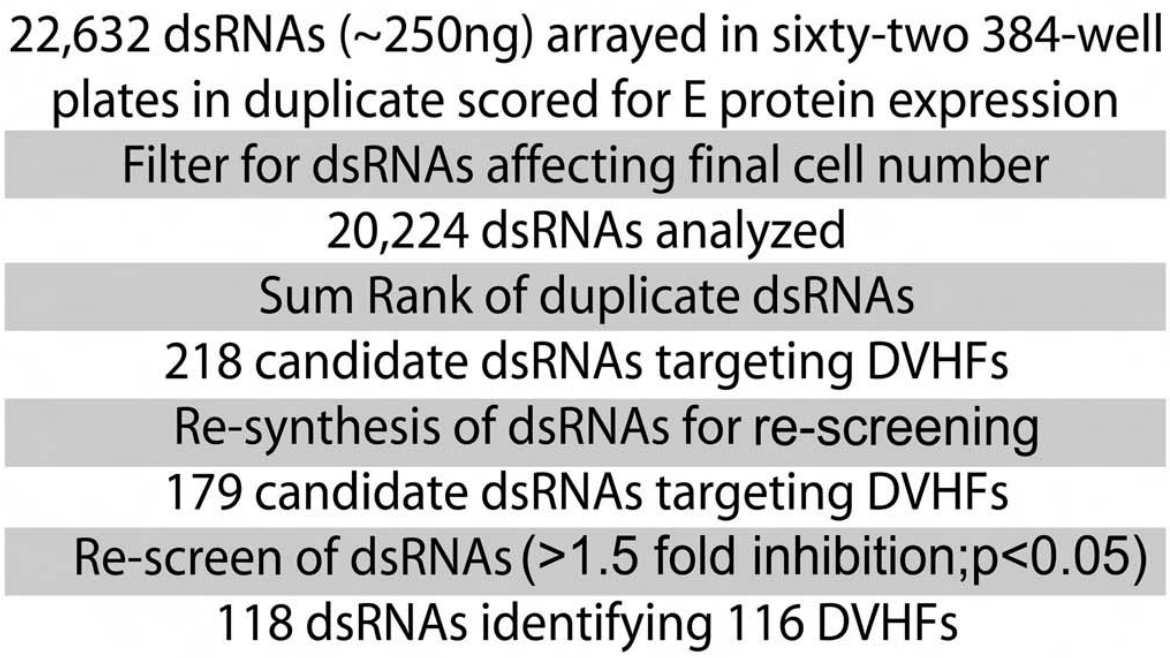
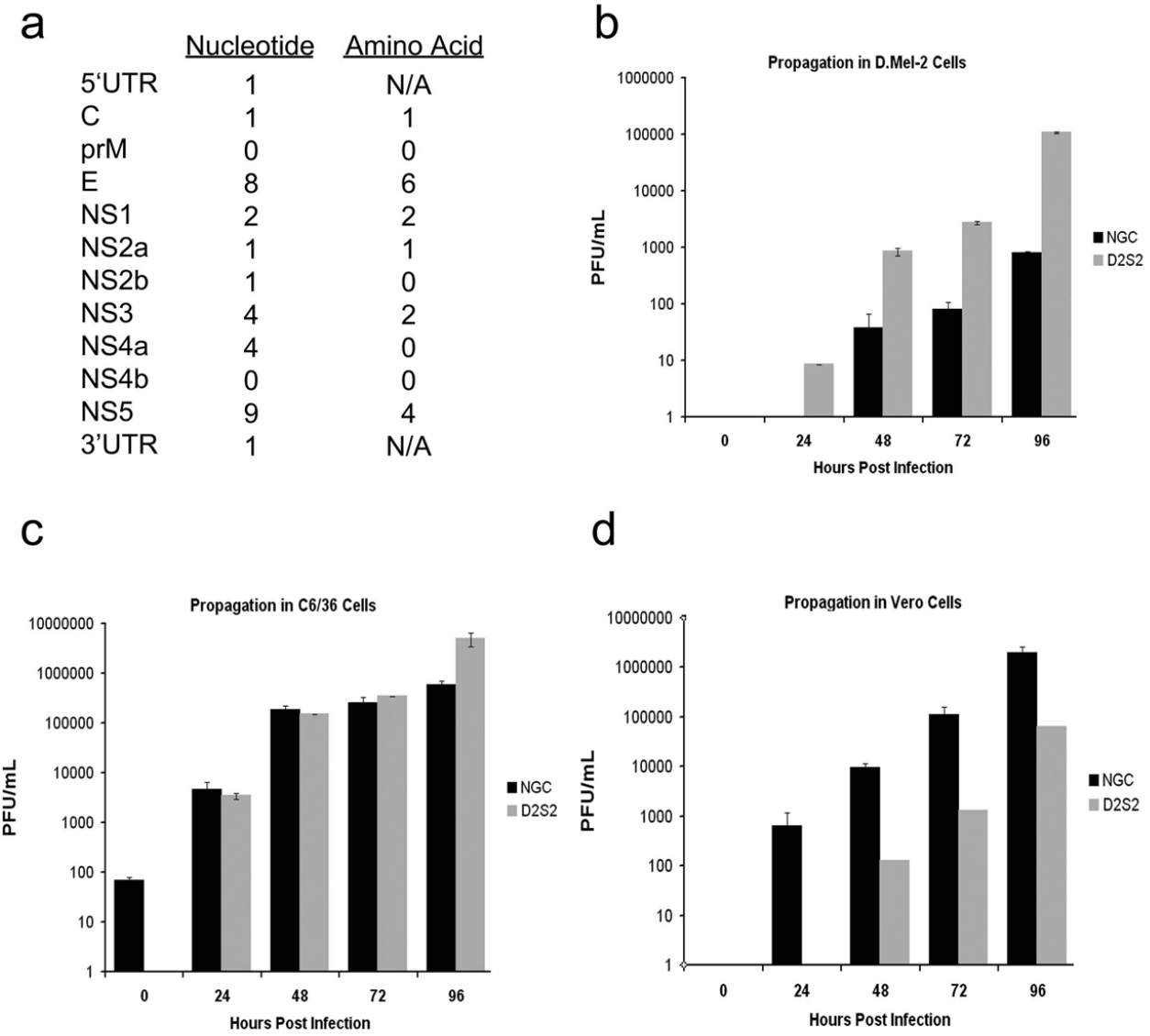
SUPPLEMENTARY INFORMATION



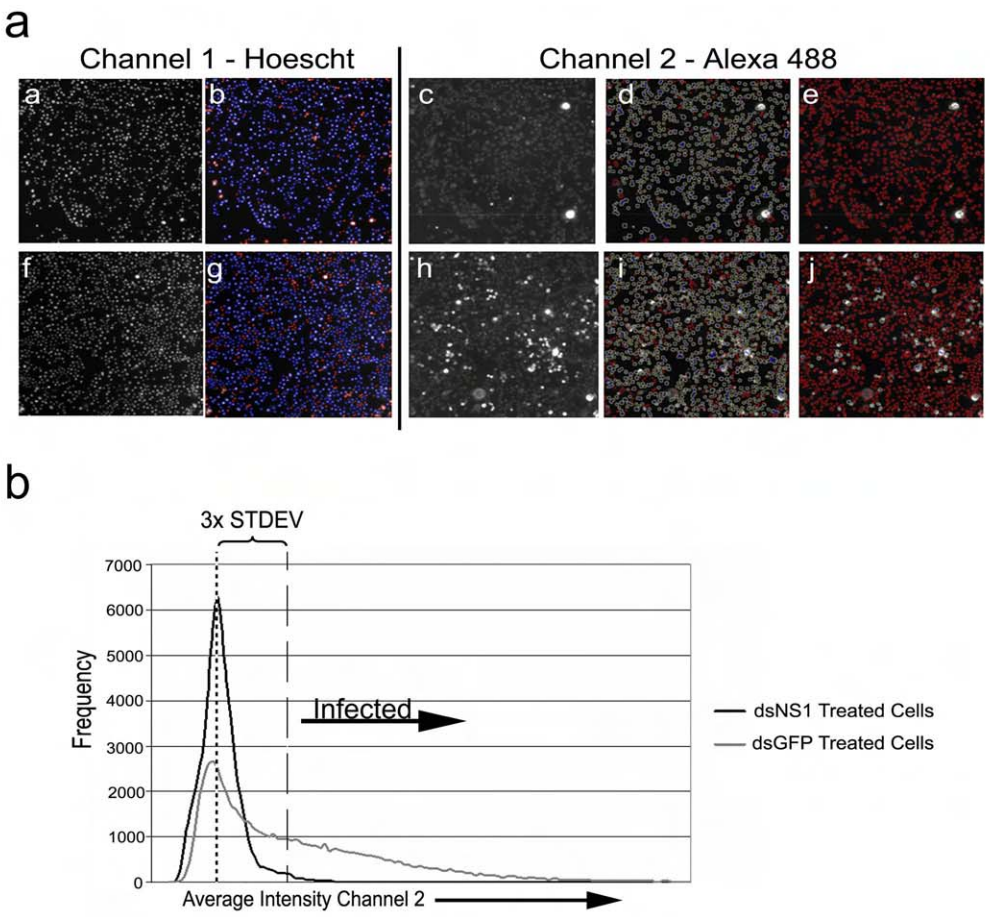
Supplementary Figure 1. Outline of experimental steps taken to identify DVHFs indicating the number of dsRNAs passing through each filter. Prior to duplicate plate comparison, each dsRNA was assayed for its effect on cell proliferation. Wells with less than 12,500 cells in either duplicate were shown to provide unreliable data and removed from further consideration. The remaining wells were then compared to their duplicates for reproducibility and ranked against the rest of the wells on the plate. Only those dsRNAs duplicates with expectation ≤ 0.065 (218) were considered candidates for further investigation. 179 of the 218 candidates were re-synthesized and tested again for reproducibility of the initial observation with the additional criteria that infectivity had to be inhibited by ≥ 1.5 fold with a p-value <0.05. 118 dsRNAs passed these benchmarks identifying 116 unique DVHFs.

