK ETWHYDHENP YRTWAYHGSY

DENV1 NS5      EVKPSGSASS MVNGVVRLLT KPWDVIPMVT QIAMTDTTPF GQQRVFKEKV DTRTPKAKRG TAQIMEVTAR WLWGFLSRNK
DENV2 NS5      ETKQTGSASS MGNGVVRLLT KPWDVVPMVT QMAMTDTTPF GQQRVFKEKV DTRTQEPKEG TKKLMKITAE WLWKELGKKK
DENV3 NS5      EVKATGSASS MINGVVKLLT KPWDVVPTVT QMAMTDTTPF GQQRVFKEKV DTRTPKPMPG TRKVMEITAG WLWRTLGRNK
DENV4 NS5      EAPSTGSASS MVNGVVKLLT KPWDVVPMVT QLAMTDTTPF GQQRVFKEKV DTRTPQPKPG TRVVMTTTAN WLWALLGRKK

DENV1 NS5      KPRICTREEF TRKVRSNAAI GAVFVDENQW NSAKEAVEDE RFWDLVHRER ELHKQGKCAT CVYNMMGKRE KKLGEFGKAK
DENV2 NS5      TPRMCTREEF TRKVRSNAAL GAIFTDENKW KSAREAVEDS RFWELVDKER NLHLEGKCET CVYNMMGKRE KKLGEFGKAK
DENV3 NS5      RPRLCTREEF TKKVRTNAAM GAVFTEENQW DSARAAVEDE EFWKLVDRER ELHKQGKCGS CVYNMMGKRE KKLGEFGKAK
DENV4 NS5      NPRLCTREEF ISKVRSNAAI GAVFQEEQGW TSASEAVNDS RFWELVDKER ALHQEGKCES CVYNMMGKRE KKLGEFGRAK

DENV1 NS5      GSRAIWYMWL GARFLEFEAL GFMNEDHWFS RENSLSGVEG EGLHKLGYIL RDISKIPGGN MYADDTAGWD TRITEDDLQN
DENV2 NS5      GSRAIWYMWL GARFLEFEAL GFLNEDHWFS RENSLSGVEG EGLHKLGYIL RDVSKKEGGA MYADDTAGWD TRITLEDLKN
DENV3 NS5      GSRAIWYMWL GARYLEFEAL GFLNEDHWFS RENSYSGVEG EGLHKLGYIL RDISKIPGGA MYADDTAGWD TRITEDDLHN
DENV4 NS5      GSRAIWYMWL GARFLEFEAL GFLNEDHWG RENSWSGVEG EGLHRLGYIL EDIDKKDGDL IYADDTAGWD TRITEDDLLN

DENV1 NS5      EAKITDIMEP EHALLATSIF KLTYQNKVVR VQRPAKNGTV MDVISRRDQR GSGQVGTYGL NTFTNMEAQL IRQMESEGIF
DENV2 NS5      EEMVTNHMEG EHKKLAEAIF KLTYQNKVVR VQRPTPRGTV MDIISRRDQR GSGQVGTYGL NTFTNMEAQL IRQMEGEGVF
DENV3 NS5      EEKITQQMDP EHRQLANAIF KLTYQNKVVK VQRPTPKGTV MDIISRKDQR GSGQVGTYGL NTFTNMEAQL IRQMEGEGVL
DENV4 NS5      EELITEQMAP HHKILAKAIF KLTYQNKVVK VLRPTPKGAV MDIISRKDQR GSGQVGTYGL NTFTNMEVQL IRQMEAEGVI

DENV1 NS5      SPSELETPNL AER-VLDWLK KHGTERLKRM AISGDDCVVK PIDDRFATAL TALNDMGKVR KDIPQWEPSK GWNDWQQVPF
DENV2 NS5      KSIQHLTVT- EEIAVQNWLA RVGRERLSRM AISGDDCVVK PLDDRFASAL TALNDMGKVR KDIQQWEPSR GWNDWTQVPF
DENV3 NS5      SKTDLENPHL LEKKITQWLE TKGVERLKRM AISGDDCVVK PIDDRFANAL LALNDMGKVR KDIPQWQPSK GWHDWQQVPF
DENV4 NS5      TRDDMHNPKG LKERVEKWLK ECGVDRLKRM AISGDDCVVK PLDERFSTSL LFLNDMGKVR KDIPQWEPSK GWKNWQEVPF

DENV1 NS5      CSHHFHQLIM KDGREIVVPC RNQDELVGRA RVSQGAGWSL RETACLGKSY AQMWQLMYFH RRDLRLAANA ICSAVPVDWV
DENV2 NS5      CSHHFHELIM KDGRVLVVPC RNQDELIGRA RISQGAGWSL RETACLGKSY AQMWSLMYFH RRDLRLAANA ICSAVPSHWV
DENV3 NS5      CSHHFHELIM KDGRKLVVPC RPQDELIGRA RISQGAGWSL KETACLGKAY AQMWALMYFH RRDLRLASNA ICSAVPVHWV
DENV4 NS5      CSHHFHKIFM KDGRSLVVPC RNQDELIGRA RISQGAGWSL RETACLGKAY AQMWSLMYFH RRDLRLASMA ICSAVPTEWF

DENV1 NS5      PTSRTTWSIH AHHQWMTTED MLSVWNRVWI EENPWMEDKT HVSSWEDVPY LGKREDRWCG SLIGLTARAT WATNIQVAIN
DENV2 NS5      PTSRTTWSIH AKHEWMTTED MLTVWNRVWI QENPWMEDKT PVESWEEIPY LGKREDQWCG SLIGLTSRAT WAKNIQTAIN
DENV3 NS5      PTSRTTWSIH AHHQWMTTED MLTVWNRVWI EDNPWMEDKT PVTTWEDVPY LGKREDQWCG SLIGLTSRAT WAQNILTAIQ
DENV4 NS5      PTSRTTWSIH AHHQWMTTED MLKVWNRVWI EDNPNMIDKT PVHSWEDIPY LGKREDLWCG SLIGLSSRAT WAKNIQTAIT

DENV1 NS5      QVRRLIGNEN YLDFMTSMKR FKNESDPEGA LW 899
DENV2 NS5      QVRSLIGNEE YTDYMPSMKR FRKEEEEAGV LW 900
DENV3 NS5      QVRSLIGNEE FLDYMPSMKR FRKEEESEGA IW 900
DENV4 NS5      QVRNLIGKEE YVDYMPVMKR YSAHFESEGV L- 900
```

S7 Fig. Protein sequence alignment of the full-length DENV1-4 NS5 proteins used in this study. The alignment was performed using the MultAlin program (http://multalin.Toulouse.inra.fr/multalin/multalin.html). The high-, low-, and neutral-consensus amino acid residues are depicted in red, blue, and black colors according to the MultAlin program, respectively. The DENV2 RdRp protein (a.a. 251-896) used for the crystallographic analyses and the fragment screening contains G321V and K891R substitutions (the same sequence as in PDB ID: 5K5M [11]).