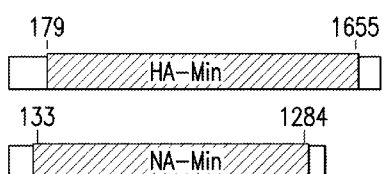




- (51) International Patent Classification:
A61P 31/16 (2006.01) C12N 7/04 (2006.01)
- (21) International Application Number:
PCT/US2014/030027
- (22) International Filing Date:
15 March 2014 (15.03.2014)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
61/794,617 15 March 2013 (15.03.2013) US
- (71) Applicant: THE RESEARCH FOUNDATION FOR
THE STATE UNIVERSITY OF NEW YORK [US/US];
35 State Street, Albany, NY 12207 (US).
- (72) Inventors: MUELLER, Steffen; 7 Gay Drive, Great Neck,
NY 11024 (US). WIMMER, Eckard; 17 Childs Lane,
East Setauket, NY 11733 (US). FUTCHER, Bruce; 47
William Penn Drive, Stony Brook, NY 11790 (US). SKI-
ENA, Steven; 6 Storyland Lane, Setauket, NY 11733
(US). YANG, Chen; 10540 62nd Road, Forest Hills, NY
11375 (US).
- (74) Agents: SOMERVILLE, Deborah, A. et al.; Kenyon &
Kenyon LLP, One Broadway, New York, NY 10004 (US).
- (81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,

[Continued on next page]

(54) Title: ATTENUATED INFLUENZA VIRUSES AND VACCINES



Virus	Mutations/Length (nt)
HA ^{Min}	353/1775
NA ^{Min}	265/1413
(NA+HA) ^{Min}	618/3188

FIG. 1A

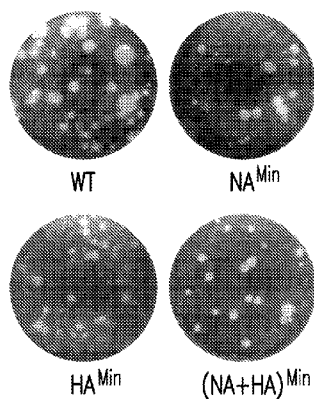


FIG. 1B

(57) Abstract: This invention provides highly attenuated influenza viruses and vaccines. The attenuated viruses and vaccines proliferate well and have high safety factors. The attenuated viruses providing protective immunity from challenge by virus of the same subtype, as well as cross protection against heterologous viruses.



KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

- (84) Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- with sequence listing part of description (Rule 5.2(a))

ATTENUATED INFLUENZA VIRUSES AND VACCINES

FEDERAL FUNDING

[0001] This invention was made with government support under grant numbers AI015122 and AI075219 awarded the National Institutes of Health. The federal government has certain rights in this invention.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0002] This application claims priority to U.S. Application No. 61/794,617, filed March 15, 2013, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0003] This invention provides highly attenuated influenza viruses and vaccines. The attenuated viruses and vaccines proliferate well and have high safety factors. The attenuated viruses providing protective immunity from challenge by virus of the same subtype, as well as cross protection against heterologous viruses.

BACKGROUND OF THE INVENTION

[0004] Influenza is a human disease that leads every year to > 30,000 deaths in the US and several hundred thousand deaths globally (1). Major neutralization antigenic proteins, hemagglutinin (HA) and neuraminidase (NA) on the virion surface, provide protecting immunity, but undergo yearly genetic variation by point mutations (genetic drift). This renders the viruses resistant to population immunity and set the stage for seasonal epidemics. Further, influenza virus may acquire a new antigenic make-up (reassortment of heterologous genes, referred to as genetic shift) leading to pandemics. Because the flu is seasonal and variable, new vaccines must be produced every year. This is made more complex since more than one type or strain of influenza virus co-circulates in any flu season, a phenomenon demanding that more than one new vaccine may have to be developed every year.

[0005] Currently, only two major types of vaccines are licensed, the intramuscularly administered inactivated vaccines ("Flu shot"), and the live attenuated vaccine (LAIV), given intra-nasally ("FluMist®"). The efficacy of the two vaccines is suboptimal. The injectable

inactivated vaccines that requires a large quantity of starting material (the equivalent of approximately 10^{10} plaque-forming units, PFU, per dose), are incapable of inducing significant cell-mediated immunity, which is being recognized as an important determinant of protection (4). Moreover, the overall efficacy of the inactivated vaccine in the U.S. adult population aged 18-65 years is only 59% (5). The LAIV “FluMist,” on the other hand, induces both humoral and cellular immunity but it is restricted in use to people 2 to 49 yr of age (6, 7). Moreover, recurrent administration of LAIV, which always uses the same attenuating viral backbone, could result in tolerance in repeat recipients (8).

[0006] Influenza viruses that have been classified as type A, B, and C, are enveloped, negative-strand RNA viruses of *Orthomyxoviridae* of which subtypes of type A are the major culprit of human disease (3). The viruses transcribe and replicate their multipartite genome in the cell nucleus, each segment encoding one or two polypeptides. Of these the most important antigenic molecules are the glycoproteins hemagglutinin (HA) and neuraminidase (NA).

SUMMARY OF THE INVENTION

[0007] A long-held dogma posits that strong presentation to the immune system of the dominant influenza virus glycoprotein antigens hemagglutinin (HA) and neuraminidase (NA) is paramount for inducing protective immunity against influenza virus infection. It has now been discovered that attenuated viruses in which expression of the two dominant influenza virus glycoprotein antigens, HA and NA, is reduced, are highly effective in providing long lasting protective immunity against lethal wild type challenge and cross protection against diverse subtypes. Further, the viruses have exceptional safety profiles. Accordingly, the invention provides an attenuated influenza virus in which expression of hemagglutinin (HA) and neuraminidase (NA) is reduced. In certain embodiments, HA and NA are the only the only virus proteins having reduced expression. In other embodiments of the invention, the expression of one or more other virus proteins may also be reduced, such as, for example, PA, PB1, PB2, NP, NS, M1, or M2. In certain embodiments, when the expression of a virus proteins other than HA and NA is reduced, the reduction is small compared to the reduction of HA and NA. According to the invention, reduction in expression of virus proteins of the invention is accomplished by changes in protein encoding sequence, for example by lowering the codon pair bias of the protein-encoding sequence, substituting rare codons, modifying G+C content, modifying CG and/or TA (or UA) dinucleotide content, or combinations.

Reduced expression can also be accomplished by modifications to the regulatory sequences of the proteins.

[0008] In one such embodiment, reducing the codon-pair bias comprises identifying a codon pair in the parent protein-encoding sequence having a codon-pair score that can be reduced, and reducing the codon-pair bias by substituting the codon pair with a codon pair that has a lower codon-pair score. In another such embodiment, reducing the codon-pair bias comprises rearranging the codons of a parent protein-encoding sequence. In certain embodiments, the reduced-expression HA protein-encoding sequence and the reduced-expression NA protein-encoding sequence individually have a codon pair bias less than -0.1, or less than -0.2, or less than -0.3, or less than -0.4. Codon pair bias of a protein-encoding sequence (i.e., an open reading frame) is calculated as described in Coleman et al., 2000 (ref. 12) and herein.

[0009] In an embodiment of the invention, expression of one or both of the HA protein-encoding sequence and the NA protein-encoding sequence is reduced by replacing one or more codons with synonymous codons that are less frequent in the host.

[0010] The invention further provides an influenza vaccine composition for inducing a protective immune response in a subject, wherein the vaccine composition comprises virus in which expression of HA is reduced and expression of NA is reduced. In certain embodiments, only expression of HA and NA is reduced. In some embodiments, expression of another virus protein is also reduced.

[0011] The invention also provides a method of eliciting a protective immune response in a subject comprising administering to the subject a prophylactically or therapeutically effective dose of a vaccine composition comprising an attenuated influenza virus, wherein expression of HA is reduced and expression of NA is reduced. In certain embodiments, only expression of HA and NA is reduced. In some embodiments, expression of another virus protein is also reduced. In an embodiment of the invention, an immune response is elicited that is effective against influenza of the same subtype as the attenuated virus of the vaccine. In another embodiment, an immune response is elicited that is effective against a heterologous influenza virus.

[0012] The invention also provides a method of making an attenuated influenza virus genome comprising a) obtaining the nucleotide sequence encoding the hemagglutinin protein of an influenza virus and the nucleotide sequence encoding the neuraminidase protein of an

influenza virus, b) recoding the hemagglutinin-encoding nucleotide sequence to reduce expression and recoding the neuraminidase-encoding nucleotide sequence to reduce expression, and substituting the recoded nucleotide sequences into an influenza virus genome to make an attenuated influenza virus genome. In certain embodiments, only expression of HA and NA is reduced. In some embodiments, expression of another virus protein is also reduced.

DESCRIPTION OF THE FIGURES

[0013] Fig. 1. Construction of variants having reduced codon pair bias and phenotypes in tissue cultures. (A) NA^{Min} and HA^{Min} were designed (leaving 120-200 nt long wt sequences at 5' and 3' ends) and constructed by chemical synthesis. They were then used to replace by reverse genetics (13) one or two corresponding genes of wt PR8. The number of synonymous mutations is shown. (B) Recovered viruses were analyzed for plaque size phenotypes on MDCK monolayers. (C) Growth kinetics of wt PR8 and reduced codon-pair bias variants were analyzed on MDCK cells after infections at an MOI of 0.01. Every three hours post-infection, cell supernatants were collected and analyzed for virus titers by plaque assays. (D) Growth kinetics of wt PR8 and (NA+HA)^{Min} virus in A549 cells. Cells were infected at an MOI of 1.

[0014] Fig 2. Protein expression and mRNA levels in (NA+HA)^{Min}-infected in tissue culture cells. MDCK cells were infected with (NA+HA)^{Min} or wt PR8 at a MOI of 5. (A) Western blot analyses were performed to determine the viral protein expression the infected cells at 3 h and 6 h p.i. (B) Northern blot analyses were performed to determine mRNA levels of HA, NA, PB1 and GAPDH in (NA+HA)^{Min} or wt PR8-infected MDCK cells. At 3, 6, and 9 h p.i., cytoplasmic mRNA were collected and analyzed. For HA^{Min} and HA^{WT} transcript probes, the same 150 nt that recognized the common 3' end of the respective genes was used. Similarly, the probes for NA^{Min} and NA^{WT} have the same 150 nt sequence corresponding to the common 3' end of the NA genes.

[0015] Fig 3. Virus phenotypes in infected mice. (A and B) Measurement of the median lethal dose (LD₅₀). Groups of five male Balb/C mice were intranasally infected with the (NA+HA)^{Min} variant at 10⁴, 10⁵, or 10⁶ PFU and the relative body weight and survival rate were monitored for 14 days p.i. Mice that lost 25% of their body weight were euthanized. LD₅₀ was calculated based on the method of Reed-Muench (24). (C and D) Measurement of the median protective dose (PD₅₀). Groups of five male Balb/C mice were

vaccinated with 10^2 , 10^1 , or 10^0 PFU of (NA+HA)^{Min} on day 0. On day 28 post vaccination, all mice were challenged with 10^5 PFU wt PR8 virus. The relative body weight and survival rate after challenge were monitored. PD₅₀ was calculated based on the method of Reed-Muench (24). (E and F) Safe and effective vaccine range of the (NA+HA)^{Min} (open box) and wt PR8 virus (gray zone) were plotted. Any vaccine dose within this region warranted survival of the animals, and also completely protected them from lethal homogeneous challenge. Error bars represent SD.