a

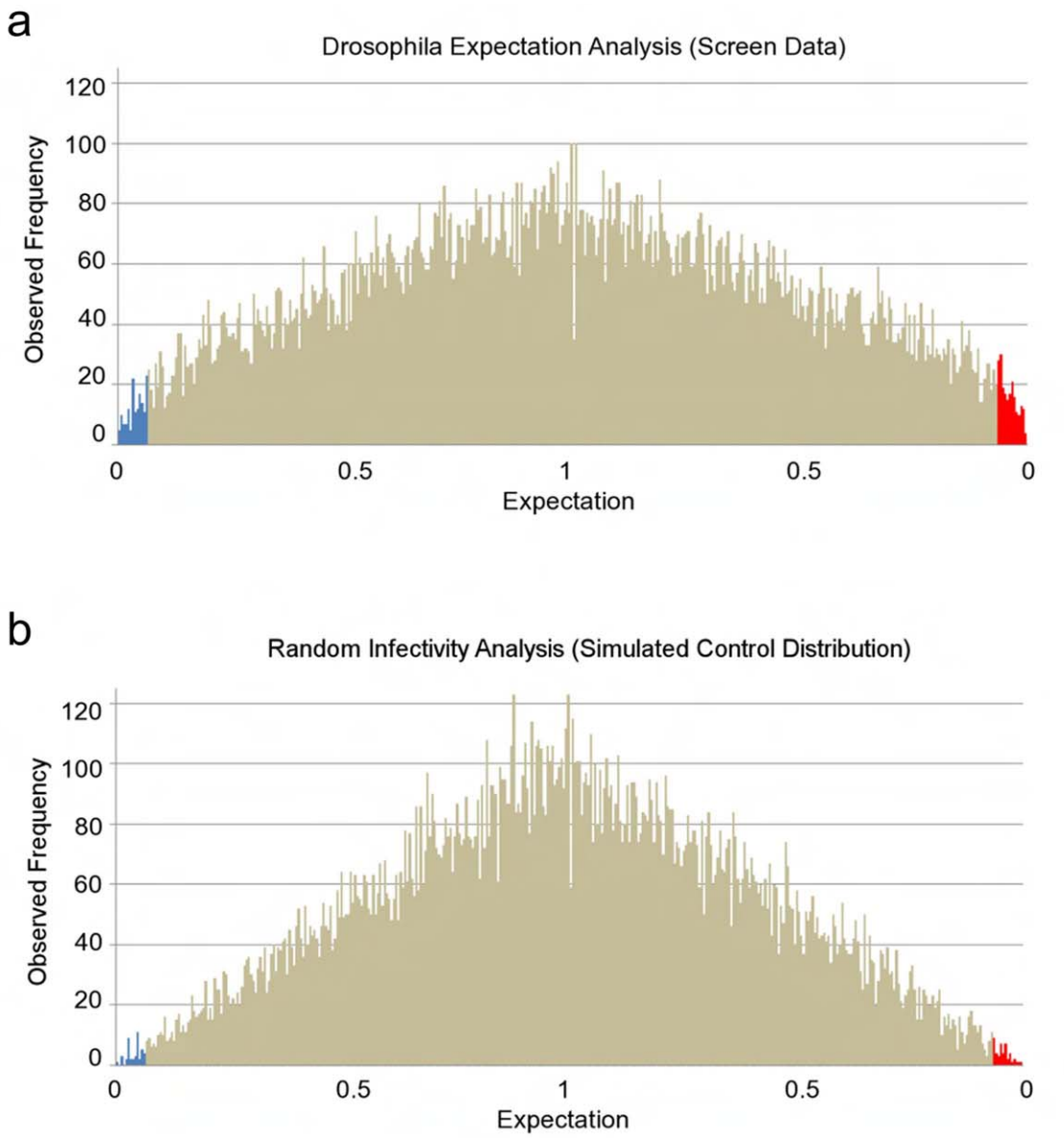
	Nucleotide	Amino Acid
5'UTR	1	N/A
C	1	1
prM	0	0
E	8	6
NS1	2	2
NS2a	1	1
NS2b	1	0
NS3	4	2
NS4a	4	0
NS4b	0	0
NS5	9	4
3'UTR	1	N/A



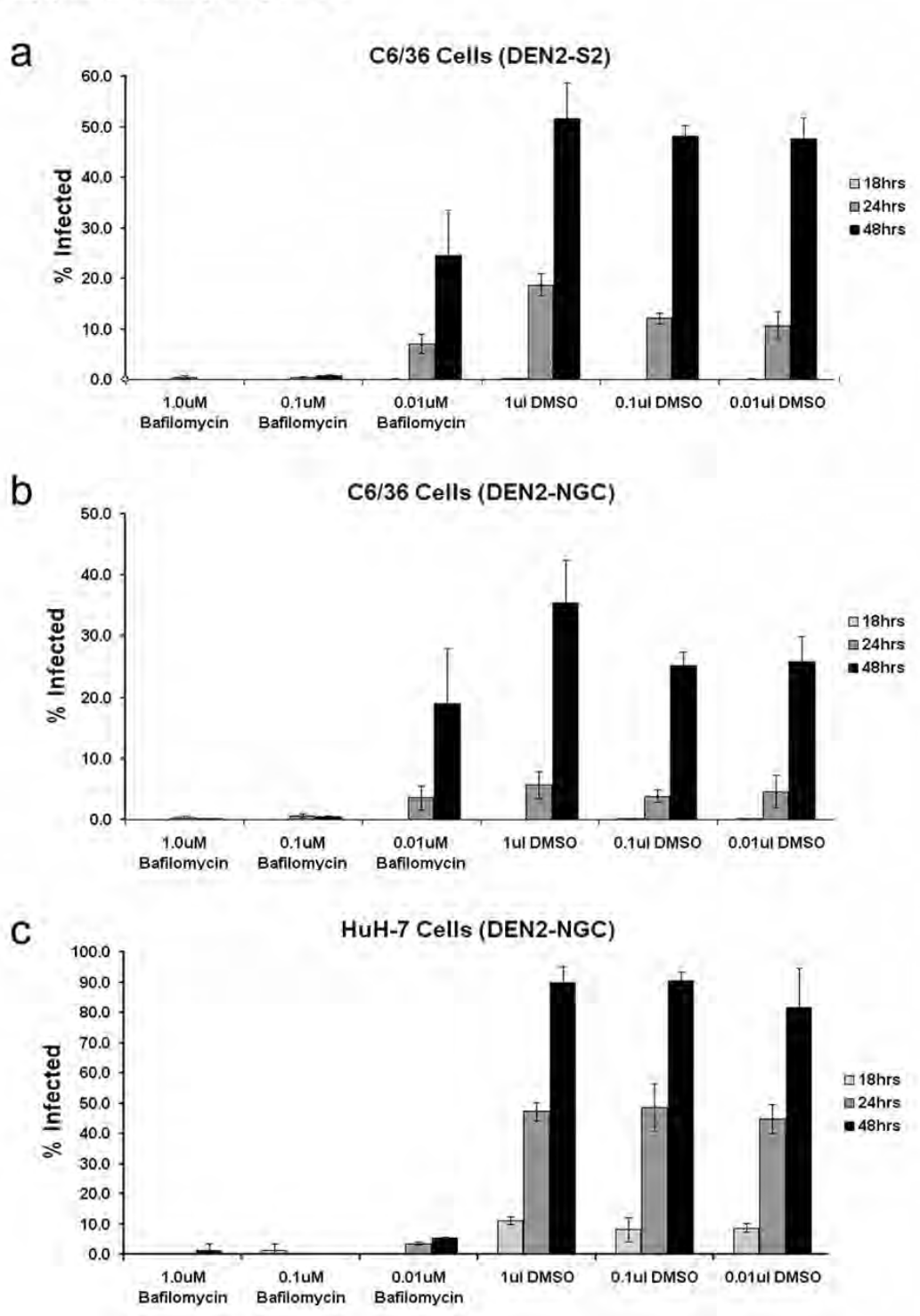
Supplementary Figure 2. Summary of DEN2-S2 mutations and viral propagation curves in *Drosophila*, mosquito and mammalian cell lines. (A) Summary of mutations observed in DEN2-S2 at the nucleotide and amino acid levels compared to the parental DEN2-NGC strain. DEN2-NGC and its D.Mel-2 adapted derivation, DEN2-S2 were tested for their ability to propagate over 96hrs in *Drosophila* D.Mel-2 cells (B), mosquito C6/36 cells (C), and mammalian Vero cells (D) were infected at a MOI of 1 with DEN2-NGC and DEN2-S2. After one hour adsorption at 28 °C (D.Mel-2 and C6/36 cells) or 37 °C (Vero), inoculation was removed, cells were washed once with PBS and growth media was added. Supernatants were collected every 24 hours, serially diluted and added to Vero monolayers for one hour at 37°C followed by addition of a 1:1 tragacanth gum/2x EMEM overlay supplemented with 2% FBS. Cultures were allowed to incubate for 4-5 days at which point they were fixed, permeabilized, stained for DEN E-protein expression. Foci were then counted and averaged. Error bars represent the standard deviation of three independent samples.



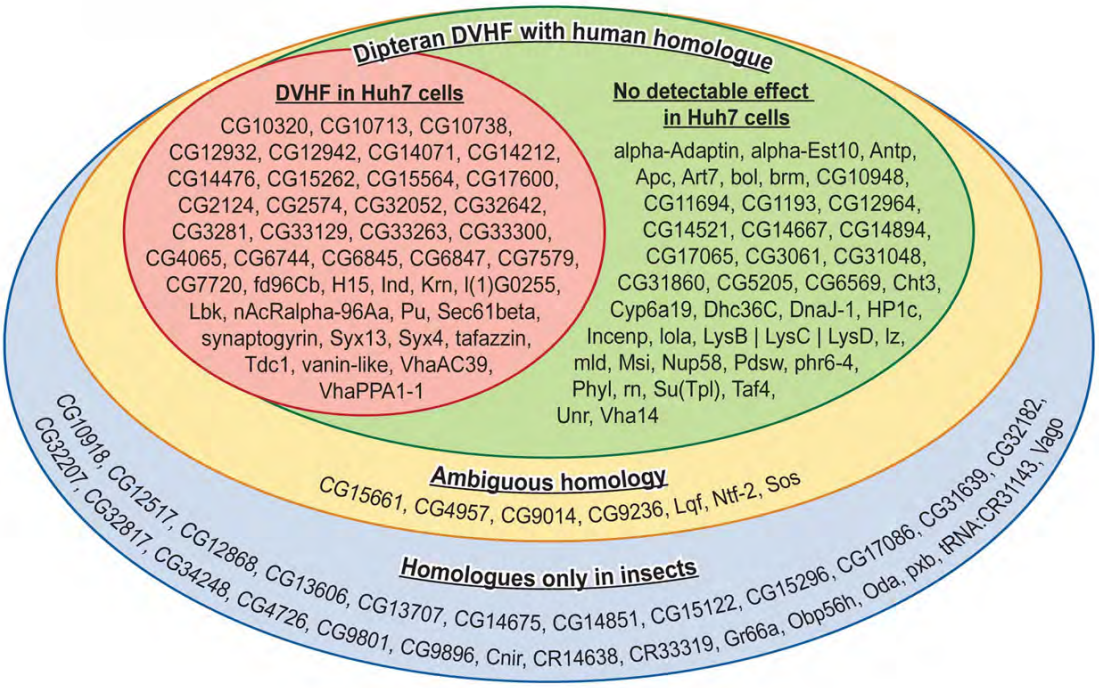
Supplementary Figure 3. Automated determination of DEN2-S2 infectivity. dsRNA treated cells exposed to DEN2-S2 for 72 hours were immunofluorescently labeled and imaged at 20x magnification with a Cellomics ArrayScan. Images were then analyzed with the Cellomics Target Activation software to identify infected cells. Panel A: Images of dsNS1 treated cells (a-e) and dsGFP treated cells (f-j) were taken in two channels: Hoescht 33342 (a, b, f, g) and Alexa-488 (c-e, h-j). Nuclear identification parameters were applied to the raw Hoescht 33342 images (a, f). Nuclei that passed these criteria are marked by a blue boundary and those that failed are marked in red (b, g). The blue boundaries around selected nuclei from the Hoescht 33342 channel were then superimposed onto the raw Alexa-488 images (c, h). A second boundary, extending 2 pixels in all directions beyond the inner blue boundary was applied to each selected object (yellow) (selected object = cells) (d, i) and the mean average intensity was calculated for each selected object. A minimum average intensity in the Alexa-488 channel was then calculated (see Panel B) and applied to each selected object. The selected objects that were above this threshold remain yellow while those that were below become red (e, j). Panel B: A frequency distribution for the average intensities of each object was generated for D.Mel-2 cells treated with either dsNS1 or dsGFP were plotted on a histogram. The mean average intensity from four cultures treated with dsNS1 RNA was calculated and the threshold for determining whether a cell was infected was then defined as being ≥ 3 standard deviations away from this average.



Supplementary Figure 4. Histogram of observed and theoretical distributions of expected Sum Rank values. For each paired well in the screen, a Sum Rank statistic was calculated. The expected frequency of each observed Sum Rank is shown on the horizontal axis, with uncommon extremes in low infectivity to the left and high infectivity to the right. The vertical axis indicates the frequency with which each expectation value was observed during the screen in D.Mel-2 cells (A) and in a computational simulation of random infectivity (B). Sum Ranks expected to occur fewer than 0.065 times per paired duplicate plate are highlighted in blue and red, representing extremes of low and high infectivity, respectively. Wells from the *Drosophila* screen (A) yielded a significantly larger number of wells with extremes of low ($\chi 2 = 62.8$, $p < 0.0001$) and high ($\chi 2 = 108$, $p < 0.0001$) infectivity compared to that expected by wells assigned random infectivity (B), suggesting detectable departures from random biological variation upon treatment of cells with dsRNAs. Using the random infectivity analysis to determine the false discovery rate suggested that roughly 24% of detected "hits" (expectation less than 0.065) were due to random chance alone, in rough agreement with the validation rate of putative hits.



Supplementary Figure 5. The V-ATPase holoenzyme, a DVHF in dipteran and human cells. Serial dilutions of the specific V-ATPase inhibitor, bafilomycin A1, were tested for their efficacy to reduce viral gene expression in mosquito C6/36 (a & b) and human HuH-7 (c) cell lines. DMSO without bafilomycin A1 serves as a vehicle control. Error bars represent standard deviation of three independent observations.



Supplementary Figure 6. Human and dipteran DVHFs. The 116 unique dipteran DVHFs include 27 gene products with homologues found exclusively among insects. The majority of the 116 had readily identifiable human homologues and these are divided here depending on the results of the human screen.

Supplementary Discussion

Candidate DENV restriction factors (DHRFs). The initial screen also detected 296 dsRNAs that significantly enhanced infectivity (Supplementary Figure 4). Whereas these dsRNAs could identify interesting gene products that restrict DENV propagation, we chose not to analyze these further at this time and focus here on the DVHFs described in the text.

Conservation between invertebrate and vertebrate hosts. Sixteen dipteran DVHFs had annotated homologues only among *Drosophila* species and another eleven only among insects (Supplementary Figure 5). These 27 are enriched in genes associated with sensation and response to chemicals, and the transport of ions (FlyMine v12.0) and several belong to families of poorly conserved genes (e.g., gustatory receptors). The DVHFs conserved in dipterans and humans were significantly enriched for genes associated with secretion, membrane docking and vesicle transport. This may not be surprising since delivery of DENV genomes to the cytoplasm and assembly of virions in the ER of both insect and human cells is likely to require these basic processes. One of the more intriguing discoveries was the conserved requirement for DC-STAMP (TM7SF4), which we propose as a candidate for a DENV receptor.

Comparison with other genome-wide screens. We compared the results of our D.Mel-2 screen with previously published dsRNA screens and found significant overlap with two other screens that identified gene products required for MAPK signaling [1] and Ca^{2+} influx [2]. Pathways that mediated Ca^{2+} influx are consistent with the proposed role of Rab5 in viral entry [3]. The only DVHFs identified in a recent screen for factors affecting influenza infection in drosophila cells were lola, Sec61ß and a V-ATPase subunit [4]. See

below for a discussion of the results of a screen for host factors important for *Drosophila* C Virus [5]. If we extended the analysis to drosophila homologues of factors identified in human cells the overlap was still not extensive. The Sec61, the mitochondrial Complex I and V-ATPase subunits, which were identified here as DVHFs, have been previously recognized as HIV dependency factors [6]. When we examined a list of hepatitis C virus factors identified in a targeted siRNA screen [7], we did not find any homologues among our dipteran DVHFs. Surprisingly, comparison of the DVHFs identified in our study with the list of host factors found to affect West Nile virus in a recent study [8] revealed that only Sec61 and V-ATPase were shared between the two studies. These authors identified a longer list of WNV host factors that also affected DENV, suggesting that host factor dependence could vary depending on the experimental details (e.g., cell types and viral construct or strain). It should be pointed out that our screen was carried out with an infectious DENV2.

Ribosomal Components. Surprisingly absent among DVHFs were ribosomal proteins, which were the majority of the hits from a genome-wide screen for factors required for efficient *Drosophila* C Virus propagation [5]. Their absence among DVHFs could be due to an effect on cell number: 65 of the 131 dsRNAs targeting these proteins were removed from analysis due to low cell density. This represented a significant over-representation of dsRNAs targeting ribosomal proteins among those that affected cell density (49.6% for ribosomal proteins vs. 10.3% overall; $\chi^2 = 213.0$, $p = 3 \times 10^{-48}$).

References for the supplementary discussion.

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2 Vig, M. et al., CRACM1 is a plasma membrane protein essential for store-operated Ca2+ entry. *Science* **312** (5777), 1220 (2006).

3 Krishnan, M. N. et al., Rab 5 is required for the cellular entry of dengue and West Nile viruses. *J Virol* **81** (9), 4881 (2007).

4 Hao, L. et al., Drosophila RNAi screen identifies host genes important for influenza virus replication. *Nature* **454** (7206), 890 (2008).

5 Cherry, S. et al., Genome-wide RNAi screen reveals a specific sensitivity of IRES-containing RNA viruses to host translation inhibition. *Genes Dev* **19** (4), 445 (2005).

6 Brass, A. L. et al., Identification of host proteins required for HIV infection through a functional genomic screen. *Science* **319** (5865), 921 (2008); Zhou, H. et al., Genome-Scale RNAi Screen for Host Factors Required for HIV Replication. *Cell Host Microbe* (2008).

7 Randall, G. et al., Cellular cofactors affecting hepatitis C virus infection and replication. *Proc Natl Acad Sci U S A* **104** (31), 12884 (2007).

8 Krishnan, M. N. et al., RNA interference screen for human genes associated with West Nile virus infection. *Nature* **455** (7210), 242 (2008).

Methods

Cell Culture

Aedes albopictus C6/36 cells (ATCC# CRL-1660) and D. Mel-2 (Invitrogen Cat#10831014) were cultured at 28°C, 5% CO2. C6/36 cells were grown in MEM (Sigma) supplemented with antibiotic, non-essential amino acids, sodium pyruvate, 5mM HEPES and 10% FBS (Hyclone). D.Mel-2 cells were grown in SF900 II SFM (Gibco) supplemented with antibiotic. Human hepatoma HuH-7 cells and African green monkey kidney Vero cells (ATCC#CCL-81) were grown at 37°C, 5% CO2 in DMEM (Sigma) supplemented with 10% FBS (Hyclone) and antibiotic. Cells were maintained in accordance with general cell culture practices.

Viral Stock Preparations

Dengue Viruses

C6/36 cells were passaged into T150 flasks at $1x10^6$ cells/mL. The following day, cultures were inoculated with 500µL of virus in 4.5mL serum-free growth media. After 1 hour incubation period with rocking, 15mLs of growth media supplemented with 2% FBS (Hyclone) and 5mM HEPES was added. 48 hours post-inoculation, supernatants were removed and replaced with fresh 2% growth media. 72 hours later, supernatants were collected, cleared of cellular debris by centrifugation, aliquoted and stored at -80°C. Yellow Fever 17D Vero cells were passaged into T150 flasks at $1x10^5$ cells/mL. The following day, cultures were inoculated with 500µL of virus in 4.5mL serum-free growth media. After 1 hour incubation period with rocking, 15mLs of growth media supplemented with 2% FBS (Hyclone) and 5mM HEPES was added. 48 hours post-inoculation, supernatants were removed and replaced with fresh 2% growth media. 72 hours later, supernatants were collected, cleared of cellular debris by centrifugation, aliquoted

and stored at -80°C.

Coxackie B3 (Strain 20)

HeLa (R19) cells were passaged into T150 flasks at $1x10^5$ cells/mL. The following day, cultures were inoculated with 500µL of virus in 4.5mL serum-free growth media. After 1 hour incubation period with rocking, 15mLs of growth media supplemented with 2% FBS (Hyclone) was added. 48 hours later, supernatants were collected, cleared of cellular debris by centrifugation, aliquoted and stored at -80°C.

Plaque Assays

Vero cells were plated onto 24 well plates at a density of $1x10^5$ cells/well. The next day, media was aspirated and 100µL of serial dilutions of viral supernatant was added to the Vero monolayers for 1hr at 37°C with rocking every 15min. Following adsorption, 0.5mLs of a 1:1 Tragacanth Gum (Sigma)/2x EMEM (CellTech) overlay solution supplemented with 2% FBS (Hyclone) was added to each well and the plates were allowed to incubate for 4-5 days. At the end of this period, overlay was removed and the cells were fixed with fresh 4% paraformaldehyde (Sigma) for 15min at room temperature (RT). The supernatant was then removed and 0.5% Triton X-100 (Sigma) in PBS was added for 15min at RT. Cells were then incubated in block solution (PBS supplemented with 0.1% Tween-20 and 1% Normal Donkey Serum) for 1 hour at RT. Primary antibody targeting the dengue envelope protein (4G2) diluted 1:2000 in block solution was then added for 1 hour followed by three washes with PBS supplemented with 0.1% Tween. HRP-conjugated anti-mouse secondary (Amersham) diluted 1:2000 in block solution was then added to the cells for 1hr at RT followed by three washes with PBS supplemented with 0.1% Tween. Viral foci were then stained with 0.5mLs of VIP

Substrate (Vector Labs) in PBS at RT according to manufacturer's protocol. Once stained, substrate was removed and the monolayers allowed to air dry prior to counting of triplicate samples.

Adaptation of DEN2-NGC to Drosophila

In order to take advantage of resources available in *Drosophila melanogaster*, we infected *D. melanogaster* D.Mel-2 cells, a sub-clone of S2 cells, with DEN1-WestPac74, DEN2-NGC, DEN2-16681, DEN3-CH5349, or DEN4-TVP360 (all kindly provided by Dr. A. de Silva UNC-Chapel Hill). Only DEN2-NGC gave significant levels of E protein expression and credible evidence of viral propagation, albeit at very low levels. DEN2NGC was adapted by serial passage in D.Mel-2 cells resulting in the viral stock DEN2S2. Passaged virus was then amplified in C6/36 three times to produce a single viral stock for all D2S2 experiments described in the text.DEN2-S2 propagated in D.Mel-2 cells 10-100 times better than DEN2-NGC (Supplementary Fig. 2a). While its ability to productively infect *A. albopictus* C6/36 cells was equivalent to that of DEN2-NGC, DEN2-S2 was attenuated in Vero cells (Supplementary Fig. 2b, c). Sequence analysis indicates that DEN2-S2 is 99.6% identical to the parental strain at the nucleotide level (DEN2-S2 sequence available upon request).

RNAi based screening

Screening in dipteran cells was performed using the *Drosophila* RNAi Screening Center (DRSC, Harvard Medical School) Genome-wide RNAi Library (DRSC 2.0) in 384-well plate format. The DRSC 2.0 library consists of 22,632 dsRNAs aliquoted into 62 384well plates. Library was screened in duplicate. Library plates, pre-aliquoted with dsRNAs, were thawed at

room temperature followed by centrifugation at 180xg in a Beckman GS-6R centrifuge for 2min at 20°C. 100ng of control dsNS1 (targeting the DEN2-S2 genome) in 5μL dH2O was added to 4 wells per plate. *Drosophila* D.Mel-2 cells, a subclone of S2 cells, (Invitrogen #10831-014) were plated at an initial density of 7000 per well in 40μL Sf-900 II SFM (Gibco#10902) using a Matrix Wellmate automated cell dispenser (Matrix). After 48 hours incubation at 28°C, the cells were infected with 10μL of Dengue-S2 virus (4,780IFU). After 72 hours incubation at 28°C, the cells were processed for immunofluorescence as described below. Screening in HuH-7 human cells was performed in 384-well format using siRNAs obtained from Qiagen. 1μmol of each siRNA was aliquoted into the assay plate in 5μL of water. 9.95μL of OPTI-MEM I (Gibco #11058) media was complexed with 0.05μL of Lipofectamine RNAiMAX (Invitrogen#13778-150) per well and incubated for 30 minutes before addition to siRNA containing well. 1500 HuH-7 cells were then plated into each of the assay wells in 50μL DMEM (Gibco #11995) supplemented with 5% FBS (Gibco#16140) and Pen/strep (Gibco#15140) to yield a total volume of 65μL and an effective siRNA concentration of 15.4nM. After 48 hrs incubation at 37°C, cells were infected with DEN2-NGC at an MOI ~ 1.4ifu/cell and incubated an additional 48 hrs before fixation and processing for immunofluorescence as described below. Similarly, HuH-7 cells were incubated 72 hours post-siRNA transfection followed by 24 hour yellow fever virus 17D infection at an MOI of ~6.5 ifu/cell or 6 hour Coxsackievirus B3 strain 20 infection at an MOI of ~ 40.9 ifu/cell.