[0016] Fig. 4. Virus titers in lungs of infected mice. (A) Groups of three male Balb/C mice were infected with 10^4 PFU of wt PR8 or (NA+HA)^{Min}. On day 1, 3, 5, 7, 9 and 11 p.i., the mice were euthanized and their lungs harvested and homogenized. Viral titers in the homogenates were determined by plaque assays on MDCK cells. * All wt PR8-infected mice were dead on day 5. † The virus titers in (NA+HA)^{Min}-infected mice after day 9 were undetectable (less than 4 PFU). (B) Comparison of virus titers in lungs of three mice each infected with wt PR8 or (NA+HA)^{Min} at a dose from 10^1 to 10^4 PFU. The lungs of the animals were harvest on day 3, and plaque assays were performed to determine virus titers. Error bars represent SD.

[0017] Fig 5. Cross protection against H3N2 virus infections in (NA+HA)^{Min}(H1N1)-vaccinated mice. Groups of five Balb/c mice were vaccinated with (NA+HA)^{Min} at different doses. On day 28 post vaccination, mice were challenged with (A and B) 100 LD₅₀ heterologous viruses A/Aichi/2/1968 (H3N2) virus (= 1.5×10^4 PFU). Survival rate and relative body weights were monitored for 14 days. All mice vaccinated with at least 10^3 PFU of (NA+HA)^{Min} (H1N1) survived the lethal challenge. The cross protection PD₅₀ against H3N2 Aichi virus calculated is 237 PFU. (C and D) Mice vaccinated with (NA+HA)^{Min} virus were also challenged with 100 LD₅₀ A/Victoria/3/75 (H3N2) virus (= 3.2×10^4 PFU). Survival rate and relative body weights were monitored for 14 days. All mice vaccinated with at least 10^3 PFU of (NA+HA)^{Min} (H1N1) survived the lethal challenge. The cross protection PD₅₀ against H3N2 Victoria virus calculated is 147 PFU based on the method of Reed-Muench (24). Error bars represent SD.

[0018] Fig 6. Hemagglutination inhibition (HAI) assay with serum of vaccinated mice. Mice were infected at different doses with PR8 or (NA+HA)^{Min}. Serum was collected on day 28 p.i. and antibody titers were determined by hemagglutination inhibition assays, as described in Material and Methods. Mice were then challenged with 10^5 PFU wt PR8 and survival rates were monitored. Gray labeled dots indicated mice that did not survive.

[0019] Fig. 7. LD₅₀ and PD₅₀ values of NA^{Min} in mice. (A and B) Groups of five male Balb/c mice were infected intranasally with different doses of NA^{Min} variant. The relative body weight and survival rate were monitored for 14 days. The LD₅₀ calculated was 2.4 x 10⁵ PFU. (C and D) Groups of five males were vaccinated with different dose of NA^{Min} variant, 28 days p.i., mice were challenged with 10⁵ PFU wt influenza A/PR/8/34 (PR8). The relative body weight and survival rate were monitored for 14 days. Error bars represent SD.

[0020] Fig. 8. Long term protection of (NA+HA)^{Min}-vaccinated mice. Groups of five Balb/c mice (5-6 weeks) were infected intranasally with (NA+HA)^{Min} at different doses. After seven months, mice were challenged with 10⁵ PFU wt PR8. Their body weight and survival rate were monitored for 14 days. Error bars represent SD.

[0021] Fig. 9. Composition of (NA+HA)^{Min} virus. WT and (NA+HA)^{Min} virus were purified by sucrose gradient. Equivalent amounts of PFUs were compared to determine the relative amounts of the indicated virus proteins. (A) Commassie stain. (B and C) silver stain. (D) Western blot.

[0022] Fig. 10. Expression of virus proteins and mRNAs in MDCK cells infected with WT influenza or (NA+HA)^{Min}. (A) ³⁵S labeled proteins in infected MDCK cells. (B) Northern analysis of viral mRNAs expressed in infected MDCK.

[0023] Fig. 11. Passive immunization with Serum from PR8-(NA+HA)^{Min} vaccinated mice protects naïve mice from homologous WT PR8 challenge. Fig. 11 shows mice passively immunized with PR8-(NA+HA)^{Min} sera survived and remained healthy upon challenge with WT virus.

[0024] Fig. 12. Passive immunization with serum from PR8-(NA+HA)^{Min} (H1N1) vaccinated mice protects naïve mice from heterologous challenge with an H3N2 virus. Fig. 11 shows mice passively immunized with PR8-(NA+HA)^{Min} sera maintained weight (Panel A) and had improved survival (Panel B) when challenged with H3N2 virus.

[0025] Fig. 13. Assessment of cross protection against H3N2 viruses conferred by immunization with PR8-(NA+HA)^{Min}. (A) Inhibition of hemagglutination by sera from PR8-(NA+HA)^{Min} immunized mice. (B) Neutralization of virus infection of MDCK cells by sera from PR8-(NA+HA)^{Min} immunized mice.

[0026] Fig. 14. Growth of WT and PR8-(NA+HA)^{Min} virus in MDCK cells and MDCK cells transfected to express α -2,6-sialyltransferase.

[0027] Fig. 15. T cell responses in lungs of Balb/C mice 7 days post-infection. Cell numbers are expressed as total cell count in lung (left panels) or percentage of CD45⁺ cells (right panels).

[0028] Fig. 16. B cell responses in lungs of Balb/C mice 7 days post-infection. Cell numbers are expressed as total cell count in lung (upper panel) or percentage of CD45⁺ cells (lower panels).

[0029] Fig. 17. T cell responses in spleens of Balb/C mice 7 days post-infection.

[0030] Fig. 18. T cell responses in spleens of Balb/C mice 7 days post-infection.

[0031] Fig. 19. Immune cell infiltration of lung tissue 3 days post-infection. (A) CD45⁺ leukocytes, (B) CD45⁺ Ly6G^{high} polymorphonuclear leukocytes (PMN), (C) CD45⁺CD11c⁺ I-A^{d+} F4/80⁻ dendritic cells, (D) CD45⁺ NKp46⁺ natural killer cells, (E) CD45⁺CD11b⁺Ly6C^{high}Ly6G⁻ inflammatory monocytes, (F) CD45⁺ I-A^{d+} F4/80⁺ macrophages, (G) CD45⁺CD3⁺CD4⁺ T helper cells, (H) CD45⁺ CD19⁺ B cells, and (I) CD45⁺CD19⁺IgM⁺ B cells.

DETAILED DESCRIPTION

[0032] The present invention relates to the production of attenuated influenza viruses that can be used to protect against viral infection and disease. A basic premise in flu vaccination is adequate delivery of HA and NA to vaccine recipients assuming that a very high dose (“Flu shot”) or a dose corresponding to live viral infection (“FluMist”) of these traditionally dominant antigenic polypeptides alone are sufficient for adequate vaccine efficacy. Those expectations aside, the present invention benefits from a contrary approach. The invention provides attenuated influenza viruses in which expression of HA and NA is reduced, which have excellent growth properties useful to vaccine production, yet possess an extraordinary safety profile and enhanced protective characteristics. The attenuated viruses proliferate nearly as well as wild type virus, have highly attenuated phenotypes, as revealed by LD₅₀ values, are unusually effective in providing protective immunity against challenge by influenza virus of the same subtype, and also provide protective immunity against challenge by influenza virus of other subtypes.

[0033] In certain attenuated viruses of the invention, the expression of one or more other virus proteins may also be reduced, such as, for example, PA, PB1, PB2, NP, NS, M1,

or M2. In certain embodiments, when the expression of a virus proteins other than HA and NA is reduced, the reduction is small compared to the reduction of HA and NA.

[0034] In certain attenuated influenza viruses of the invention, expression of hemagglutinin (HA) and neuraminidase (NA) is reduced, and expression of other influenza proteins (i.e., NP, M (including M1 and M2), NS, PA, PB1, and PB2 protein is not substantially changed (i.e., substantially reduced or increased). In an embodiment of the invention, expression of NP, PA, PB1, and PB2 is not substantially reduced. That expression of the NP, M (including M1 and M2), NS, PA, PB1, and PB2 protein encoding sequences is not substantially reduced means that in embodiments where there is a small change in expression of one or more of those proteins (e.g., NP, PA, PB1, PB2, M, and or M), the change in expression of those proteins has little or no effect on attenuation. Little or no effect on attenuation includes one or both of the following: 1) Any reduced expression of NP, M (including M1 and M2), NS, PA, PB1, or PB2 does not reduce viral replication or viral infectivity more than 20% when the NP, M (including M1 and M2), NS, PA, PB1, or PB2 is expressed at the reduced level in a test influenza virus in which only the level of that protein is reduced; 2) The level of expression of NP, M (including M1 and M2), NS, PA, PB1, or PB2 is reduced by less than 20% in the attenuated virus in which expression of HA and NA is reduced.

[0035] In certain embodiments of the invention, the attenuated influenza viruses of the invention comprise a recoded hemagglutinin (HA) nucleic acid and a recoded neuraminidase (NA) nucleic acid. In certain of these embodiments, another virus protein, such as NP, M (including M1 and M2), NS, PA, PB1, or PB2, is recoded. In others of these embodiments, other protein encoding sequences (i.e., NP, M (including M1 and M2), NS, PA, PB1, and PB2 protein encoding sequences are not recoded. That the NP, M (including M1 and M2), NS, PA, PB1, and PB2 protein encoding sequences are not recoded does not exclude mutations and other variations in those sequences, but only means that any mutations or variations made in those sequences have little or no effect on attenuation. Little or no effect on attenuation includes one or both of the following: 1) The mutations or variations in the NP, M (including M1 and M2), NS, PA, PB1, or PB2 sequence do not reduce viral replication or viral infectivity more than 20% when the variant NP, M (including M1 and M2), NS, PA, PB1, or PB2 nucleic acid sequence is the only variant in a test influenza virus; 2) Mutations or variations in any of the NP, M (including M1 and M2), NS, PA, PB1, or PB2 nucleic acid represent fewer than 10% of the nucleotides in that coding sequence.

[0036] The viruses of the invention are highly attenuated. In embodiments of the invention, compared to wild type, the viruses are at least 5,000 fold attenuated, or at least 10,000 fold attenuated, or at least 20,000 fold attenuated, or at least 33,000 fold attenuated, or at least 50,000 fold attenuated, or at least 100,000 fold attenuated in the BALB/c mouse model compared to a wild type virus having proteins of the same sequence but encoded by a different nucleotide sequence.

[0037] The attenuated viruses are also highly protective against wild type virus of the same subtype. In embodiments of the invention, the protective dose (PD_{50}) of the viruses is less than 100 PFU, or less than 50 PFU, or less than 20 PFU, or less than 10 PFU, or less than 5 PFU, when measured by a mouse model, such as exemplified herein.