Mosquito rearing and cell line culture

Rockefeller/UGAL strain *Aedes aegypti* mosquitoes were maintained in the insectary facility at 27°C and 80% humidity with a 12-12 hour photoperiod. After egg hatching, larvae were maintained in plastic containers with distilled water and fed with pulverized fish food. Pupae were collected and transferred to cages provided with 10% sucrose, where adults stayed after emersion. The *Ae. albopictus* C6/36 cell line was maintained in 25cm^2 culture flasks kept inside an incubator at 32°C with 5% CO_2. The medium utilized to grow the cells was composed by minimal essential medium (MEM), 10% heat inactivated FBS, 1% L-glutamine, and 1% non-essential amino acids.

DENV-2 infection of mosquitoes

DENV-2 from the New Guinea C strain was propagated in C6/36 cells following standard procedures[1]. For this, C6/36 cells were grown in 75-cm2 flasks until they reached 80 % of confluence. Following, the cells were infected with virus with a multiplicity of infection (MOI) of 3.5 virus particles/cell. Infected cells were incubated for 7 days at 32°C with 5% CO2, after which they were harvested with a cell scraper and lysed by repeated freezing and thawing in dry CO_2 and a 32°C water bath to release the viral particles. The virus suspension was then mixed with equal amount of commercial human blood and 10% human serum, kept at 32°C for 30 min and immediately used to feed double-stranded RNA injected female *A. aegypti* (http://www.jove.com/index/Details.stp?ID=220). All procedures involving DENV-2 infections were carried out in a Biological Safety Level 2 laboratory.

Mosquito gene-silencing assays

RNA interference (RNAi)-mediated gene-silencing assays were carried out according to standard methodology[2]. For this, approximately 69 ηl of a dsRNA suspension (3 μg/μl in water) were injected into the thorax of cold-anesthetized 3- to 4-day-old female mosquitoes using a nano-injector as previously described (http://www.jove.com/index/Details.stp?ID=230). Double-stranded RNA injected females were kept in small cups provided with 10% sucrose in the insectary at the conditions mentioned above. Three days after injection, mosquitoes were fed on a DENV-2-supplemented blood meal. For virus titer measurement, mosquitoes were briefly collected and washed in 70% ethanol, and then rinsed in sterile distilled water, at 7 days after blood meal. Mosquito dissections were done in sterile PBS under a stereo microscope, and the midguts were transferred to microcentrifuge tubes containing 150 μl of MEM. The tissues were then homogenized with a pellet pestle in a sterile environment. Six independent biological replicate assays were produced for each tested gene.

qPCR analysis of viral RNA

Total RNA from infected cells was isolated using Trizol (Invitrogen). cDNA was generated using random hexamers to prime reverse transcription reactions using MMLV reverse transcriptase (Invitrogen). cDNAs were then diluted 1:10 with nuclease-free water. RTqPCR was performed with the cDNA using the iQ™ SYBR Green Supermix Kit (Bio-Rad) according to the manufacturer's instructions. Reactions were run on a MyiQ™ iCycler (Bio-Rad) and analyzed with the MyiQ™ Optical System Software (Bio-Rad). qPCR conditions were an initial 95°C for 5 min., followed by 40 cycles of 95°C for 15sec. and 60°C for 30sec. Primers are: DV2C_FWD 5'-AATATGCTGAAACGCGAGAGA-3' DV2C-REV 5'-

GGGATTGTTAGGAAACGAAGG-3' GAPDH_FWD 5'-GAGTCAACGGATTTGGTCGT-3' GAPDH-REV 5'-TTGATTTTGGAGGGATCTCG-3' Standard curves for copy number determination were generated using DENV2-NGC and GAPDH containing plasmid DNA. For each sample the DENV2 RNA copy number was normalized to the GAPDH RNA copy number.

Immunofluorescence

Cells were fixed with fresh 4% paraformaldehyde (Sigma) for 15min at RT. The supernatant was then removed and 0.5% Triton X-100 (Sigma) in PBS was added for 15min at RT. Cells were then incubated in block solution (PBS supplemented with 0.1% Tween-20 and 1% Normal Donkey Serum) for 1 hour at RT. Primary antibody targeting the dengue envelope protein (4G2) diluted 1:2000 in block solution was then added for 1 hour followed by washes with PBS supplemented with 0.1% Tween. Alexa-488 conjugated, anti-mouse secondary antibody (Invitrogen#A11017)) diluted 1:2000 in block solution supplemented with 13.3µg/ml of Hoescht 33342 (Sigma) was then added for 1 hour followed by three PBS/0.1%Tween wash steps. Wells were then filled with PBS, sealed and imaged on the Cellomics ArrayScan Vti HCS. Immunofluorescent staining for yellow fever virus 17D was performed exactly the same as above. Immunofluorescent staining for Coxsackievirus B3 strain 20 was similar to above except the primary antibody was Dako Monoclonal Mouse Anti-Enterovirus Code M7064. The 110mg/L stock was diluted 1:200 in blocking solution.

High-content cell based imaging

Screening plates were imaged and analyzed using a Cellomics ArrayScan Vti HCS automated fluorescent imaging system (ThermoFisher). DMel-2 cell images were acquired at 20x

magnification. HuH-7 cells were acquired at 10x magnification. Infected DMel-2 cells were defined in one of two ways, using the reference wells (RF; wells with a dsRNA targeting the DEN2-S2 NS1 genomic region), or a filter we named the daily filter (DF). RF identification defined infected cells as those cells which displayed an average fluorescent intensity that was three standard deviations higher than the mean of the average fluorescent intensity of the dsNS1 treated cell population in the reference wells within the same plate (Figure S2). DF identification involved manually defining the threshold fluorescent intensity of an infected cell from the wells treated with a dsRNA targeting GFP on a plate by plate basis. Only cells that were unambiguously above background levels of staining were selected. Once the threshold was determined, it was then checked against the dsNS1 treated wells in the same plate to ensure no background level staining remained in the selected population. The DF was more stringent than the RF method.

Sum Rank Algorithm

During analysis of the D. Mel-2 screen, we observed that infectivity rates 1) were not normally distributed within each plate and 2) varied substantially in magnitude between plates (data not shown). Parametric tests based on the assumption of normality or drawing from similar distributions, such as t-tests or z-scores, were therefore considered inappropriate. We developed a nonparametric approach, the Sum Rank algorithm, in order to produce an appropriate summary statistic of each dsRNA tested in duplicate using two separate 384 well plates. Preliminary analyses also suggested that low cell density (valid object counts as determined by counting nuclei stained with Hoechst) could affect percent infectivity data (data not shown). Therefore dsRNA wells with fewer than 12500 cells/well were removed from the Sum Rank analysis, along with the 16 control wells present on every plate, to prevent bias

within the screen. Within each plate, wells were ranked by the percentage of infected cells, with the well with the lowest percentage infected cells given rank = 1. For each dsRNA, tested in duplicate, we calculated a Sum Rank statistic (eq 1).

Sum Rank = Rank on plate #1 + Rank on plate #2 (eq 1)

The null distribution for the Sum Rank statistic was mathematically derived, validated through Monte Carlo simulations in R, and experimentally confirmed during the screen (Supplementary Fig. 4). The null hypothesis of the Sum Rank test is that infectivity rank within a plate is randomly distributed, or equivalently that all wells are equally infectable. This assumption can be invalid if there are local biases in infectivity within a plate, for example if edges are infected more than center wells. Such effects are present in most genomic screens, including our assay. As a result we may have false positive or false negative rates higher than would be predicted by theory alone. We have not yet assessed the magnitude or implication of such spatial biases within duplicate plates, but believe it is important to acknowledge that such effects are common in genome-wide screens and should be discussed openly to promote improvement of future screens. Spatial biases can be expected to affect any statistical analyses and not just the Sum Rank method. In brief, the Sum Rank score can range from 2 to twice the number of valid wells on a plate (384 – 16 controls = 368 maximum valid wells). Sum Ranks at either extreme are less likely to be observed by random chance. The number of times a given Sum Rank (SR) is expected to occur near the lower extreme (Sum Rank = 2) for a single pair of duplicate plates is given by Equation 2.

E[*SR*]=(*SR* -1) / (# Valid Wells) (eq 2)

The number of times a given Sum Rank is expected to occur near the high extreme (Sum Rank = (2 * Number of Valid Wells)) follows a symmetrical distribution and is given by Equation 3.

E[*SR*] = ((#Valid Wells * 2) – (*SR – 1)*) / (# Valid Wells) (eq 3) Sum Ranks were calculated for every dsRNA in the *Drosophila* genome, with **E[*SR*]** scores below 0.065 used to select potential targets (218 dsRNAs) for further analysis.

References for methods

1. Troyer, J. M. et al. A live attenuated recombinant dengue-4 virus vaccine candidate with restricted capacity for dissemination in mosquitoes and lack of transmission from vaccinees to mosquitoes. Am J Trop Med Hyg 65, 414-9 (2001).
2. Dong, Y. et al. Anopheles gambiae immune responses to human and rodent Plasmodium parasite species. PLoS Pathog 2, e52 (2006).

Supplementary Table 1. Dipteran DVHFs listed by gene name

Gene	CGs	FBGN	DRSC Amplicon	FOLD DECREASE	p Value	19 bp Matches
alpha-Adaptin	CG4260, CG31654	FBgn0015567	DRSC27715	2.3	1.8E-02	0
alpha-Est10	CG1131	FBgn0015569	DRSC12613	2.7	2.3E-04	1
Antp	CG1028	FBgn0000095	DRSC23104	3.2	6.7E-03	11
Apc	CG1451	FBgn0015589	DRSC14114	1.9	4.1E-03	0
Art7	CG9882	FBgn0034817	DRSC26145	2.1	2.4E-03	0
bol	CG4760, CG4727	FBgn0011206	DRSC08964	2.4	1.3E-03	0
brm	CG18438, CG5942	FBgn0000212	DRSC11330	3.0	2.7E-03	1
CG10320	CG10320	FBgn0034645	DRSC04060	5.4	3.3E-04	0
CG10713	CG10713	FBgn0036360	DRSC24532	734.8	4.3E-04	0
CG10738	CG10738	FBgn0036368	DRSC09792	1.7	7.3E-03	2
CG10918	CG10918	FBgn0031178	DRSC24162	1.6	4.2E-02	0
CG10948	CG10948	FBgn0036317	DRSC09806	3.3	6.9E-05	0
CG11694	CG11694	FBgn0037571	DRSC24061	2.0	1.8E-02	0
CG1193	CG1193	FBgn0037375	DRSC25414	4.0	3.8E-03	0
CG12517	CG12517	FBgn0032311	DRSC02173	1.9	2.6E-02	0
CG12868	CG12868	FBgn0033945	DRSC06207	2.1	2.3E-03	1
CG12932	CG12932	FBgn0033419	DRSC06245	1.6	1.7E-02	1
CG12942	CG12942	FBgn0033569	DRSC06253	10.9	1.1E-04	1
CG12964	CG12964	FBgn0034022	DRSC23210	4.9	2.6E-03	1
CG13606	CG13606	FBgn0039161	DRSC14609	22.9	7.2E-07	0
CG13707	CG13707	FBgn0035578	DRSC08316	2.5	5.1E-04	0
CG14071	CG14071	FBgn0032312	DRSC02374	3.2	1.7E-03	0
CG14212	CG14212	FBgn0031045	DRSC19568	3.9	1.6E-04	1
CG14476	CG14476	FBgn0027588	DRSC21036	4.8	3.4E-04	0
CG14521	CG14521	FBgn0039617	DRSC14873	4.6	2.8E-05	0
CG14667	CG14667	FBgn0037317	DRSC12253	1.7	6.8E-03	2
CG14675	CG14675	FBgn0037385	DRSC12261	2.5	4.1E-04	0
CG14851	CG14851	FBgn0038240	DRSC21500	10.7	9.7E-04	1
CG14894	CG14894	FBgn0038428	DRSC26111	3.3	1.3E-03	0
CG15122	CG15122	FBgn0034457	DRSC26227	3.3	3.2E-04	0
CG15262	CG15262	FBgn0028852	DRSC01975	2.6	4.1E-04	0
CG15296	CG15296	FBgn0030215	DRSC26051	3.2	1.5E-03	0
CG15564	CG15564	FBgn0039833	DRSC15102	4.2	3.3E-05	0
CG15661	CG15661	FBgn0034605	DRSC04252	1.7	3.6E-02	2
CG17065	CG17065	FBgn0031099	DRSC20544	128.1	8.1E-05	1
CG17086	CG17086	FBgn0032310	DRSC02566	1.6	2.8E-02	1
CG17600	CG17600, CG17602	FBgn0031195	DRSC20640	4.1	1.0E-04	0
CG18166	CG18166	FBgn0029526	DRSC17271	2.6	1.3E-02	2
CG3176	CG3176	FBgn0029524				
CG32817	CG32817	FBgn0052817				
CG2124	CG2124	FBgn0030217	DRSC18208	3.6	1.5E-04	0
CG2574	CG2574	FBgn0030386	DRSC19862	16.6	1.7E-05	0
CG3061	CG3061	FBgn0038195	DRSC26419	1.8	7.4E-03	0
CG31048	CG31048, CG14530, CG11754	FBgn0051048	DRSC14373	2.0	1.9E-03	3
CG31639	CG31639	FBgn0051639	DRSC00910	2.9	5.4E-04	1
CG31860	CG31860, CG17215	FBgn0051860	DRSC02591	13.6	3.2E-06	0
CG32052	CG32052,	FBgn0044328	DRSC27465	2.1	4.7E-03	0