[0038] The attenuated viruses of the invention also exhibit a large margin of safety (i.e., the difference between LD_{50} and PD_{50}), thus have high safety factors, defined herein as the ratio of LD_{50}/PD_{50} . In certain embodiments of the invention, the safety factor is at least 10^2 , or at least 10^3 , or at least 10^4 , or at least 10^5 , or at least 2×10^5 , or at least 5×10^5 , or at least 10^6 , or at least 2×10^6 , or at least 5×10^6 . In certain embodiments, the safety factor is from 10^2 to 10^3 , or from 10^3 to 10^4 , or from 10^4 to 10^5 , or from 10^5 to 10^6 .

[0039] The attenuated viruses of the invention are also highly protective against heterologous viruses. In certain embodiments of the invention, the protective dose (PD_{50}) of an attenuated virus of the invention is less than 1000 PFU, or less than 500 PFU, or less than 200 PFU, or less than 100 PFU, when measured by a mouse model, such as exemplified herein

[0040] The recoding of HA and NA protein encoding sequences of the attenuated viruses of the invention can have been made utilizing any algorithm or procedure known in the art or newly devised for recoding a protein encoding sequence. According to the invention, nucleotide substitutions are engineered in multiple locations in the HA and NA coding sequences, wherein the substitutions introduce a plurality of synonymous codons into the genome. In certain embodiments, the synonymous codon substitutions alter codon bias, codon pair bias, the density of infrequent codons or infrequently occurring codon pairs, RNA secondary structure, CG and/or TA (or UA) dinucleotide content, C+G content, translation frameshift sites, translation pause sites, the presence or absence microRNA recognition sequences or any combination thereof, in the genome. The codon substitutions may be engineered in multiple locations distributed throughout the HA and NA coding sequences, or

in the multiple locations restricted to a portion of the HA and NA coding sequences. Because of the large number of defects (i.e., nucleotide substitutions) involved, the invention provides a means of producing stably attenuated viruses and live vaccines.

[0041] As discussed further below, in some embodiments, a virus coding sequence is recoded by substituting one or more codon with synonymous codons used less frequently in the influenza host (e.g., humans, birds, pigs). In some embodiments, a virus coding sequence is recoded by substituting one or more codons with synonymous codons used less frequently in the influenza virus. In certain embodiments, the number of codons substituted with synonymous codons is at least 5. In some embodiments, at least 10, or at least 20 codons are substituted with synonymous codons.

[0042] In some embodiments, virus codon pairs are recoded to reduce (i.e., lower the value of) codon-pair bias. In certain embodiments, codon-pair bias is reduced by identifying a codon pair in an HA or NA coding sequence having a codon-pair score that can be reduced and reducing the codon-pair bias by substituting the codon pair with a codon pair that has a lower codon-pair score. In some embodiments, this substitution of codon pairs takes the form of rearranging existing codons of a sequence. In some such embodiments, a subset of codon pairs is substituted by rearranging a subset of synonymous codons. In other embodiments, codon pairs are substituted by maximizing the number of rearranged synonymous codons. It is noted that while rearrangement of codons leads to codon-pair bias that is reduced (made more negative) for the virus coding sequence overall, and the rearrangement results in a decreased CPS at many locations, there may accompanying CPS increases at other locations, but on average, the codon pair scores, and thus the CPB of the modified sequence, is reduced. In some embodiments, recoding of codons or codon-pairs can take into account altering the G+C content of the HA and NA coding sequences. In some embodiments, recoding of codons or codon-pairs can take into account altering the frequency of CG and/or TA dinucleotides in the HA and NA coding sequences.

[0043] In certain embodiments, the recoded (i.e., reduced-expression) HA protein-encoding sequence has a codon pair bias less than -0.1, or less than -0.2, or less than -0.3, or less than -0.4. In certain embodiments, the recoded (i.e., reduced-expression) NA protein-encoding sequence has a codon pair bias less than -0.1, or less than -0.2, or less than -0.3, or less than -0.4. In certain embodiments, the codon pair bias of the recoded HA protein encoding sequence is reduced by at least 0.1, or at least 0.2, or at least 0.3, or at least 0.4, compared to the parent HA protein encoding sequence from which it is derived. In certain

embodiments, the codon pair bias of the recoded NA protein encoding sequence is reduced by at least 0.1, or at least 0.2, or at least 0.3, or at least 0.4, compared to the parent NA protein encoding sequence from which it is derived. In certain embodiments, rearrangement of synonymous codons of the HA protein-encoding sequence provides a codon-pair bias reduction of at least 0.1, or at least 0.2, or at least 0.3, or at least 0.4, parent HA protein encoding sequence from which it is derived. In certain embodiments, rearrangement of synonymous codons of the NA protein-encoding sequence provides a codon-pair bias reduction of at least 0.1, or at least 0.2, or at least 0.3, or at least 0.4, parent NA protein encoding sequence from which it is derived.

[0044] Usually, these substitutions and alterations are made and reduce expression of the encoded virus proteins without altering the amino acid sequence of the encoded protein. In certain embodiments, the invention also includes alterations in the HA and/or NA coding sequences that result in substitution of non-synonymous codons an amino acid substitutions in the encoded protein, which may or may not be conservative.

[0045] Most amino acids are encoded by more than one codon. *See* the genetic code in Table 1. For instance, alanine is encoded by GCU, GCC, GCA, and GCG. Three amino acids (Leu, Ser, and Arg) are encoded by six different codons, while only Trp and Met have unique codons. “Synonymous” codons are codons that encode the same amino acid. Thus, for example, CUU, CUC, CUA, CUG, UUA, and UUG are synonymous codons that code for Leu. Synonymous codons are not used with equal frequency. In general, the most frequently used codons in a particular organism are those for which the cognate tRNA is abundant, and the use of these codons enhances the rate and/or accuracy of protein translation. Conversely, tRNAs for the rarely used codons are found at relatively low levels, and the use of rare codons is thought to reduce translation rate and/or accuracy.

Table 1. Genetic Code^a					
	U	C	A	G	
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	STOP	STOP	A
	Leu	Ser	STOP	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

^a The first nucleotide in each codon encoding a particular amino acid is shown in the left-most column; the second nucleotide is shown in the top row; and the third nucleotide is shown in the right-most column.

[0046] Codon bias

[0047] As used herein, a “rare” codon is one of at least two synonymous codons encoding a particular amino acid that is present in an mRNA at a significantly lower frequency than the most frequently used codon for that amino acid. Thus, the rare codon may be present at about a 2-fold lower frequency than the most frequently used codon. Preferably, the rare codon is present at least a 3-fold, more preferably at least a 5-fold, lower frequency than the most frequently used codon for the amino acid. Conversely, a “frequent” codon is one of at least two synonymous codons encoding a particular amino acid that is present in an mRNA at a significantly higher frequency than the least frequently used codon for that amino acid. The frequent codon may be present at about a 2-fold, preferably at least a 3-fold, more preferably at least a 5-fold, higher frequency than the least frequently used codon for the amino acid. For example, human genes use the leucine codon CTG 40% of the time, but use the synonymous CTA only 7% of the time (see Table 2). Thus, CTG is a frequent codon, whereas CTA is a rare codon. Roughly consistent with these frequencies of usage, there are 6 copies in the genome for the gene for the tRNA recognizing CTG, whereas there are only 2 copies of the gene for the tRNA recognizing CTA. Similarly, human genes use the frequent codons TCT and TCC for serine 18% and 22% of the time, respectively, but the rare codon TCG only 5% of the time. TCT and TCC are read, via wobble, by the same

tRNA, which has 10 copies of its gene in the genome, while TCG is read by a tRNA with only 4 copies. It is well known that those mRNAs that are very actively translated are strongly biased to use only the most frequent codons. This includes genes for ribosomal proteins and glycolytic enzymes. On the other hand, mRNAs for relatively non-abundant proteins may use the rare codons.

Table 2. Codon usage in Homo sapiens (source: http://www.kazusa.or.jp/codon/)				
Amino Acid	Codon	Number	/1000	Fraction
Gly	GGG	636457.00	16.45	0.25
Gly	GGA	637120.00	16.47	0.25
Gly	GGT	416131.00	10.76	0.16
Gly	GGC	862557.00	22.29	0.34
Glu	GAG	1532589.00	39.61	0.58
Glu	GAA	1116000.00	28.84	0.42
Asp	GAT	842504.00	21.78	0.46
Asp	GAC	973377.00	25.16	0.54
Val	GTG	1091853.00	28.22	0.46
Val	GTA	273515.00	7.07	0.12
Val	GTT	426252.00	11.02	0.18
Val	GTC	562086.00	14.53	0.24
Ala	GCG	286975.00	7.42	0.11
Ala	GCA	614754.00	15.89	0.23
Ala	GCT	715079.00	18.48	0.27
Ala	GCC	1079491.00	27.90	0.40
Arg	AGG	461676.00	11.93	0.21
Arg	AGA	466435.00	12.06	0.21
Ser	AGT	469641.00	12.14	0.15
Ser	AGC	753597.00	19.48	0.24
Lys	AAG	1236148.00	31.95	0.57
Lys	AAA	940312.00	24.30	0.43
Asn	AAT	653566.00	16.89	0.47
Asn	AAC	739007.00	19.10	0.53
Met	ATG	853648.00	22.06	1.00
Ile	ATA	288118.00	7.45	0.17
Ile	ATT	615699.00	15.91	0.36
Ile	ATC	808306.00	20.89	0.47
Thr	ACG	234532.00	6.06	0.11

Thr	ACA	580580.00	15.01	0.28
Thr	ACT	506277.00	13.09	0.25
Thr	ACC	732313.00	18.93	0.36
Trp	TGG	510256.00	13.19	1.00
End	TGA	59528.00	1.54	0.47
Cys	TGT	407020.00	10.52	0.45
Cys	TGC	487907.00	12.61	0.55
End	TAG	30104.00	0.78	0.24
End	TAA	38222.00	0.99	0.30
Tyr	TAT	470083.00	12.15	0.44
Tyr	TAC	592163.00	15.30	0.56
Leu	TTG	498920.00	12.89	0.13
Leu	TTA	294684.00	7.62	0.08
Phe	TTT	676381.00	17.48	0.46
Phe	TTC	789374.00	20.40	0.54
Ser	TCG	171428.00	4.43	0.05
Ser	TCA	471469.00	12.19	0.15
Ser	TCT	585967.00	15.14	0.19
Ser	TCC	684663.00	17.70	0.22
Arg	CGG	443753.00	11.47	0.20
Arg	CGA	239573.00	6.19	0.11
Arg	CGT	176691.00	4.57	0.08
Arg	CGC	405748.00	10.49	0.18
Gln	CAG	1323614.00	34.21	0.74
Gln	CAA	473648.00	12.24	0.26
His	CAT	419726.00	10.85	0.42
His	CAC	583620.00	15.08	0.58
Leu	CTG	1539118.00	39.78	0.40
Leu	CTA	276799.00	7.15	0.07
Leu	CTT	508151.00	13.13	0.13
Leu	CTC	759527.00	19.63	0.20
Pro	CCG	268884.00	6.95	0.11
Pro	CCA	653281.00	16.88	0.28
Pro	CCT	676401.00	17.48	0.29
Pro	CCC	767793.00	19.84	0.32

[0048] The propensity for highly expressed genes to use frequent codons is called “codon bias.” A gene for a ribosomal protein might use only the 20 to 25 most frequent of the 61 codons, and have a high codon bias (a codon bias close to 1), while a poorly expressed gene might use all 61 codons, and have little or no codon bias (a codon bias close to 0). It is thought that the frequently used codons are codons where larger amounts of the cognate tRNA are expressed, and that use of these codons allows translation to proceed more rapidly, or more accurately, or both. The PV capsid protein, for example, is very actively translated, and has a high codon bias.

[0049] Codon pair bias

[0050] In addition, a given organism has a preference for the nearest codon neighbor of a given codon A, referred to a bias in codon pair utilization. A change of codon pair bias, without changing the existing codons, can influence the rate of protein synthesis and production of a protein.

[0051] Codon pair bias may be illustrated by considering the amino acid pair Ala-Glu, which can be encoded by 8 different codon pairs. If no factors other than the frequency of each individual codon (as shown in Table 2) are responsible for the frequency of the codon pair, the expected frequency of each of the 8 encodings can be calculated by multiplying the frequencies of the two relevant codons. For example, by this calculation the codon pair GCA-GAA would be expected to occur at a frequency of 0.097 out of all Ala-Glu coding pairs (0.23×0.42 ; based on the frequencies in Table 2). In order to relate the expected (hypothetical) frequency of each codon pair to the actually observed frequency in the human genome the Consensus CDS (CCDS) database of consistently annotated human coding regions, containing a total of 14,795 human genes, was used. This set of genes is the most comprehensive representation of human coding sequences. Using this set of genes the frequencies of codon usage were re-calculated by dividing the number of occurrences of a codon by the number of all synonymous codons coding for the same amino acid. As expected the frequencies correlated closely with previously published ones such as the ones given in Table 2. Slight frequency variations are possibly due to an oversampling effect in the data provided by the codon usage database at Kazusa DNA Research Institute (<http://www.kazusa.or.jp/codon/codon.html>) where 84949 human coding sequences were included in the calculation (far more than the actual number of human genes). The codon frequencies thus calculated were then used to calculate the expected codon-pair frequencies by first multiplying the frequencies of the two relevant codons with each other (see Table 3

expected frequency), and then multiplying this result with the observed frequency (in the entire CCDS data set) with which the amino acid pair encoded by the codon pair in question occurs. In the example of codon pair GCA-GAA, this second calculation gives an expected frequency of 0.098 (compared to 0.097 in the first calculation using the Kazusa dataset). Finally, the actual codon pair frequencies as observed in a set of 14,795 human genes was determined by counting the total number of occurrences of each codon pair in the set and dividing it by the number of all synonymous coding pairs in the set coding for the same amino acid pair (Table 3; observed frequency). Frequency and observed/expected values for the complete set of 3721 (61^2) codon pairs, based on the set of 14,795 human genes, are provided herewith as Supplemental Table 1.

Table 3 - Codon Pair Scores Exemplified by the Amino Acid Pair Ala-Glu				
amino acid pair	codon pair	expected frequency	observed frequency	obs/exp ratio
AE	GCAGAA	0.098	0.163	1.65
AE	GCAGAG	0.132	0.198	1.51
AE	GCCGAA	0.171	0.031	0.18
AE	GCCGAG	0.229	0.142	0.62
AE	GCGGAA	0.046	0.027	0.57
AE	GCGGAG	0.062	0.089	1.44
AE	GCTGAA	0.112	0.145	1.29
AE	GCTGAG	0.150	0.206	1.37
Total		1.000	1.000	

[0052] If the ratio of observed frequency/expected frequency of the codon pair is greater than one the codon pair is said to be overrepresented. If the ratio is smaller than one, it is said to be underrepresented. In the example the codon pair GCA-GAA is overrepresented 1.65 fold while the coding pair GCC-GAA is more than 5-fold underrepresented.

[0053] Many other codon pairs show very strong bias; some pairs are under-represented, while other pairs are over-represented. For instance, the codon pairs GCCGAA (AlaGlu) and GATCTG (AspLeu) are three- to six-fold under-represented (the preferred pairs being GCAGAG and GACCTG, respectively), while the codon pairs GCCAAG (AlaLys) and AATGAA (AsnGlu) are about two-fold over-represented. It is noteworthy that codon pair bias has nothing to do with the frequency of pairs of amino acids, nor with the frequency of

individual codons. For instance, the under-represented pair GATCTG (AspLeu) happens to use the most frequent Leu codon, (CTG).

[0054] As discussed more fully below, codon pair bias takes into account the score for each codon pair in a coding sequence averaged over the entire length of the coding sequence. According to the invention, codon pair bias is determined by $CPB = \sum_{i=1}^k \frac{CPS_i}{k-1}$.

[0055] Accordingly, similar codon pair bias for a coding sequence can be obtained, for example, by minimized codon pair scores over a subsequence or moderately diminished codon pair scores over the full length of the coding sequence.

[0056] Calculation of codon pair bias.

[0057] Every individual codon pair of the possible 3721 non-"STOP" containing codon pairs (e.g., GTT-GCT) carries an assigned "codon pair score," or "CPS" that is specific for a given "training set" of genes. The CPS of a given codon pair is defined as the log ratio of the observed number of occurrences over the number that would have been expected in this set of genes (in this example the human genome). Determining the actual number of occurrences of a particular codon pair (or in other words the likelihood of a particular amino acid pair being encoded by a particular codon pair) is simply a matter of counting the actual number of occurrences of a codon pair in a particular set of coding sequences. Determining the expected number, however, requires additional calculations. The expected number is calculated so as to be independent of both amino acid frequency and codon bias similarly to Gutman and Hatfield. That is, the expected frequency is calculated based on the relative proportion of the number of times an amino acid is encoded by a specific codon. A positive CPS value signifies that the given codon pair is statistically over-represented, and a negative CPS indicates the pair is statistically under-represented in the human genome.

[0058] To perform these calculations within the human context, the most recent Consensus CDS (CCDS) database of consistently annotated human coding regions, containing a total of 14,795 genes, was used. This data set provided codon and codon pair, and thus amino acid and amino-acid pair frequencies on a genomic scale.

[0059] The paradigm of Federov et al. (2002), was used to further enhanced the approach of Gutman and Hatfield (1989). This allowed calculation of the expected frequency of a given codon pair independent of codon frequency and non-random associations of neighboring codons encoding a particular amino acid pair.

$$S(P_{ij}) = \ln \left(\frac{N_o(P_{ij})}{N_e(P_{ij})} \right) = \ln \left(\frac{N_o(P_{ij})}{F(C_i)F(C_j)N_o(X_{ij})} \right)$$

[0060] In the calculation, P_{ij} is a codon pair occurring with a frequency of $N_o(P_{ij})$ in its synonymous group. C_i and C_j are the two codons comprising P_{ij} , occurring with frequencies $F(C_i)$ and $F(C_j)$ in their synonymous groups respectively. More explicitly, $F(C_i)$ is the frequency that corresponding amino acid X_i is coded by codon C_i throughout all coding regions and $F(C_i) = N_o(C_i)/N_o(X_i)$, where $N_o(C_i)$ and $N_o(X_i)$ are the observed number of occurrences of codon C_i and amino acid X_i respectively. $F(C_j)$ is calculated accordingly. Further, $N_o(X_{ij})$ is the number of occurrences of amino acid pair X_{ij} throughout all coding regions. The codon pair bias score $S(P_{ij})$ of P_{ij} was calculated as the log-odds ratio of the observed frequency $N_o(P_{ij})$ over the expected number of occurrences of $N_e(P_{ij})$.

[0061] Using the formula above, it was then determined whether individual codon pairs in individual coding sequences are over- or under-represented when compared to the corresponding genomic $N_e(P_{ij})$ values that were calculated by using the entire human CCDS data set. This calculation resulted in positive $S(P_{ij})$ score values for over-represented and negative values for under-represented codon pairs in the human coding regions (Fig. 7).

[0062] The “combined” codon pair bias of an individual coding sequence was calculated by averaging all codon pair scores according to the following formula:

$$S(P_{ij}) = \sum_{i=1}^k \frac{S(P_{ij})l}{k-1}.$$

[0063] The codon pair bias of an entire coding region is thus calculated by adding all of the individual codon pair scores comprising the region and dividing this sum by the length of the coding sequence.

[0064] **Calculation of codon pair bias, implementation of algorithm to alter codon-pair bias.**

[0065] An algorithm was developed to quantify codon pair bias. Every possible individual codon pair was given a “codon pair score”, or “CPS”. CPS is defined as the natural log of the ratio of the observed over the expected number of occurrences of each codon pair over all human coding regions, where humans represent the host species of the instant vaccine virus to be recoded.

$$CPS = \ln \left(\frac{F(AB)}{\frac{F(A) \times F(B)}{F(X) \times F(Y)} \times F(XY)} \right)$$

[0066] Although the calculation of the observed occurrences of a particular codon pair is straightforward (the actual count within the gene set), the expected number of occurrences of a codon pair requires additional calculation. We calculate this expected number to be independent both of amino acid frequency and of codon bias, similar to Gutman and Hatfield. That is, the expected frequency is calculated based on the relative proportion of the number of times an amino acid is encoded by a specific codon. A positive CPS value signifies that the given codon pair is statistically over-represented, and a negative CPS indicates the pair is statistically under-represented in the human genome

[0067] Using these calculated CPSs, any coding region can then be rated as using over- or under-represented codon pairs by taking the average of the codon pair scores, thus giving a Codon Pair Bias (CPB) for the entire gene.

$$CPB = \sum_{i=1}^k \frac{CPS_i}{k-1}$$

[0068] The CPB has been calculated for all annotated human genes using the equations shown and plotted (Fig. 4). Each point in the graph corresponds to the CPB of a single human gene. The peak of the distribution has a positive codon pair bias of 0.07, which is the mean score for all annotated human genes. Also there are very few genes with a negative codon pair bias. Equations established to define and calculate CPB were then used to manipulate this bias.

[0069] Algorithm for reducing codon-pair bias.

[0070] Recoding of protein-encoding sequences may be performed with or without the aid of a computer, using, for example, a gradient descent, or simulated annealing, or other minimization routine. An example of the procedure that rearranges codons present in a starting sequence can be represented by the following steps:

[0071] 1) Obtain wildtype viral genome sequence.

[0072] 2) Select protein coding sequences to target for attenuated design.

[0073] 3) Lock down known or conjectured DNA segments with non-coding functions.

[0074] 4) Select desired codon distribution for remaining amino acids in redesigned proteins.

[0075] 5) Perform random shuffle of at least two synonymous unlocked codon positions and calculate codon-pair score.

[0076] 6) Further reduce (or increase) codon-pair score optionally employing a simulated annealing procedure.

[0077] 7) Inspect resulting design for excessive secondary structure and unwanted restriction site:

if yes -> go to step (5) or correct the design by replacing problematic regions with wildtype sequences and go to step (8).

[0078] 8. Synthesize DNA sequence corresponding to virus design.

[0079] 9. Create viral construct and assess viral phenotype:

if too attenuated, prepare subclone construct and goto 9;

if insufficiently attenuated, goto 2.