	CG8163					
CG32182	CG32182	FBgn0052182	DRSC09508	1.9	1.7E-02	3
CG32207 CG33255	CG32207 CG33255	FBgn0052207 FBgn0053255	DRSC09617	2.0	5.5E-03	11
CG32642	CG32642	FBgn0052642	DRSC18959	2.0	4.9E-02	1
CG3281	CG3281	FBgn0037967	DRSC28414	2.0	3.2E-02	0
CG33129 *	CG33129, CG6089, CG6087	FBgn0053129	DRSC02924	2.1	1.0E-02	1
CG33263	CG33263, CG14106	FBgn0053263	DRSC10108	1.5	3.4E-02	0
CG33300	CG33300	FBgn0053300	DRSC01101	7.6	2.3E-05	1
CG34248	CG34248	FBgn0085277	DRSC09426	1.9	7.2E-03	0
CG4065	CG4065	FBgn0034982	DRSC26149	2.0	2.4E-03	0
CG4726	CG4726	FBgn0031307	DRSC00664	3.2	1.2E-04	1
CG4957	CG4957	FBgn0032205	DRSC02793	2.1	2.3E-03	1
CG5205	CG5205	FBgn0038344	DRSC15736	2.9	4.7E-04	0
CG6569	CG6569	FBgn0038909	DRSC16067	1.7	1.6E-02	0
CG6744	CG6744	FBgn0037901	DRSC25938	3.3	1.2E-04	0
CG6845	CG6845	FBgn0035099	DRSC26319	1.8	2.5E-02	0
CG6847	CG6847	FBgn0030884	DRSC20009	9.2	1.2E-05	2
CG7579	CG7579	FBgn0036528	DRSC10885	1.5	2.7E-02	0
CG7720	CG7720	FBgn0038652	DRSC16306	6.2	1.2E-05	0
CG9014	CG9014	FBgn0028847	DRSC01979	5.2	2.1E-05	0
CG9236	CG9236	FBgn0034558	DRSC04535	1.7	1.5E-02	0
CG9801	CG9801	FBgn0037623	DRSC16568	2.3	9.1E-04	0
CG9896	CG9896	FBgn0034808	DRSC04594	1.9	4.1E-03	0
Cht3	CG18140	FBgn0022701	DRSC03766	1.7	3.5E-02	0
cnir	CG17262	FBgn0243513	DRSC26787	3.0	2.5E-03	0
CR14638	CG14638	FBgn0037223	DRSC12224	1.8	4.2E-03	1
CR33319	CG18078	FBgn0053319	DRSC01826	14.6	5.2E-05	2
Cyp6a19	CG10243	FBgn0033979	DRSC07379	4.8	1.8E-04	0
Dhc36C	CG5526	FBgn0013810	DRSC03315	2.5	4.7E-03	0
DnaJ-1	CG10578	FBgn0015657	DRSC11145	2.0	4.0E-03	0
fd96Cb	CG11922	FBgn0004898	DRSC25322	163.3	4.5E-04	0
Gr66a	CG7189	FBgn0035870	DRSC10783	2.0	1.7E-02	0
H15	CG6604	FBgn0016660	DRSC22199	2.0	3.9E-02	28
HP1c	CG6990	FBgn0039019	DRSC28423	2.7	1.1E-02	0
Incenp	CG12165	FBgn0033156	DRSC06116	1.8	3.0E-02	1
ind	CG11551	FBgn0025776	DRSC23095	2.6	1.2E-02	0
Krn	CG32179, CG8056	FBgn0052179	DRSC11202	2.0	2.3E-03	0
l(1)G0255	CG4094	FBgn0028336	DRSC18344	2.2	6.8E-03	1
lbk	CG8434	FBgn0034083	DRSC07178	5.6	4.4E-05	0
lola	CG30013, CG12052, CG18379, CG30014, CG18380, CG18378, CG18376, CG18381, CG30012	FBgn0005630	DRSC05222	17.6	5.8E-06	1
lqf	CG32386, CG8532	FBgn0028582	DRSC11363	2.8	5.4E-04	2
LysB, LysC, LysD	CG1179, CG9111, CG9118	FBgn0004425, FBgn0004426, FBgn0004427	DRSC21249	1.6	2.8E-02	3

lz	CG1689	FBgn0002576	DRSC18790	25.6	3.8E-05	12
mld	CG33343, CG34100, CG9469, CG13620, CG31312	FBgn0083077	DRSC13681	2.7	1.6E-02	26
Msi	CG32178	FBgn0043025	DRSC09507	2.0	9.0E-03	0
nAcRalpha-96Aa	CG5610	FBgn0000036	DRSC13672	2.5	1.5E-02	10
Ntf-2	CG1740	FBgn0031145	DRSC20552	1.5	4.4E-02	1
Nup58	CG7360	FBgn0038722	DRSC27863	6.4	7.3E-03	0
Obp56h	CG13874	FBgn0034475	DRSC06433	2.3	8.8E-04	1
Oda	CG16747	FBgn0014184	DRSC07626	5.3	4.8E-04	1
Pdsw	CG8844	FBgn0021967	DRSC00715	4.3	5.9E-05	0
phr6-4	CG2488	FBgn0016054	DRSC26873	2.5	4.0E-04	0
phyl	CG10108	FBgn0013725	DRSC07663	1.5	2.5E-02	1
Pu	CG9441	FBgn0003162	DRSC04645	1.7	3.4E-02	1
pxb	CG14874, CG33207, CG14873	FBgn0053207	DRSC22225	2.0	3.9E-02	0
rn	CG32466, CG10040, CG14600, CG14603, CG14601	FBgn0003263	DRSC12544	2.1	8.7E-04	35
Sec61beta	CG10130	FBgn0010638	DRSC21512	3.7	5.0E-03	3
Sos	CG7793	FBgn0001965	DRSC03439	2.0	4.7E-03	5
Su(Tpl)	CG32217, CG8037	FBgn0014037	DRSC10954	5.3	1.3E-04	1
synaptogyrin	CG10808	FBgn0033876	DRSC06003	2.2	8.4E-04	0
Syx13	CG11278	FBgn0036341	DRSC09836	1.8	4.8E-03	1
Syx4	CG2715	FBgn0024980	DRSC27586	2.0	5.8E-03	0
Taf4	CG5444	FBgn0010280	DRSC11297	3.2	1.4E-04	1
tafazzin	CG8766	FBgn0026619	DRSC07704	1.5	3.1E-02	0
Tdc1	CG30445, CG3686	FBgn0050445	DRSC04942	2.2	2.2E-03	0
tRNA:CR31143	CR31143	FBgn0051143	DRSC13633	3.5	6.0E-03	13
Unr	CG7015	FBgn0035895	DRSC10761	2.8	3.1E-04	1
Vago	CG2081	FBgn0030262	DRSC26320	2.2	1.4E-03	0
vanin-like	CG3648, CG32754	FBgn0040069	DRSC17440	2.7	1.1E-02	0
Vha14	CG8210	FBgn0010426	DRSC07571	2.6	2.2E-04	0
VhaAC39	CG2934	FBgn0028665	DRSC27608	3.1	7.3E-03	0
VhaPPA1-1 *	CG7007	FBgn0028662	DRSC16170	10.9	4.3E-06	0

Supplementary Table 2. DVHF identified in Huh-7 cells.

HUGO ID	pValue (infectivity) [1]	Fold Change (infectivity)	%Fld Chng/ VO Fld chng [2]	siRNA Sequence
ATP6AP1	8.9E-10	7.7	4.4	CACAGTGACATTCAAGTTCAT
ATP6AP2	1.4E-08	3.8	2.3	GGGAACGAGTTTAGTATATTA
ATP6V0A2	7.0E-05	1.6	0.8	CAGGAAATTAATAGAGCTGAT
ATP6V0A4	1.0E-05	1.8	0.9	CACATTTAACAGGACCAATAA
ATP6V0B	3.8E-10	11.8	2.2	CATGGCAATTGTCATTAGCAA
ATP6V0B	1.8E-05	1.7	0.6	CCCAGCCTCTTTGTAAAGATT
ATP6V0C	1.1E-07	2.6	3.1	CAGCCACAGAATATTATGTAA
ATP6V0C	1.5E-06	2.1	1.9	CTGGATGTTTATTTATAAAGA
ATP6V0D1	5.1E-09	4.3	2.9	CACTTTCATGTTCCTCCCTAA
ATP6V0D1	3.6E-07	2.4	0.5	CCGCGCCTTCATCATCACCAT
ATP6V0E1	4.3E-06	1.9	0.7	AACCCTCTCTTTGGACCGCAA
ATP6V0E2	2.8E-05	1.6	1.3	AAGGGATATGTGAGATCCAAA
ATP6V1B1	1.3E-10	40.6	13.2	CCGGGTCAAGTTTGCCCAGTA
ATP6V1B1	3.3E-10	12.1	7.1	CCCGGCAGTAGCTGCAACCTA
ATP6V1B2	1.5E-10	34.2	15.9	CACGGTTAATGAAGTCTGCTA
ATP6V1B2	1.6E-10	25.5	6.0	CTCGATTACTCAAATCCCTAT
ATP6V1C2	5.6E-08	4.7	1.0	CAGGTATGGACTACCAGTGAA
ATP6V1C2	3.9E-07	2.3	1.7	CTGGAGAGGATGAATACTGTA
ATP6V1D	3.3E-05	2.4	0.7	AAAGAAGATAATAGAGACTAA
ATP6V1G2	1.1E-08	3.8	2.5	CACCACCTGCTCACTGGTCAA
ATP6V1G3	2.0E-08	3.5	2.2	CAGAATAATCTCTCAGATGAA
ATP6V1H	1.7E-10	24.8	7.4	CAGCAGAAGTACGATGATGAA
ATP6V1H	5.4E-09	4.1	3.9	CAAGAGATGCTTCAAACTGAA
BTD	3.8E-03	1.6	1.2	ATGCGATTGGTCTCAAGCTAA
CHRNA2	7.7E-08	3.0	1.7	CAGCCTCTGTTTGACCATGAA
CHRNA2	4.1E-05	1.6	1.0	CACGGGCACCTACAACAGCAA
CNOT2	7.9E-10	8.3	2.2	CCAGGACTTCTCAATACACAA
CNOT2	2.3E-04	1.5	1.1	CTGGAATATGACAAATTAGAA
DCST2	1.4E-09	6.9	3.2	CTGCATGATGGTCATACCACA
DCST2	4.7E-03	1.5	0.6	CCACTTCTCTGTGGATCTCAA
DDC	5.0E-08	3.0	1.1	TCGGCTAAAGGGTTCCAACAA
DDC	1.2E-04	1.6	0.8	CAGGCTTATATCCGCAAGCAT
DIAPH3	1.1E-06	2.1	1.9	AAGAGTGAATATAGCAACTTA
EXDL2	9.4E-08	3.5	1.2	GTGGGTAAATTTGGAAGGCAA
FASTKD5	1.5E-09	6.1	3.1	TACAGATGATTTGATGAATAA
FH	2.0E-08	3.5	2.3	GAGATCTACGATGAACTTTAA
FLJ20254	1.5E-10	37.0	12.2	CACCTGTGACATGGCCTGCAA
FLJ20254	4.6E-10	12.1	8.0	TACAGAAGTCTTTGCAAGAAA
FOXB1	1.3E-04	1.8	1.1	TCGCAAACAGCCACCAGCCAA
GALNT10	3.3E-05	2.2	0.5	CAGGCAATTACTGGCCTCAAA
GANAB	2.4E-08	3.6	3.2	GAGGTGTGGTATGACATTCAA

[1] Infectivity measured as the percentage of cells infected (see Methods)

[2] Ratio of infectivity fold change over cell number fold change.

GCH1	1.5E-05	2.0	1.8	CCCGGTTTCCTTTGTGGTCTA
GSX1	2.8E-09	5.0	1.5	CTCTGTGGACAGCAGCTCTAA
GSX1	4.9E-07	2.2	1.5	CGAGTTCGCTTCTAATATGTA
HRNR	4.7E-08	3.2	1.5	CTGGCTCAGGGTGGTCTTCAA
LRIG3	1.7E-05	1.7	1.5	CAGGAACTTCATCTCAGCCAA
LRIG3	2.7E-04	1.5	1.5	CAGCTGGACCATAACAACCTA
MAK10	1.8E-06	2.2	1.8	CAAGATTAATAGATAGAATAA
MAK10	4.3E-06	2.0	1.5	CAGAAAGGCCGTAGTAGTAAA
MUC2	3.1E-09	4.7	3.4	CCCGCTGGGATTCGAAGTGAA
MUC2	2.5E-04	1.7	0.5	CCGGTTTGGCAACAACACCAA
NDUFB3	5.2E-07	4.1	1.2	CAGATTGAGGATGCACATATA
NPR2	1.1E-08	4.7	1.3	AAGGATGCCCTAGATGAGCTA
NPR2	8.7E-08	3.5	1.6	ACCCAACTGAATGAAGAGCTA
NRG1	6.5E-10	8.9	4.5	TCGGCTGCAGGTTCCAAACTA
PHF2	2.9E-07	3.6	2.1	AAGATGAATCTTCAACTTTAA
PHOSPHO2	2.2E-09	5.3	2.0	AAGGGTGTAAGAGAACATGAA
PNLIPRP1	1.9E-04	1.5	0.3	CCCGATGGGTTTGCTGCATAT
PRG4	7.7E-09	4.2	2.6	AAGGAAGAAATCAATAAATAT
PRG4	3.4E-08	3.0	3.6	CAACATGTAATTATTTAATAA
PRR12	6.8E-10	8.0	3.4	TTCGGTGTACAGAGAAATTAT
PRR12	2.2E-04	1.5	1.1	AACCGTGTCCTCAGGAGCTAA
SEC61B	2.1E-09	6.1	3.8	CCCAACATTTCTTGGACCAAA
SEC61B	9.0E-09	3.8	2.9	AAAGTTGGCCCTGTTCCAGTA
SLC5A12	2.6E-07	2.3	2.1	TGGCTTAATCATGTACTCTCA
SLC5A12	4.8E-06	1.9	0.5	ATGGATCTCGACTACATATAT
SMPDL3B	1.3E-04	1.6	0.8	TGGGCGAATTGTGGTCCTCAA
STX12	3.2E-04	1.8	0.7	TCCCTTAGACATGTACCGGAA
STX4	6.1E-05	1.7	1.1	CAGCTCGGACGAAGAGGACAA
SYNGR1	1.8E-10	23.1	13.8	AGCGTCAAGGACCGCAAGAAA
SYNGR1	2.1E-03	1.5	0.4	CTGGTTCGTGGGATTCTGCTA
TAZ	6.2E-10	9.3	2.8	CCGCCACATCTGGAACCTGAA
TBX20	2.3E-06	3.5	2.0	AAAGGTGAAACTCACCAACAA
TRIP11	8.5E-05	1.6	1.3	ATCAAGCGTTACAAGAGACTA
UBE2E3	3.0E-08	3.8	1.8	CACAATAAACATGCTCCTGAA
ZBTB41	5.5E-10	8.7	1.5	TCCGTCATGATCACCTTACAA
ZBTB41	8.7E-05	1.6	1.1	AAGGCAGATAGTATATATATA
ZNF91	4.5E-04	1.5	0.6	AAGCATTTATATGGTCTTCAA

Supplementary Table 3. Dipteran DVHFs and their human homologues

FBGN	Gene	Function (Flybase)	HUGO	Homo sapien's protein name	E-value
FBgn0015567	alpha-Adaptin	molecular function is described as: protein transporter activity; protein binding. It is involved in the biological processes: synaptic vesicle transport; asymmetric cell division; neurotransmitter secretion; synaptic vesicle coating; vesicle coating; vesicle-mediated transport; intracellular protein transport; protein complex assembly	AP2A2	adaptor-related protein complex 2, alpha 2 subunit	0
FBgn0015569	alpha-Est10	molecular function is described as: carboxylesterase activity; cholinesterase activity. The biological processes in which it is involved are not known.	ACHE	acetylcholinesterase isoform E4-E5 precursor , and others	2.00E-48
FBgn0000095	Antp	molecular function is described as: specific RNA polymerase II transcription factor activity; sequence-specific DNA binding; transcription factor activity. It is involved in the biological processes: specification of segmental identity, antennal segment; midgut development; regulation of transcription from RNA polymerase II promoter; segment specification; heart development; lymph gland development; regulation of transcription, DNA-dependent	HOXB7	homeobox B7	7.00E-35
FBgn0015589	Apc	molecular function is described as: beta-catenin binding; microtubule binding; structural constituent of cytoskeleton. It is involved in the biological processes described with 15 unique terms, many of which group under: anatomical structure development; cell adhesion; regulation of Wnt receptor signaling pathway; organ development; central nervous system development; regulation of biological process; organelle organization and biogenesis; instar larval development; programmed cell death; cell proliferation; cell-cell adhesion; embryonic development via the syncytial blastoderm; cell death; larval chitin-based cuticle development; regulation of signal transduction; microtubule-based process; cell motility; cell communication; gamete generation	APC	adenomatous polyposis coli	5.00E-133
FBgn0034817	Art7	molecular function is described as protein-arginine N-methyltransferase activity. It is involved in the biological process peptidyl-arginine methylation, to asymmetrical-dimethyl arginine	PRMT7	protein arginine methyltransferase 7	1.00E-131
FBgn0011206	bol	molecular function is described as: mRNA binding; nucleotide binding. It is involved in the biological processes: male meiosis; spermatogenesis; meiotic G2/MI transition; spermatocyte division; GO:0006445; positive regulation of meiosis	BOLL	boule isoform 1	5.00E-33
FBgn0000212	brm	molecular function is described as: DNA-dependent ATPase activity; general RNA polymerase II transcription factor activity; transcription coactivator activity; protein binding; DNA helicase activity; nucleic acid binding; ATP binding; DNA binding; helicase activity. It is involved in the biological processes: imaginal disc-derived wing vein specification; chromatin-mediated maintenance of transcription; regulation of transcription from RNA polymerase II promoter; hemocyte proliferation; muscle development; dendrite morphogenesis; neuron development; phagocytosis, engulfment; oogenesis	SMARCA4	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin a4	0
FBgn0034645	CG10320	molecular function is described as: NADH dehydrogenase activity; NADH dehydrogenase (ubiquinone) activity. It is involved in the biological processes: RNA import into nucleus; mitochondrial electron transport, NADH to ubiquinone	NDUFB3	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 3	2.00E-08
FBgn0036360	CG10713	molecular function is unknown. The biological processes in which it is involved are not known	HRNR	hornerin	4.00E-08

Supplementary Table 3. Dipteran DVHFs and their human homologues

FBgn0036368	CG10738	molecular function is described as: guanylate cyclase activity; receptor activity; ATP binding; protein-tyrosine kinase activity. It is involved in the biological processes: signal transduction; cyclic nucleotide metabolic process; nitric oxide mediated signal transduction; protein amino acid phosphorylation; intracellular signaling cascade; cyclic nucleotide biosynthetic process	NPR2	natriuretic peptide receptor B precursor	4.00E-175
FBgn0031178	CG10918	molecular function is unknown. The biological processes in which it is involved are not known		No significant similarity found	
FBgn0036317	CG10948	molecular function is described as: mRNA binding; nucleic acid binding; nucleotide binding. The biological processes in which it is involved are not known	ENOX2	ecto-NOX disulfide-thiol exchanger 2 isoform b	9.00E-80
FBgn0037571	CG11694	molecular function is unknown. The biological processes in which it is involved are not known	EEA1	early endosome antigen 1, 162kD	3.00E-05
FBgn0037375	CG1193	molecular function is described as: ATPase activity; microtubule binding; ATP binding. It is involved in the biological processes: microtubule severing; microtubule-based process; intracellular protein transport	KATNAL1	katanin p60 subunit A-like 1	7.00E-116
FBgn0032311	CG12517	molecular function is unknown. The biological processes in which it is involved are not known.			
FBgn0033945	CG12868	molecular function is unknown. The biological processes in which it is involved are not known		No significant similarity found	
FBgn0033419	CG12932	molecular function is unknown. The biological processes in which it is involved are not known	HRNR	hornerin	2.00E-04
FBgn0033569	CG12942	molecular function is described as: transcription regulator activity; zinc ion binding; nucleic acid binding. It is involved in the biological processes: cell proliferation; nucleobase, nucleoside, nucleotide and nucleic acid metabolic process; regulation of transcription from RNA polymerase II promoter; transcription from RNA polymerase II promoter	ZBTB41	zinc finger and BTB domain containing 41 (NJB Note: lots of ZNF)	7.00E-31
FBgn0034022	CG12964	molecular function is unknown. The biological processes in which it is involved are not known	PAXIP1	PAX interacting protein 1	6.00E-15
FBgn0039161	CG13606	molecular function is unknown. The biological processes in which it is involved are not known		No significant similarity found	
FBgn0035578	CG13707	molecular function is unknown. The biological processes in which it is involved are not known		No significant similarity found	
FBgn0032312	CG14071	molecular function is unknown. The biological processes in which it is involved are not known	TRIP11	thyroid hormone receptor interactor 11	0.003
FBgn0031045	CG14212	molecular function is described as phosphoric monoester hydrolase activity. It is involved in the biological process metabolic process	PHOSPHO2	phosphatase, orphan 2	9.00E-25
FBgn0027588	CG14476	molecular function is described as alpha-glucosidase activity. It is involved in the biological processes: polysaccharide metabolic process; carbohydrate metabolic process	GANAB	alpha glucosidase II alpha subunit isoform 2	0
FBgn0039617	CG14521	molecular function is unknown. It is involved in the biological processes: cell adhesion; cell communication; cell-cell adhesion; signal transduction	HNT	neurotrimin isoform 2 (NJB note: lots of orthologs)	1.00E-26
FBgn0037317	CG14667	molecular function is described as: zinc ion binding; nucleic acid binding. The biological processes in which it is involved are not known	ZNF628	zinc finger protein 628	1.00E-08
FBgn0037385	CG14675	molecular function is described as: oxygen binding; heme binding; iron ion binding. It is involved in the biological process oxygen transport.		No significant similarity found	
FBgn0038240	CG14851	molecular function is unknown. The biological processes in which it is involved are not known		PREDICTED: hypothetical protein LOC729471	3.00E-05
FBgn0038428	CG14894	molecular function is described as binding. It is involved in the biological processes: protein complex assembly; protein folding; protein metabolic process.	TTC1	tetratricopeptide repeat domain 1	2.00E-59
FBgn0034457	CG15122	molecular function is unknown. The biological processes in which it is involved are not known		No significant similarity found	
FBgn0028852	CG15262	molecular function is described as transcription regulator activity. It is involved in the biological process regulation of transcription	CNOT2	CCR4-NOT transcription complex, subunit 2	5.00E-19