[0080] Attenuation of viruses by reducing codon pair bias is disclosed in WO 2008/121992 and WO 2011/044561, which are incorporated by reference.

[0081] Attenuated influenza viruses

[0082] According to the invention, viral attenuation is accomplished by reducing expression of HA and NA coding sequences. One way to reduce expression of the coding sequences is by a reduction in codon pair bias, but other methods can also be used, alone or in combination. While codon bias may be changed, adjusting codon pair bias is particularly advantageous. For example, attenuating a virus through codon bias generally requires elimination of common codons, and so the complexity of the nucleotide sequence is reduced. In contrast, codon pair bias reduction or minimization can be accomplished while maintaining far greater sequence diversity, and consequently greater control over nucleic acid secondary structure, annealing temperature, and other physical and biochemical properties.

[0083] Codon pair bias of a protein-encoding sequence (i.e., an open reading frame) is calculated as set forth above and described in Coleman et al., 2000 (ref. 12).

[0084] Viral attenuation and induction or protective immune responses can be confirmed in ways that are well known to one of ordinary skill in the art, including but not limited to, the methods and assays disclosed herein. Non-limiting examples include plaque

assays, growth measurements, reduced lethality in test animals, and protection against subsequent infection with a wild type virus.

[0085] In preferred embodiments, the invention provides viruses that are highly attenuated, and induce immunity against a plurality of influenza types and/or subtypes. Such flu varieties include viruses bearing all possible HA-NA combinations. Currently, there are 16 recognized hemagglutinins and nine neuraminidases, each of which has mutational variants. Examples of type A subtypes include, but are not limited to, H10N7, H10N1, H10N2, H10N3, H10N4, H10N5, H10N6, H10N7, H10N8, H10N9, H11N1, H11N2, H11N3, H11N4, H11N6, H11N8, H11N9, H12N1, H12N2, H12N4, H12N5, H12N6, H12N8, H12N9, H13N2, H13N3, H13N6, H13N9, H14N5, H14N6, H15N2, H15N8, H15N9, H16N3, H1N1, H1N2, H1N3, H1N5, H1N6, H1N8, H1N9, H2N1, H2N2, H2N3, H2N4, H2N5, H2N6, H2N7, H2N8, H2N9, H3N1, H3N2, H3N3, H3N4, H3N5, H3N6, H3N8, H3N9, H4N1, H4N2, H4N3, H4N4, H4N5, H4N6, H4N7, H4N8, H4N9, H5N1, H5N2, H5N3, H5N4, H5N6, H5N7, H5N8, H5N9, H6N1, H6N2, H6N3, H6N4, H6N5, H6N6, H6N7, H6N8, H6N9, H7N1, H7N2, H7N3, H7N4, H7N5, H7N7, H7N8, H7N9, H8N2, H8N4, H8N5, H9N1, H9N2, H9N3, H9N4, H9N5, H9N6, H9N7, H9N8, H9N9. Some subtypes of interest include, but are not limited to, H1N1 (one variant of which caused Spanish flu in 1918, another of which is pandemic in 2009), H2N2 (a variant of which caused Asian Flu in 1957), H3N2 (a variant of which caused Hong Kong Flu in 1968, H5N1 (a current pandemic threat), H7N7 (which has unusual zoonotic potential), and H1N2 (endemic in humans and pigs). Examples of attenuated influenza protein coding sequences are provided below.

Table 4. Reduced-Expression Influenza A Virus Genes						
Gene	WT Coding Sequence			Recoded Coding Sequence		
	SEQ ID NO:	CDS	CPB	SEQ ID NO	Recoded Codons	CPB
H10N7 (A/northern shoveler/California/HKWF392sm/2007)(Avian)						
HA	1	1-1683	0.018	2	1-561	-0.441
NA	3	1-1494	0.009	4	1-498	-0.449
H1N1 (A/New York/3568/2009)(Human)						
HA	5	1-1698	0.043	6	1-566	-0.410
NA	7	1-1407	0.005	8	1-469	-0.456
H1N2 (A/New York/211/2003)(Human)						
HA	9	1-1695	0.036	10	1-565	-0.421
NA	11	1-1407	0.034	12	1-469	-0.476

H2N2 (A/Albany/22/1957)(Human)						
HA	13	1-1686	0.040	14	1-562	-0.422
NA	15	1-1407	0.008	16	1-469	-0.453
H3N2 (A/New York/933/2006)(Human)						
HA	17	1-1698	0.027	18	1-566	-0.447
NA	19	1-1407	0.041	20	1-469	-0.463
H5N1 (A/Jiangsu/1/2007)(Human)						
HA	21	1-1701	0.017	22	1-567	-0.435
NA	23	1-1347	0.009	24	1-449	-0.407
H7N2 (A/chicken/NJ/294508-12/2004)(Avian)						
HA	25	1-1656	0.036	26	1-552	-0.377
NA	27	1-1359	0.013	28	1-453	-0.491
H7N3 (A/Canada/rv504/2004)(Human)						
HA	29	1-1701	0.029	30	1-567	-0.405
NA	31	1-1407	0.042	32	1-469	-0.413
H7N7 (A/Netherlands/219/03)(Human)						
HA	33	1-1707	0.008	34	1-569	-0.447
NA	35	1-1413	-0.009	36	1-471	-0.423
H9N2 (A/Hong Kong/1073/99)(Human)						
HA	37	1-1680	0.021	38	1-560	-0.440
NA	39	1-1401	0.020	40	1-467	-0.453

[0086] Vaccine compositions

[0087] The present invention provides a vaccine composition for inducing a protective immune response in a subject comprising any of the attenuated viruses described herein and a pharmaceutically acceptable carrier.

[0088] It should be understood that an attenuated virus of the invention, where used to elicit a protective immune response in a subject or to prevent a subject from becoming afflicted with a virus-associated disease, is administered to the subject in the form of a composition additionally comprising a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known to those skilled in the art and include, but are not limited to, one or more of 0.01-0.1M and preferably 0.05M phosphate buffer, phosphate-buffered saline (PBS), or 0.9% saline. Such carriers also include aqueous or non-aqueous solutions, suspensions, and emulsions. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, saline and buffered media. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic

esters such as ethyl oleate. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's and fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers such as those based on Ringer's dextrose, and the like. Solid compositions may comprise nontoxic solid carriers such as, for example, glucose, sucrose, mannitol, sorbitol, lactose, starch, magnesium stearate, cellulose or cellulose derivatives, sodium carbonate and magnesium carbonate. For administration in an aerosol, such as for pulmonary and/or intranasal delivery, an agent or composition is preferably formulated with a nontoxic surfactant, for example, esters or partial esters of C6 to C22 fatty acids or natural glycerides, and a propellant. Additional carriers such as lecithin may be included to facilitate intranasal delivery. Pharmaceutically acceptable carriers can further comprise minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives and other additives, such as, for example, antimicrobials, antioxidants and chelating agents, which enhance the shelf life and/or effectiveness of the active ingredients. The instant compositions can, as is well known in the art, be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to a subject.

[0089] In various embodiments of the instant vaccine composition, the attenuated virus (i) does not substantially alter the synthesis and processing of viral proteins in an infected cell; (ii) produces similar amounts of virions per infected cell as wt virus; and/or (iii) exhibits substantially lower virion-specific infectivity than wt virus. In further embodiments, the attenuated virus induces a substantially similar immune response in a host animal as the corresponding wt virus.

[0090] This invention also provides a modified host cell line specially isolated or engineered to be permissive for an attenuated virus that is inviable in a wild type host cell. Since the attenuated virus cannot grow in normal (wild type) host cells, it is absolutely dependent on the specific helper cell line for growth. This provides a very high level of safety for the generation of virus for vaccine production. Various embodiments of the instant modified cell line permit the growth of an attenuated virus, wherein the genome of said cell line has been altered to increase the number of genes encoding rare tRNAs.

[0091] In addition, the present invention provides a method for eliciting a protective immune response in a subject comprising administering to the subject a prophylactically or therapeutically effective dose of any of the vaccine compositions described herein. This invention also provides a method for preventing a subject from becoming afflicted with a

virus-associated disease comprising administering to the subject a prophylactically effective dose of any of the instant vaccine compositions. In embodiments of the above methods, the subject has been exposed to a pathogenic virus. “Exposed” to a pathogenic virus means contact with the virus such that infection could result.

[0092] The invention further provides a method for delaying the onset, or slowing the rate of progression, of a virus-associated disease in a virus-infected subject comprising administering to the subject a therapeutically effective dose of any of the instant vaccine compositions.

[0093] As used herein, “administering” means delivering using any of the various methods and delivery systems known to those skilled in the art. Administering can be performed, for example, intranasally, intraperitoneally, intracerebrally, intravenously, orally, transmucosally, subcutaneously, transdermally, intradermally, intramuscularly, topically, parenterally, via implant, intrathecally, intralymphatically, intralesionally, pericardially, or epidurally. An agent or composition may also be administered in an aerosol, such as for pulmonary and/or intranasal delivery. Administering may be performed, for example, once, a plurality of times, and/or over one or more extended periods.

[0094] Eliciting a protective immune response in a subject can be accomplished, for example, by administering a primary dose of a vaccine to a subject, followed after a suitable period of time by one or more subsequent administrations of the vaccine. A suitable period of time between administrations of the vaccine may readily be determined by one skilled in the art, and is usually on the order of several weeks to months. The present invention is not limited, however, to any particular method, route or frequency of administration.

[0095] A “subject” means any animal or artificially modified animal. Animals include, but are not limited to, humans, non-human primates, cows, horses, sheep, pigs, dogs, cats, rabbits, ferrets, rodents such as mice, rats and guinea pigs, and birds. Artificially modified animals include, but are not limited to, SCID mice with human immune systems, and CD155tg transgenic mice expressing the human poliovirus receptor CD155. In a preferred embodiment, the subject is a human. Preferred embodiments of birds are domesticated poultry species, including, but not limited to, chickens, turkeys, ducks, and geese.

[0096] A “prophylactically effective dose” is any amount of a vaccine that, when administered to a subject prone to viral infection or prone to affliction with a virus-associated

disorder, induces in the subject an immune response that protects the subject from becoming infected by the virus or afflicted with the disorder. “Protecting” the subject means either reducing the likelihood of the subject’s becoming infected with the virus, or lessening the likelihood of the disorder’s onset in the subject, by at least two-fold, preferably at least ten-fold. For example, if a subject has a 1% chance of becoming infected with a virus, a two-fold reduction in the likelihood of the subject becoming infected with the virus would result in the subject having a 0.5% chance of becoming infected with the virus. Most preferably, a “prophylactically effective dose” induces in the subject an immune response that completely prevents the subject from becoming infected by the virus or prevents the onset of the disorder in the subject entirely.

[0097] As used herein, a “therapeutically effective dose” is any amount of a vaccine that, when administered to a subject afflicted with a disorder against which the vaccine is effective, induces in the subject an immune response that causes the subject to experience a reduction, remission or regression of the disorder and/or its symptoms. In preferred embodiments, recurrence of the disorder and/or its symptoms is prevented. In other preferred embodiments, the subject is cured of the disorder and/or its symptoms.