Supplementary Table 3. Dipteran DVHFs and their human homologues

FBgn0030215	CG15296	molecular function is unknown. The biological processes in which it is involved are not known		No significant similarity found	
FBgn0039833	CG15564	molecular function is unknown. The biological processes in which it is involved are not known	PRR12	proline rich 12 [	8.00E-05
FBgn0034605	CG15661	molecular function is described as glucuronosyltransferase activity. It is involved in the biological process metabolic process			
FBgn0031099	CG17065	molecular function is described as N-acetylglucosamine-6-phosphate deacetylase activity. It is involved in the biological processes: polysaccharide metabolic process; N-acetylglucosamine metabolic process	AMDHD2	amidohydrolase domain containing 2	4.00E-129
FBgn0032310	CG17086	molecular function is unknown. The biological processes in which it is involved are not known			
FBgn0031195	CG17600	molecular function is unknown. The biological processes in which it is involved are not known	DIAPH3	diaphanous homolog 3 isoform a	1.00E-04
FBgn0030217	CG2124	molecular function is unknown. The biological processes in which it is involved are not known	FASTKD5	FAST kinase domains 5	1.00E-18
FBgn0030386	CG2574	molecular function is described as: ligase activity; ubiquitin-protein ligase activity. It is involved in the biological processes: protein metabolic process; regulation of protein metabolic process; post-translational protein modification.	UBE2E3	ubiquitin-conjugating enzyme E2E 3	1.00E-46
FBgn0038195	CG3061	molecular function is described as: unfolded protein binding; heat shock protein binding. It is involved in the biological processes: defense response; protein folding; protein metabolic process; response to stress	DNAJB12	DnaJ (Hsp40) homolog, subfamily B, member 12	3.00E-81
FBgn0051048	CG31048	molecular function is described as: small GTPase regulator activity; GTP binding; guanyl-nucleotide exchange factor activity; GTPase binding. It is involved in the biological processes: multicellular organismal development; endocytosis; intracellular protein transport; intracellular signaling cascade; mesoderm development; muscle development; phagocytosis; signal transduction	DOCK3	dedicator of cytokinesis 3, 1, 2, 4, 5	0
FBgn0051639	CG31639	molecular function is unknown. The biological processes in which it is involved are not known		No significant similarity found	
CG18166: FBgn0029526, CG32817: FBgn0052817, CG3176: FBgn0029524	CG3176 CG18166 CG32817	| molecular function is unknown. The biological processes in | which it is involved are not known		No significant similarity found	
FBgn0051860	CG31860	molecular function is described as zinc ion transmembrane transporter activity. It is involved in the biological process zinc ion transport.	SLC30A2	solute carrier family 30, member 2 isoform 1	2.00E-83
FBgn0044328	CG32052	molecular function is described as sphingomyelin phosphodiesterase activity. The biological processes in which it is involved are not known	SMPDL3B	acid sphingomyelinase-like phosphodiesterase 3B isoform 1	2.00E-64
FBgn0052182	CG32182	molecular function is unknown. The biological processes in which it is involved are not known		No significant similarity found	
CG33255: FBgn0053255, CR32205: FBgn0052205, CG32207: FBgn0052207	CG32207 CR32205 CG33255	| molecular function is unknown. The biological processes in | which it is involved are not known.		No significant similarity found	
FBgn0052642	CG32642	molecular function is unknown. The biological processes in which it is involved are not known	PRG4	proteoglycan 4	1.00E-15

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FBgn0037967	CG3281	molecular function is described as: transcription regulator activity; DNA binding; zinc ion binding. It is involved in the biological processes: nucleobase, nucleoside, nucleotide and nucleic acid metabolic process; regulation of transcription from RNA polymerase II promoter; transcription from RNA polymerase II promoter; nucleosome assembly	ZNF91	zinc finger protein 91 (NJB note lots of orthologs)	5.00E-41
FBgn0053129	CG33129	molecular function is unknown. The biological processes in which it is involved are not known	FLJ20254	Hypothetical protein FLJ20254	4.00E-33
FBgn0053263	CG33263	molecular function is described as chitin binding. It is involved in the biological process chitin metabolic process	PHF2	PHD finger protein 2	7.00E-04
FBgn0053300	CG33300	molecular function is unknown. The biological processes in which it is involved are not known. One allele is reported. No phenotypic data is available	MUC2	mucin 2 precursor	2.00E-175
FBgn0085277	CG34248				
FBgn0034982	CG4065	molecular function is unknown. The biological processes in which it is involved are not known	MAK10	corneal wound healing-related protein	2.00E-143
FBgn0031307	CG4726	molecular function is described as high affinity inorganic phosphate:sodium symporter activity. It is involved in the biological process transport.			
FBgn0032205	CG4957	molecular function is described as: integrase activity; DNA binding; zinc ion binding. It is involved in the biological process DNA integration			
FBgn0038344	CG5205	molecular function is described as: helicase activity; RNA helicase activity; ATP-dependent helicase activity; ATP binding; nucleic acid binding. It is involved in the biological process nuclear mRNA splicing, via spliceosome	ASCC3	activating signal cointegrator 1 complex subunit 3 isoform a, and PREDICTED: similar to U5 snRNP-specific protein	0
FBgn0038909	CG6569	molecular function is unknown. The biological processes in which it is involved are not known	MYH11	smooth muscle myosin heavy chain 11 isoform SM1B (njb note lots of orthologes)	9.00E-14
FBgn0037901	CG6744	molecular function is described by 3'-5' exonuclease activity; nucleic acid binding. It is involved in the biological process nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	EXDL2	exonuclease 3'-5' domain-like 2	4.00E-94
FBgn0035099	CG6845	molecular function is unknown. The biological processes in which it is involved are not known	DCST2	DC-STAMP domain containing 2	1.00E-43
FBgn0030884	CG6847	molecular function is described as triacylglycerol lipase activity. It is involved in the biological process lipid metabolic process	PNLIPRP1	pancreatic lipase-related protein 1	1.00E-55
FBgn0036528	CG7579	molecular function is described as polypeptide N-acetylgalactosaminyltransferase activity. It is involved in the biological processes: polysaccharide metabolic process; protein amino acid glycosylation; oligosaccharide biosynthetic process	GALNT10	GalNAc transferase 10 isoform a	5.00E-66
FBgn0038652	CG7720	molecular function is described as: sodium:iodide symporter activity; cation transmembrane transporter activity. It is involved in the biological processes: cation transport; coenzyme metabolic process; extracellular transport; prosthetic group metabolic process; transport	SLC5A12	solute carrier family 5 (sodium/glucose cotransporter), member 12	2.00E-79
FBgn0028847	CG9014	molecular function is described as: protein binding; zinc ion binding; hydrolase activity, hydrolyzing O-glycosyl compounds. It is involved in the biological process carbohydrate metabolic process			
FBgn0034558	CG9236	molecular function is described as: calcium-dependent protein serine/threonine phosphatase regulator activity; calcium ion binding. The biological processes in which it is involved are not known			
FBgn0037623	CG9801	molecular function is described as catalytic activity. The biological processes in which it is involved are not known		No significant similarity found	
FBgn0034808	CG9896	molecular function is unknown. The biological processes in which it is involved are not known		No significant similarity found.	

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FBgn0022701	Cht3	molecular function is described as: chitinase activity; hydrolase activity, hydrolyzing N-glycosyl compounds; cation binding; chitin binding. It is involved in the biological processes: cuticle chitin catabolic process; cell-cell signaling; signal transduction	CHIA	chitinase, acidic isoform c & chitotriosidase	2.00E-78
FBgn0243513	cnir	molecular function is unknown. It is involved in the biological processes: vesicle-mediated transport; intracellular signaling cascade.			
FBgn0037223	CR14638	molecular function is unknown. The biological processes in which it is involved are not known			
FBgn0053319	CR33319	molecular function is unknown. The biological processes in which it is involved are not known		RNA only, no protein seq predicited.	
FBgn0033979	Cyp6a19	molecular function is described as: electron carrier activity; oxidoreductase activity; heme binding; iron ion binding; monooxygenase activity. It is involved in the biological processes: steroid metabolic process; electron transport.	CYP3A5	cytochrome P450, family 3, subfamily A, polypeptide 5 (NJB note: several polypeptides)	8.00E-57
FBgn0013810	Dhc36C	molecular function is described as: ATPase activity, coupled; motor activity; microtubule motor activity; structural constituent of cytoskeleton; ATP binding; ATPase activity; glycerol-3-phosphate dehydrogenase activity. It is involved in the biological processes: microtubule-based movement; cell motility; glycerol-3-phosphate metabolic process	DNAH7	dynein, axonemal, heavy chain 7, 3, 10, 17, 11, 9, 5, 8	0
FBgn0015657	DnaJ-1	molecular function is described as: unfolded protein binding; heat shock protein binding. It is involved in the biological processes: response to heat; defense response; protein folding; response to stress	DNAJB4	DnaJ (Hsp40) homolog, subfamily B, member 4	1.00E-101
FBgn0004898	fd96Cb	molecular function is described as: transcription factor activity; sequence-specific DNA binding. It is involved in the biological processes: embryonic development; regulation of transcription from RNA polymerase II promoter; regulation of transcription, DNA-dependent	FOXB1	forkhead box B1	8.00E-48
FBgn0035870	Gr66a	molecular function is described as taste receptor activity. It is involved in the biological processes: sensory perception of taste; response to caffeine		No significant similarity found	
FBgn0016660	H15	molecular function is described as transcription factor activity. It is involved in the biological processes: heart development; cardioblast cell fate commitment; embryonic heart tube development; mesoderm development; regulation of transcription from RNA polymerase II promoter; regulation of transcription, DNA-dependent	TBX20	T-box transcription factor TBX20 isoform A, B	1.00E-83
FBgn0039019	HP1c	molecular function is described as chromatin binding. It is involved in the biological processes: chromatin assembly or disassembly; regulation of transcription from RNA polymerase II promoter	CBX1	chromobox homolog 1 (HP1 beta homolog Drosophila) (Njb note: CBX1,3,5)	2.00E-29
FBgn0033156	Incenp	molecular function is described as: microtubule binding; protein binding. It is involved in the biological processes: histone phosphorylation; metaphase plate congression; protein localization; mitotic spindle organization and biogenesis	INCENP	inner centromere protein antigens 135/155kDa isoform 1, and mucin 17	2.00E-20
FBgn0025776	ind	molecular function is described as: transcription factor activity; sequence-specific DNA binding. It is involved in the biological processes: regulation of transcription; ventral cord development; dorsal/ventral pattern formation; neuroblast fate determination; brain development; ectoderm development; central nervous system development; pattern specification process; regulation of transcription, DNA-dependent.	GSX1	GS homeobox 1	1.00E-22