[0098] Certain embodiments of any of the instant immunization and therapeutic methods further comprise administering to the subject at least one adjuvant. An “adjuvant” shall mean any agent suitable for enhancing the immunogenicity of an antigen and boosting an immune response in a subject. Numerous adjuvants, including particulate adjuvants, suitable for use with both protein- and nucleic acid-based vaccines, and methods of combining adjuvants with antigens, are well known to those skilled in the art. Suitable adjuvants for nucleic acid based vaccines include, but are not limited to, Quil A, imiquimod, resiquimod, and interleukin-12 delivered in purified protein or nucleic acid form. Adjuvants suitable for use with protein immunization include, but are not limited to, alum, Freund’s incomplete adjuvant (FIA), saponin, Quil A, and QS-21.

[0099] The invention also provides a kit for immunization of a subject with an attenuated virus of the invention. The kit comprises the attenuated virus, a pharmaceutically acceptable carrier, an applicator, and an instructional material for the use thereof. In further embodiments, the attenuated virus may be one or more poliovirus, one or more rhinovirus, one or more influenza virus, etc. More than one virus may be preferred where it is desirable to immunize a host against a number of different isolates of a particular virus. The invention includes other embodiments of kits that are known to those skilled in the art. The instructions

can provide any information that is useful for directing the administration of the attenuated viruses.

[0100] Throughout this application, various publications, reference texts, textbooks, technical manuals, patents, and patent applications have been referred to. The teachings and disclosures of these publications, patents, patent applications and other documents in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which the present invention pertains. However, the citation of a reference herein should not be construed as an acknowledgement that such reference is prior art to the present invention.

[0101] It is to be understood and expected that variations in the principles of invention herein disclosed can be made by one skilled in the art and it is intended that such modifications are to be included within the scope of the present invention. The following Examples further illustrate the invention, but should not be construed to limit the scope of the invention in any way. Detailed descriptions of conventional methods, such as those employed in the construction of recombinant plasmids, transfection of host cells with viral constructs, polymerase chain reaction (PCR), and immunological techniques can be obtained from numerous publications, including Sambrook et al. (1989) and Coligan et al. (1994). All references mentioned herein are incorporated in their entirety by reference into this application. The contents of WO 2008/121992 and WO 2011/044561 are incorporated by reference.

EXAMPLES

[0102] EXAMPLE 1 - Construction and characterization of an HA and NA codon pair-bias reduced influenza virus in tissue culture

[0103] To achieve attenuation of influenza virus PR8, codon pair bias was reduced (introducing underrepresented codon pairs) in viral genes HA and NA according to computer algorithms (12, 13) and chemical synthesis (14), in order to reduce the expression level of the targeted viral genes.

[0104] Cells and viruses. MDCK, A549 and HEK293 T cell lines were maintained in DMEM supplemented with 10% FBS at 37°C. Influenza A/PR/8/34 (PR8) was cultured in MDCK cells.

[0105] Variant (NA+HA)^{Min} (618/3188 nt changes), combining the HA^{Min} (SEQ ID NO:53) and NA^{Min} (SEQ ID NO:60) genes, expressed growth and plaque phenotypes in MDCK cells comparable to those of the individual HA^{Min} and NA^{Min} variants (Fig 1B, C). Similarly, a variant with a codon-pair bias reduced NA gene (NA^{Min}, 265/1413 synonymous mutations; Fig. 1A) also replicated well in MDCK cells (Fig. 1C) and expressed an only slightly smaller plaque size phenotype (Fig. 1B) than wt PR8. In A549 cells the (NA+HA)^{Min} variant was highly attenuated (Fig 1D), growing to a final titer three to four orders of magnitudes lower than wt PR8. A549 cells retain a complex signaling network that is related to the innate host response (15, 16).

[0106] EXAMPLE 2 - Levels of NA mRNA and HA protein are reduced in (NA+HA)^{Min}-infected cells

[0107] The apparent yield of HA polypeptide was examined by western blotting in MDCK cells at 3 h and 6 h post infection (p.i.) with 5 MOI of wt virus or (NA+HA)^{Min}. Remarkably, at 6 h p.i., expression of HA protein was significantly reduced in (NA+HA)^{Min}-infected cells when compared to PR8-infected cells whereas PB1 and NS1 were synthesized to equal levels by viruses (Fig 2A). Using the levels of PB1 and GAPDH mRNAs as control, the Northern blot analysis of mRNA levels in (NA+HA)^{Min}-infected cells indicated only a slight reduction of HA^{Min} mRNA at 3h and 6h (Fig. 2B).

[0108] In contrast, Northern blot analyses indicated an extensive reduction of the recoded NA^{Min} mRNA after 6h and particularly after 9 h p.i. (Fig. 2B). Early in infection (3h), the level of NA^{Min} mRNA was slightly reduced.

[0109] Example 3 - Characterization of the reduced codon-pair bias variants as vaccine candidates in mice

[0110] The growth phenotype and pathogenesis of the (NA+HA)^{Min} variant was examined in an animal model. Groups of five BALB/c mice received (NA+HA)^{Min} at doses of 10⁴, 10⁵ or 10⁶ PFU intra-nasally, and body weight and survival of the animals was monitored continuously for 14 days p.i. (Fig. 3A, B). Morbidity and mortality (weight loss, reduced activity, death) was monitored. The Lethal Dose 50 (LD₅₀) of the wildtype virus and the vaccine candidates was calculated by the method of Reed and Muench (Reed, L.J.; Muench, H., 1938, The American Journal of Hygiene 27: 493–497). Remarkably, the (NA+HA)^{Min} variant did not induce apparent disease after a dose up to 10⁵ PFU. Even at 10⁶ PFU, mice only suffered transient weight loss, but all animals survived. Therefore, the

theoretical LD₅₀ of the (NA+HA)^{Min} variant was calculated to be equal or greater than 3.16 x 10⁶ PFU, which exceeds that of wt PR8 by a factor of at least 100,000 (Table 1).

[0111] Whereas the (NA+HA)^{Min}, HA^{Min}, and NA^{Min} variants replicated with nearly equal efficiency and similar kinetics as wt PR8 in MDCK cells (Fig. 1C), the LD₅₀ of the variants were by orders of magnitude different: PR8 = 32 PFU, HA^{Min} = 1.7 x 10³ PFU (13), NA^{Min} = 2.4 x 10⁵ PFU (Fig. 7, Table 5), and (NA+HA)^{Min} > 3.3 x 10⁶. By itself, the NA^{Min} gene is about 100-fold more attenuated than the HA^{Min} gene, but reducing expression of NA and NP in the same virus significantly increases attenuation of the virus.

Table 5 – LD ₅₀ and PD ₅₀ of Attenuated Virus		
	LD ₅₀	PD ₅₀
WT PR8	3.2 x 10 ¹	~ 1
NA ^{Min}	2.4 x 10 ⁵	< 32
HA ^{Min}	1.7 x 10 ³	n.d.
(NA+HA) ^{Min}	> 3.3 x 10 ⁶	2.4

[0112] Vaccine candidates should be capable of providing, at low dose, long-term protection from challenge with a lethal dose of wt virus. The dose of (NA+HA)^{Min} required to protect 50% of vaccinated animals from subsequent lethal wild type challenge (defined as “protective dose 50”, PD₅₀) was determined. Groups of five Balb/c mice were vaccinated with a single dose of 10⁰, 10¹, or 10² PFU of (NA+HA)^{Min}. 28 days after vaccination, the animals were challenged with 10⁵ PFU (3000 x LD₅₀) of wt PR8 virus. As with the original infections, we monitored body weight and survival of the animals 14 days after challenge. Remarkably, although (NA+HA)^{Min} was highly attenuated in mice, it was also highly proficient at protecting against lethal challenge with wt virus. As little as 10 PFU of (NA+HA)^{Min} protected all five mice from lethal challenge (Fig 3C, 3D). The PD₅₀ value calculated by the method of Reed-Muench was only 2.4 PFU. (Table 5) To our knowledge this is the lowest reported protective dose of an experimental vaccine in a mouse model.

[0113] Vaccine safety and protective range was evaluated with various doses of either (NA+HA)^{Min} variant or wt PR8. As shown in Fig. 3E, a zone of five orders of magnitude (from 10 PFU to 10⁶ PFU) can be considered the “region of safety” of (NA+HA)^{Min} vaccination since all mice receiving increasing doses of “vaccine” within this region were protected from lethal challenge with wt virus. In contrast, the safe and effective region for wt PR8 was extremely limited (Fig 3F).

[0114] Example 4 - The Growth of (NA+HA)^{Min} is greatly reduced in the lungs of vaccinated mice.

[0115] To determine parameters of the (NA+HA)^{Min} pathogenicity *in vivo*, groups of BALB/c mice were infected with 10⁴ PFU of wt PR8 or (NA+HA)^{Min}. On day 1, 3, 5, 7, 9 and 11, three mice each from the wt and (NA+HA)^{Min} groups were euthanized, their lungs were homogenized, and virus titers in the homogenates were determined by plaque assays. As expected, wt PR8 replicated well, but even (NA+HA)^{Min} replicated noticeably in lungs of the vaccinated animals. Both PR8 and variant achieved maximum titers around day 3 (Fig. 4A) although there was a ~100 fold difference in the titers between the two viruses. All wt PR8-infected mice died on day 5, whereas all (NA+HA)^{Min}-infected mice remained healthy. (NA+HA)^{Min} was eventually cleared at 8 to 9 days p.i. (Fig. 4A). When mice were inoculated at different doses, the (NA+HA)^{Min} titers were always 100 – 1000 fold lower in lungs when compare to those of wt PR8 on day 3 p.i. (Fig 4B). Strikingly, at a vaccination dose of 10 PFU when (NA+HA)^{Min} barely replicated in the lungs of the animals, it nevertheless provided complete protection against wt PR8 challenge (Fig. 4B and 3D). Interestingly, the attenuation of (NA+HA)^{Min} in mice correlates with the attenuation of (NA+HA)^{Min} in A549 cells (Fig 1D).

[0116] Example 5 - Cross protection and long term protection induced by the (NA+HA)^{Min} variant

[0117] The (NA+HA)^{Min} variant of PR8, which belongs to the influenza H1N1 subtype, was further tested for its capacity to cross protect animals against infections with a heterologous influenza virus strain, such as a mouse adapted H3N2 strain (A/Aichi/2/1968) (21). Groups of five BALB/c mice were vaccinated with (NA+HA)^{Min} virus at doses ranging from 10² to 10⁴ PFU and challenged 28 days post vaccination with 100 x LD₅₀ doses of A/Aichi/2/1968 (H3N2) virus (1.5 x 10⁴ PFU). Remarkably, 1000 PFU of (NA+HA)^{Min} were sufficient to protect mice from the heterologous lethal challenge, corresponding to a PD₅₀ value of only 237 PFU (Fig. 5A, 5B). A similar result was obtained when the vaccinated (NA+HA)^{Min} mice were challenged with a different strain of mouse adapted H3N2, A/Victoria/3/75. Again, as little as 1000 PFU of the H1N1 PR8-(NA+HA)^{Min} variant protected all mice from lethal challenge with 100 x LD₅₀ dose (3.2 x 10⁴ PFU) of A/Victoria/3/75. The PD₅₀ of (NA+HA)^{Min} protecting against A/Victoria/3/75 (H3N2) was only 147 PFU (Fig. 5C, 5D). Both results indicate that (NA+HA)^{Min} of H1N1 PR8 can induce a robust cross protective immune response in mice against H3N2 subtypes. .