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FBgn0052179	Krn	molecular function is described as: epidermal growth factor receptor binding; growth factor activity. It is involved in the biological processes: MAPKKK cascade; positive regulation of epidermal growth factor receptor activity; ommatidial rotation; epidermal growth factor receptor signaling pathway; border follicle cell migration.	NRG1	neuregulin 1 isoform ndf43 (njb note: and other isoforms)	6.00E-08
FBgn0028336	l(1)G0255	molecular function is described as fumarate hydratase activity. It is involved in the biological processes: tricarboxylic acid cycle; fumarate metabolic process	FH	fumarate hydratase precursor	0
FBgn0034083	lbk	molecular function is described as protein binding. It is involved in the biological processes: bristle morphogenesis; cell adhesion; transmission of nerve impulse; oogenesis. 4 alleles are reported	LRIG3	leucine-rich repeats and immunoglobulin-like domains 3	5.00E-128
FBgn0005630	lola	molecular function is described as: specific RNA polymerase II transcription factor activity; transcription activator activity; protein binding; RNA polymerase II transcription factor activity; zinc ion binding; nucleic acid binding; motor activity; structural molecule activity. It is involved in the biological processes: axon guidance; axonogenesis; positive regulation of transcription, DNA-dependent; axon midline choice point recognition; antimicrobial humoral response; regulation of transcription from RNA polymerase II promoter; chromatin assembly or disassembly; sex determination; transmission of nerve impulse; ciliary or flagellar motility	KLHL3	kelch-like 3	2.00E-10
FBgn0028582	lqf	molecular function is unknown. It is involved in the biological processes: neurotransmitter secretion; synaptic vesicle endocytosis; endocytosis; negative regulation of cardioblast cell fate specification; regulation of Notch signaling pathway			
LysD: FBgn0004427 LysC: FBgn0004426 LysB: FBgn0004425	LysB | LysC | LysD	molecular function is described as lysozyme activity. It is involved in the biological processes: antimicrobial humoral response; cell wall catabolic process	LYZ	lysozyme precursor	2.00E-22
FBgn0002576	lz	molecular function is described as: RNA polymerase II transcription factor activity; RNA polymerase II transcription factor activity, enhancer binding; transcription factor activity; DNA binding; sequence-specific DNA binding; electron transporter, transferring electrons within the cyclic electron transport pathway of photosynthesis activity; ATP binding. It is involved in the biological processes described with 26 unique terms, many of which group under: anatomical structure development; sensory organ development; hemocyte differentiation; organ development; wound healing; organ morphogenesis; regulation of metabolic process; response to stress; lymph gland hemocyte differentiation; transcription from RNA polymerase II promoter.	RUNX1	runt-related transcription factor 1 isoform b	1.00E-51
FBgn0083077	mld	molecular function is described as: zinc ion binding; nucleic acid binding. It is involved in the biological process ecdysone biosynthetic process	ZNF236	zinc finger protein 236	3.00E-18
FBgn0043025	Msi	molecular function is described as: growth factor activity; deaminase activity. It is involved in the biological processes: spermatid development; purine ribonucleoside monophosphate biosynthetic process.	CECR1	cat eye syndrome critical region protein 1 isoform a precursor	1.00E-62

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FBgn0000036	nAcRalpha-96Aa	molecular function is described as: nicotinic acetylcholine-activated cation-selective channel activity; acetylcholine receptor activity; neurotransmitter receptor activity. It is involved in the biological processes: cation transport; muscle contraction; nerve-nerve synaptic transmission; neuromuscular synaptic transmission; ion transport	CHRNA2	cholinergic receptor, nicotinic, alpha polypeptide 2	2.00E-126
FBgn0031145	Ntf-2	molecular function is described as protein transmembrane transporter activity. It is involved in the biological process protein import into nucleus			
FBgn0038722	Nup58	molecular function is described as nucleocytoplasmic transporter activity. It is involved in the biological process nucleocytoplasmic transport	NUPL1	nucleoporin like 1 isoform a, b, c	5.00E-49
FBgn0034475	Obp56h	molecular function is described as odorant binding. It is involved in the biological processes: sensory perception of chemical stimulus; sensory perception of smell; olfactory behavior; response to pheromone; transport		No significant similarity found	
FBgn0014184	Oda	molecular function is described as ornithine decarboxylase inhibitor activity. It is involved in the biological process cell differentiation			
FBgn0021967	Pdsw	molecular function is described by NADH dehydrogenase (ubiquinone) activity; NADH dehydrogenase activity. It is involved in the biological process mitochondrial electron transport, NADH to ubiquinone	NDUFB10	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 10, 22kDa	3.00E-21
FBgn0016054	phr6-4	molecular function is described as: DNA (6-4) photolyase activity; nucleic acid binding. It is involved in the biological process DNA repair	CRY2	cryptochrome 2 (photolyase-like)	5.00E-155
FBgn0013725	phyl	molecular function is described as: protein binding; zinc ion binding. It is involved in the biological processes: R1/R6 cell fate commitment; R7 cell fate commitment; Ras protein signal transduction; peripheral nervous system development; R7 cell development; sensory organ boundary specification; sensory organ precursor cell fate determination	C5orf5	hypothetical protein LOC51306 isoform 3	0.01
FBgn0003162	Pu	molecular function is described as: GTP cyclohydrolase I activity; GTP cyclohydrolase activity. It is involved in the biological processes: ommochrome biosynthetic process; tetrahydrobiopterin biosynthetic process; purine base metabolic process; aromatic compound biosynthetic process	GCH1	GTP cyclohydrolase 1 isoform 1	9.00E-79
FBgn0053207	pxb	molecular function is unknown. It is involved in the biological processes: smoothened signaling pathway; learning and/or memory; olfactory learning	LOC731133	PREDICTED: hypothetical protein	2.00E-04
FBgn0003263	rn	molecular function is described as: transcription factor activity; zinc ion binding. It is involved in the biological processes: imaginal disc-derived leg morphogenesis; regulation of transcription; cell proliferation; regulation of transcription from RNA polymerase II promoter; compound eye development	ZNF384	nuclear matrix transcription factor 4 isoform b	3.00E-69
FBgn0010638	Sec61beta	molecular function is described as protein transporter activity. It is involved in the biological process SRP-dependent cotranslational protein targeting to membrane, translocation	SEC61B	Sec61 beta subunit	1.00E-30
FBgn0001965	Sos	molecular function is described as: protein binding; Ras guanyl-nucleotide exchange factor activity; DNA binding; Rho guanyl-nucleotide exchange factor activity. It is involved in the biological processes: Ras protein signal transduction; sevenless signaling pathway; actin filament organization; regulation of cell shape; determination of anterior/posterior axis, embryo; torso signaling pathway; nervous system development; nucleosome assembly; regulation of Rho protein signal transduction			

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FBgn0014037	Su(Tpl)	molecular function is described as: transcription elongation regulator activity; RNA polymerase II transcription elongation factor activity. The biological processes in which it is involved are not known	ELL2	elongation factor, RNA polymerase II, 2	1.00E-30
FBgn0033876	synaptogyrin	molecular function is unknown. It is involved in the biological processes: regulation of calcium ion-dependent exocytosis; synaptic vesicle exocytosis	SYNGR1	synaptogyrin 1 isoform 1a , 1b, 2	2.00E-43
FBgn0036341	Syx13	molecular function is described as SNAP receptor activity. It is involved in the biological processes: synaptic vesicle docking during exocytosis; neurotransmitter secretion; vesicle-mediated transport; cytokinesis after meiosis I; cytokinesis after mitosis; female meiosis; male meiosis; mitosis; protein targeting; intracellular protein transport	STX12	syntaxin 12	2.00E-28
FBgn0024980	Syx4	molecular function is described as SNAP receptor activity. It is involved in the biological processes: neurotransmitter secretion; vesicle-mediated transport; synaptic vesicle docking during exocytosis; protein targeting; regulation of exocytosis	STX4	syntaxin 4	1.00E-26
FBgn0010280	Taf4	molecular function is described as: general RNA polymerase II transcription factor activity; transcription initiation factor activity; transcription factor activity. It is involved in the biological processes: regulation of transcription, DNA-dependent; transcription initiation from RNA polymerase II promoter; positive regulation of transcription from RNA polymerase II promoter; muscle development; dendrite morphogenesis	TAF4B	TAF4b RNA polymerase II, TATA box binding protein associated factor (NJB note: and mucin 2 precursor)	4.00E-72
FBgn0026619	tafazzin	molecular function is described as phosphatidylcholine:cardiolipin O-linoleoyltransferase. It is involved in the biological processes: phospholipid metabolic process; cardiolipin biosynthetic process	TAZ	tafazzin isoform 2	1.00E-64
FBgn0050445	Tdc1	molecular function is described as: tyrosine decarboxylase activity; aromatic-L-amino-acid decarboxylase activity; pyridoxal phosphate binding. It is involved in the biological processes: amino acid metabolic process; transmission of nerve impulse; amino acid and derivative metabolic process; carboxylic acid metabolic process	DDC	dopa decarboxylase (aromatic L-amino acid decarboxylase)	2.00E-136
FBgn0051143	tRNA:CR31143	molecular function is unknown. The biological processes in which it is involved are not known			
FBgn0035895	Unr	molecular function is described as: nucleic acid binding; mRNA binding; protein binding; mRNA 3'-UTR binding; DNA binding. It is involved in the biological processes: negative regulation of translation; dosage compensation, by hyperactivation of X chromosome; regulation of transcription, DNA-dependent	CSDE1	upstream of NRAS isoform 1	7.00E-114
FBgn0030262	Vago	molecular function is unknown. The biological processes in which it is involved are not known		No significant similarity found.	
FBgn0040069	vanin-like	molecular function is described as pantetheinase activity. It is involved in the biological processes: cell motility; cell-cell adhesion; coenzyme metabolic process; cytoskeleton organization and biogenesis; prosthetic group metabolic process; signal transduction; vitamin biosynthetic process; nitrogen compound metabolic process	BTD	biotinidase precursor (NJB note: also Vanin 1 - 3)	5.00E-40
FBgn0010426	Vha14	molecular function is described as: hydrogen-exporting ATPase activity, phosphorylative mechanism; hydrogen ion transporting ATPase activity, rotational mechanism; hydrogen ion transporting ATP synthase activity, rotational mechanism. It is involved in the biological processes: proton transport; ATP synthesis coupled proton transport	ATP6V1F	ATPase, H+ transporting, lysosomal 14kD, V1 subunit F (NJB Note: receptor-mediated endocytosis)	7.00E-47

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FBgn0028665	VhaAC39	molecular function is described as: hydrogen-exporting ATPase activity, phosphorylative mechanism; hydrogen ion transporting ATPase activity, rotational mechanism; hydrogen ion transporting ATP synthase activity, rotational mechanism. It is involved in the biological processes: proton transport; ATP synthesis coupled proton transport	ATP6V0D1	ATPase, H+ transporting, lysosomal, V0 subunit d1 1.00E-170
FBgn0028662	VhaPPA1-1	molecular function is described as: hydrogen-exporting ATPase activity, phosphorylative mechanism; hydrogen ion transporting ATPase activity, rotational mechanism; ATP binding; hydrogen ion transporting ATP synthase activity, rotational mechanism. It is involved in the biological processes: cation transport; mitotic spindle organization and biogenesis; ATP synthesis coupled proton transport	ATP6V0B	ATPase, H+ transporting, lysosomal 21kDa, V0 subunit b isoform 1, 2 2.00E-63

Supplementary Table 4. Effect of RNAi-mediated knockdown of human DVHFs on infection by Yellow Fever-17D and Coxsackie-B3 viruses.

Virus / Gene product	DEN2-NGC[i]	YFV-17D[ii]	CB3[iii]
CNOT2	*CNOT2_4* *CNOT2_8*	*CNOT2_4*	*CNOT2_4* *CNOT2_8*
NPR2[iv]	*NPR2_2* *NPR2_5*	*NPR2_5*	*NPR2_5*
SEC61B[v]	*SEC61B_5* *SEC61B_6*	*SEC61B_5*	*SEC61B_5*
EXDL2	*EXDL2_1* *EXDL2_5*[vi]		
FLJ20254[vii]	*FLJ20254_1* *FLJ20254_2* *FLJ20254_3*	*FLJ20254_2* *FLJ20254_3*	*FLJ20254_1* *FLJ20254_2*
TAZ[viii]	*TAZ_2* *TAZ_5*	*TAZ_5*	*TAZ_2* *TAZ_5*

[i] siRNAs listed (in italics) inhibited viral gene expression ≥ 2 fold. Shaded boxes indicate when two or more siRNAs against a gene product resulted in ≥ 2 fold inhibition. DEN2-NGC gene expression was measured by quantifying percentage of cells positive for E protein expression.
[ii] 17D gene expression was measured using the same monoclonal ab to E protein (pan-flavi recognition).
[iii] CB3 gene products were recognized by anti-enterovirus mouse monoclonal 5-D8/1 (DAKO).
[iv] A third siRNA inhibited CB3 but not DEN2-NGC or YFV-17D
[v] Inhibition of DEN2-NGC was weak
[vi] Also named C14orf114_2
[vii] A fourth siRNA inhibited CB3 but not DEN2-NGC or YFV-17D
[viii] TAZ knockdown led to diminished cell counts.