[0118] (NA+HA)^{Min}-vaccinated animals were tested to determine whether they were protected against challenge after an extended period of time. Groups of five mice were vaccinated with different doses (10^1 to 10^5 PFU) of (NA+HA)^{Min} and the animals were challenged seven months later with 10^5 PFU of wt PR8. All vaccinated animals were completely protected without signs of disease (Fig. 8).

[0119] Example 6 - The (NA+HA)^{Min} variant induces a robust antibody response.

[0120] The host response to (NA+HA)^{Min} inoculation suggested a strong host response, including adaptive immunity. Groups of five Balb/c mice were vaccinated with varying doses of (NA+HA)^{Min} or wt PR8 (see Fig. 6). Sera were collected on day 28 p.i., and antibody responses were determined by hemagglutination inhibition (HAI) assays performed according to the protocol in the WHO Manual on Animal Influenza Diagnosis and Surveillance (23). The mice were challenged with a lethal dose of PR8 (10^5 PFU). An HAI titer of 40 or more in the serum is generally considered to be protective (22). This level was reached with just 10^1 PFU of (NA+HA)^{Min} (Fig 6) and protected vaccinated mice from challenge with 10^5 PFU wt PR8 virus (Fig 6).

[0121] Example 7 – Virus composition.

[0122] Both WT and (NA+HA)^{Min} virus were purified by sucrose gradient. 5×10^7 PFU of both viruses were loaded onto SDS gels followed by Coomassie blue stain (0.1% Coomassie blue R250 for 45 min.) (Fig. 9A) or silver stain (Bio-Rad silver stain kit) (Fig. 9B and C) to detect virion protein composition. At the same PFU, WT virions contain more HA1 molecules than the (NA+HA)^{Min} virus, while the latter contains more M1 proteins.

[0123] WT and (NA+HA)^{Min} virus were also analyzed by Western blot. 2×10^7 PFU of WT and (NA+HA)^{Min} viruses were loaded onto SDS-PAGE gels and analyzed for content of PB1, NP, HA2, and M1. At the same PFU of purified virions, the virus preparations have similar amounts of NP and PB1 protein. Purified WT virions, however, have more HA2 protein, while purified (NA+HA)^{Min} virions have more M1 protein. (Fig 9D).

[0124] Example 8 - Expression of virus proteins and mRNAs in infected MDCK cells.

[0125] HA protein expression was measured by ³⁵S methionine incorporation. MDCK cells were infected with 10 MOI wild type PR8, or (NA+HA)^{Min} virus. At 3 h post infection, cells were starved for 45 min, and then labeled for 30 min. Following cell lysis, equal amounts of cell lysates were resolved by SDS PAGE and labeled proteins were

visualized by autoradiography. Expression of the HA protein is notably reduced relative to other viral proteins in (NA+HA)^{Min} virus-infected cells. (Fig.10A).

[0126] Viral mRNA in virus infected MDCK cells nucleus was analyzed by Northern blot. MDCK cells were infected with both WT and (NA+HA)^{Min} viruses at an MOI of 1. At 6h, and 9h post infection, cells were lysed using Life Technologies PARIS Kit. Nucleus and cytoplasmic portions were separated and mRNA were extracted from both portions. Northern blotting was performed using isolated mRNAs. The nuclear NP mRNA signals were relatively similar between WT and (NA+HA)^{Min} virus infected cells at all time points. Yet, WT virus infected cells, compared to (NA+HA)^{Min} viruses infected cells, contained more nuclear HA and NA mRNA, and less nuclear PB1 mRNA. (Fig. 10B)

[0127] Example 9 – Passive Immunization by serum transfer from PR8-(NA+HA)^{Min} vaccinated mice protects naïve mice from homologous WT PR8 challenge.

[0128] Groups of five Balb/C mice were vaccinated with 10⁴ PFU (NA+HA)^{Min} virus or PBS. 28 days after vaccination mouse sera were collected, and transferred to five naïve Balb/C mice in a volume of 250 ul. 24 h post transfer, mice were challenged with 10⁵ PFU of WT PR8, corresponding to 3000x LD₅₀. All passively immunized mice survived and remained healthy upon challenge, while mock transferred mice died in 8 days. These results suggest that antibodies are the major mediator of immune protection induced by (NA+HA)^{Min} virus vaccination. (Fig. 11).

[0129] Example 10 – Passive Immunization by serum transfer from PR8-(NA+HA)^{Min} vaccinated mice protects naïve mice from heterologous H3N2 challenge.

[0130] Groups of five Balb/C mice were infected with 3 x 10⁵ PFU H1N1-(NA+HA)^{Min} virus or PBS. On day 28, all mice were euthanized and their blood was collected. Sera were prepared on the same day and immediately transferred to groups of five naïve Balb/c mice (i.p injection with 250 µl of sera). 24 h post transfer, mice were challenged with 10 x LD₅₀ of H1N1 - WT PR8, H3N2 Aichi or H3N2 Victoria viruses. Their body weights (Fig. 12A) and survival rates (Fig. 12B) were monitored for 14 days post infection. 60% of sera transferred mice were protected from lethal H3N2 Aichi challenge, and survival times upon challenge of lethal H3N2 Victoria virus were extended.

[0131] Example 11 – Cross protection

[0132] Cross protection was investigated by assay of hemagglutination inhibition and neutralization. To determine inhibition of hemagglutination, groups of five Balb/C mice

were vaccinated with $10^2 - 10^4$ PFU of H1N1-(NA+HA)^{Min} virus. Sera were collected on day 28 p.i. Hemagglutination inhibition assays were performed by incubating the serum with H1N1 PR8, H3N2 Aichi or H3N2 Victoria viruses. (Fig. 13A). H1N1-(NA+HA)^{Min} virus infected mice contain abundant anti-H1N1 HA antibodies with a HAI titer from 100 – 640. The sera, however, do not contain much of the anti-H3N2 HA antibodies, since the HAI titer are 40 regardless of the vaccine dose. This data suggests that survival of (NA+HA)^{Min} virus-vaccinated mice from heterologous challenge (as illustrated in Example 5) is mainly due to immunity not correlated with antibodies, such as cellular immunity.

[0133] To test neutralization, MDCK cells were seeded onto 96 well plate on day 0. 2 fold dilutions of sera from vaccinated mice were incubated with 100 TCID₅₀ viruses for 1h and then added to pre-seeded MDCK cells on day 1. Cells were stained with crystal violet on day 4 to determine neutralization titers.

[0134] Groups of five Balb/C mice were vaccinated with 10^5 PFU of H1N1-(NA+HA)^{Min} virus. Sera were collected on day 28 p.i. Neutralization assays were performed by incubating the sera with H1N1 PR8, H3N2 Aichi or H3N2 Victoria viruses. H1N1-(NA+HA)^{Min} virus infected mice were capable of neutralizing H1N1 PR8 with a neutralization titers above 1200. The sera, interestingly, were also able to neutralize H3N2 viruses. (Fig. 13B).

[0135] Example 12 – Neuraminidase encoded by (NA+HA)^{Min}.

[0136] Viral neuraminidase cleaves terminal sialic acid residues from glycan structures on the surface of an infected cell, which promotes the release of progeny viruses. MDCK cells and MDCK-SIAT1 cells which overexpress overexpressing the α -2,6-Sialyltransferase, were infected with WT or (NA+HA)^{Min} viruses at MOI of 0.01. Virus titers were examined at 48 h p.i. In MDCK-SIAT1 cells, which overexpressed influenza receptor sialic acid, both WT and (NA+HA)^{Min} viruses grew better than MDCK cell lines. (Fig. 14). This indicates that (NA+HA)^{Min} virus comprises neuraminidase molecules encoded by NA^{Min} that cleave sialic acid residues normally.

[0137] Example 13 - T and B cell responses in lungs and spleen.

[0138] T cell responses in lungs. Groups of five Balb/C mice were with 10 PFU of WT (a dose close the LD50 of this virus) or 10 PFU (NA+HA)^{Min} (a dose over 300,000-fold below the LD50 for this virus). On day 7 post infection, mice were euthanized and their lungs were collected for flow cytometry. (NA+HA)^{Min} infected mice showed lower numbers

of CD4+T and CD8+T cells than WT-infected mice, since (NA+HA)^{Min} infection is cleared by 7 days, while WT infection is still ongoing. (Fig. 15).

[0139] B cell responses in lungs. Groups of five Balb/C mice were infected with 10 PFU of WT or (NA+HA)^{Min} viruses. On day 7 post infection, mice were euthanized and their lungs were collected for flow cytometry. WT infected mice showed higher numbers of B cells than both the (NA+HA)^{Min} viruses and the mock group, indicating the WT viruses were much harder to clear than the other two. Yet, the percentage of CD45⁺ B cells in (NA+HA)^{Min} virus infected mice were similar, or slightly higher, than the WT PR8 infected mice, which indicates they share similar ability in inducing long term protective antibodies. (Fig. 16)

[0140] T cell responses in spleen. Groups of five Balb/C mice were infected with 10 PFU of WT or (NA+HA)^{Min} viruses. On day 7 post infection, mice were euthanized and their spleens were collected for flow cytometry. Both WT and (NA+HA)^{Min} virus infected mice showed higher number of CD4+T and CD8+T cells than the mock group, indicating a strong adaptive immune responses triggered by both viruses. (Fig. 17).

[0141] B cell responses in spleen. Groups of five Balb/C mice were infected with 10 PFU of WT or (NA+HA)^{Min} viruses. On day 7 post infection, mice were euthanized and their spleens were collected for flow cytometry. (NA+HA)^{Min} infected mice showed significantly higher numbers of B cells than mock group, indicating (NA+HA)^{Min} virus is highly efficient in inducing protective antibodies. (Fig. 18).

[0142] In summary, at 7 days post infection, the response to WT virus in lung tissue involved greater numbers of CD4+T, CD8+ T and B cells to clear the viruses than the response to (NA+HA)^{Min}. In spleen, (NA+HA)^{Min} and WT infected mice both showed elevated T and B cells, indicating strong adaptive immune responses. Also, the T cell proportion of cells in spleen responding to infection by (NA+HA)^{Min} was higher than the proportion responding to infection by WT virus. (Fig. 17).

[0143] Example 14 – Flow cytometry analyses of immune cells infiltrating lung tissue.

[0144] Groups of five male Balb/C mice received 10⁴ PFU wild type PR8 (a lethal dose equal to 300-fold the LD₅₀ for this virus), 10⁴ PFU (NA+HA)^{Min} (a safe dose at least 300-fold below the LD₅₀ for this virus), or PBS. Note: A the chosen dose of 10⁴ PFU wild type PR8-infected mice invariably succumb to the infection between 4 and 9 days. On day 3

post infection, lungs were collected and flow cytometry analyses were performed. Fig. 19 shows the results for various immune cells as follows: (A) CD45⁺ leukocytes, (B) CD45⁺ Ly6G^{high} polymorphonuclear leukocytes (PMN), (C) CD45⁺CD11c⁺ I-A^{d+} F4/80⁻ dendritic cells, (D) CD45⁺ NKp46⁺ natural killer cells, (E) CD45⁺CD11b⁺Ly6C^{high}Ly6G⁻ inflammatory monocytes, (F) CD45⁺ I-A^{d+} F4/80⁺ macrophages, (G) CD45⁺CD3⁺CD4⁺ T helper cells, (H) CD45⁺ CD19⁺ B cells, and (I) CD45⁺CD19⁺IgM⁺ B cells were monitored. Most notably (NA+HA)^{Min} infection induced a significantly higher amount of natural killer cells, implicated in viral clearance, as well as a reduced infiltration of PMN, which are known to be associated with immune induced lung damage following natural influenza virus infection. Thus the marked lack of PMN infiltration during (NA+HA)^{Min} infection may explain the high degree of attenuation (i.e the absence of virus induced disease and pathology) of (NA+HA)^{Min}.

References

1. Thompson, W.W., Comanor, L., & Shay, D.K. (2006) Epidemiology of seasonal influenza: use of surveillance data and statistical models to estimate the burden of disease. *J. Infect. Dis.* 194 Suppl 2:S82-91.
2. Smith, D.J., *et al.* (2004) Mapping the antigenic and genetic evolution of influenza virus. *Science* 305(5682):371-376.
3. Bouvier, N.M. & Palese, P. (2008) The biology of influenza viruses. *Vaccine* 26 Suppl. 4:D49-53.
4. Simonsen, L., *et al.* (2005) Impact of influenza vaccination on seasonal mortality in the U.S. elderly population. *Arch. Intern. Med.* 165(3):265-272.
5. Osterholm, M.T., Kelley, N.S., Sommer, A., & Belongia, E.A. (2012) Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect. Dis.* 12(1):36-44.
6. Belshe, R.B., *et al.* (2007) Live attenuated versus inactivated influenza vaccine in infants and young children. *N. Engl. J. Med.* 356(7):685-696.
7. Hussain, A.I., Cordeiro, M., Sevilla, E., & Liu, J. (2010) Comparison of egg and high yielding MDCK cell-derived live attenuated influenza virus for commercial production of trivalent influenza vaccine: in vitro cell susceptibility and influenza virus replication kinetics in permissive and semi-permissive cells. *Vaccine* 28(22):3848-3855
8. Wang, Z., Tobler, S., Roayaei, J., & Eick, A. (2009) Live attenuated or inactivated influenza vaccines and medical encounters for respiratory illnesses among US military personnel. *JAMA* 301(9):945-953.
9. Gutman, G.A. & Hatfield, G.W. (1989) Nonrandom utilization of codon pairs in *Escherichia coli*. *Proc. Natl. Acad. Sci U. S. A.* 86(10):3699-3703.
10. Moura, G., *et al.* (2007) Large scale comparative codon-pair context analysis unveils general rules that fine-tune evolution of mRNA primary structure. *PLoS One* 2(9):e847.
11. Wang, F.P. & Li, H. (2009) Codon-pair usage and genome evolution. *Gene* 433(1-2):8-15.
12. Coleman, J.R., *et al.* (2008) Virus attenuation by genome-scale changes in codon pair bias. *Science* 320(5884):1784-1787.
13. Mueller, S., *et al.* (2010) Live attenuated influenza virus vaccines by computer-aided rational design. *Nat Biotechnol* 28(7):723-726.

14. Cello, J., Paul, A.V., & Wimmer, E. (2002) Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. *Science* 297(5583):1016-1018.
15. Sutejo, R., *et al.* (2012) Activation of type I and III interferon signalling pathways occurs in lung epithelial cells infected with low pathogenic avian influenza viruses. *PLoS One* 7(3):e33732.
16. Dove, B.K., *et al.* (2012) A quantitative proteomic analysis of lung epithelial (A549) cells infected with 2009 pandemic influenza A virus using stable isotope labelling with amino acids in cell culture. *Proteomics* 12(9):1431-1436.
17. Doma, M.K. & Parker, R. (2006) Endonucleolytic cleavage of eukaryotic mRNAs with stalls in translation elongation. *Nature* 440(7083):561-564.
18. Liu, C., Eichelberger, M.C., Compans, R.W., & Air, G.M. (1995) Influenza type A virus neuraminidase does not play a role in viral entry, replication, assembly, or budding. *J. Virol.* 69(2):1099-1106.
19. Palese, P., Tobita, K., Ueda, M., & Compans, R.W. (1974) Characterization of temperature sensitive influenza virus mutants defective in neuraminidase. *Virology* 61(2):397-410.
20. Muster, T., *et al.* (1995) Mucosal model of immunization against human immunodeficiency virus type 1 with a chimeric influenza virus. *J. Virol.* 69(11):6678-6686.
21. Koutsonanos, D.G., *et al.* (2009) Transdermal influenza immunization with vaccine-coated microneedle arrays. *PLoS One* 4(3):e4773.
22. de Jong, J.C., *et al.* (2003) Haemagglutination-inhibiting antibody to influenza virus. *Dev Biol (Basel)* 115:63-73.
23. WHO (2002) WHO Manual on Animal Influenza Diagnosis and Surveillance. www.who.int/vaccine_research/diseases/influenza/WHO_manual_on_animaldiagnosis_and_surveillance_2002_5.pdf.
24. Reed, L., Muench, M. (1938) A simple method for estimating fifty percent endpoints. *Am J. Hyg* 27(3):493-497.

Supplemental Table 1 – Expected and Observed Codon Pair Frequencies and Codon Pair Scores for 14,795 Human Genes					
amino acid pair	codon pair	expected	observed	observed / expected	CPS
AA	GCGGCG	630.04	2870	4.555	1.516
AA	GCGGCC	2330.20	4032	1.730	0.548
AA	GCTGCT	3727.41	5562	1.492	0.400
AA	GCAGCA	2856.40	4196	1.469	0.385
AA	GCAGCT	3262.97	4711	1.444	0.367
AA	GCTGCA	3262.97	4357	1.335	0.289
AA	GCTGCC	5667.77	7014	1.238	0.213
AA	GCAGCC	4961.56	6033	1.216	0.196
AA	GCAGCG	1341.51	1420	1.059	0.057
AA	GCTGCG	1532.46	1533	1.000	0.000
AA	GCGGCT	1532.46	1472	0.961	-0.040
AA	GCCGCG	2330.20	2042	0.876	-0.132
AA	GCGGCA	1341.51	1142	0.851	-0.161
AA	GCCGCC	8618.21	5141	0.597	-0.517
AA	GCCGCT	5667.77	1378	0.243	-1.414
AA	GCCGCA	4961.56	1122	0.226	-1.487
AC	GCCTGC	2333.61	3975	1.703	0.533
AC	GCCTGT	1965.56	2436	1.239	0.215
AC	GCGTGC	630.96	560	0.888	-0.119
AC	GCTTGT	1292.65	1142	0.883	-0.124
AC	GCATGT	1131.59	881	0.779	-0.250
AC	GCGTGT	531.45	322	0.606	-0.501
AC	GCTTGC	1534.70	894	0.583	-0.540
AC	GCATGC	1343.47	554	0.412	-0.886
AD	GCAGAT	2373.33	4215	1.776	0.574
AD	GCTGAT	2711.15	3887	1.434	0.360
AD	GCTGAC	3062.55	4374	1.428	0.356
AD	GCGGAC	1259.11	1625	1.291	0.255
AD	GCAGAC	2680.95	3395	1.266	0.236
AD	GCGGAT	1114.64	839	0.753	-0.284
AD	GCCGAC	4656.80	2726	0.585	-0.535
AD	GCCGAT	4122.47	920	0.223	-1.500
AE	GCAGAA	3517.48	5814	1.653	0.503
AE	GCAGAG	4703.98	7094	1.508	0.411
AE	GCGGAG	2209.23	3171	1.435	0.361
AE	GCTGAG	5373.53	7362	1.370	0.315
AE	GCTGAA	4018.14	5186	1.291	0.255
AE	GCCGAG	8170.80	5082	0.622	-0.475
AE	GCGGAA	1651.99	949	0.574	-0.554
AE	GCCGAA	6109.85	1097	0.180	-1.717
AF	GCCTTC	4447.90	7382	1.660	0.507
AF	GCATTT	2237.22	2332	1.042	0.041
AF	GCTTTT	2555.66	2580	1.010	0.009
AF	GCCTTT	3886.04	3842	0.989	-0.011

AF	GCTTTC	2925.16	2315	0.791	-0.234
AF	GCGTTC	1202.63	636	0.529	-0.637
AF	GCGTTT	1050.71	518	0.493	-0.707
AF	GCATTC	2560.68	1261	0.492	-0.708
AG	GCGGGC	1369.64	2638	1.926	0.655
AG	GCGGGG	986.17	1738	1.762	0.567
AG	GCTGGG	2398.67	3855	1.607	0.474
AG	GCTGGT	1590.73	2524	1.587	0.462
AG	GCTGGA	2457.02	3783	1.540	0.432
AG	GCAGGA	2150.87	3074	1.429	0.357
AG	GCAGGG	2099.79	2782	1.325	0.281
AG	GCAGGT	1392.52	1748	1.255	0.227
AG	GCTGGC	3331.38	3961	1.189	0.173
AG	GCAGGC	2916.28	3119	1.070	0.067
AG	GCGGGT	654.00	617	0.943	-0.058
AG	GCGGGA	1010.16	793	0.785	-0.242
AG	GCCGGG	3647.33	2240	0.614	-0.488
AG	GCCGGC	5065.58	2977	0.588	-0.532
AG	GCCGGT	2418.80	581	0.240	-1.426
AG	GCCGGA	3736.06	795	0.213	-1.547
AH	GCGCAC	748.29	983	1.314	0.273
AH	GCCCAC	2767.53	3465	1.252	0.225
AH	GCTCAT	1319.86	1471	1.115	0.108
AH	GCACAT	1155.40	1122	0.971	-0.029
AH	GCCCAT	2006.93	1827	0.910	-0.094
AH	GCTCAC	1820.07	1526	0.838	-0.176
AH	GCACAC	1593.29	1312	0.823	-0.194
AH	GCGCAT	542.64	248	0.457	-0.783
AI	GCCATC	3894.51	7798	2.002	0.694
AI	GCCATT	3079.73	3761	1.221	0.200
AI	GCAATA	815.43	924	1.133	0.125
AI	GCAATT	1773.02	1684	0.950	-0.052
AI	GCCATA	1416.41	1257	0.887	-0.119
AI	GCTATT	2025.39	1709	0.844	-0.170
AI	GCTATA	931.50	771	0.828	-0.189
AI	GCTATC	2561.23	1194	0.466	-0.763
AI	GCGATT	832.70	373	0.448	-0.803
AI	GCAATC	2242.09	984	0.439	-0.824
AI	GCGATA	382.97	149	0.389	-0.944
AI	GCGATC	1053.00	404	0.384	-0.958
AK	GCCAAG	5767.01	9818	1.702	0.532
AK	GCAAAA	2563.57	3011	1.175	0.161
AK	GCCAAA	4452.91	4794	1.077	0.074
AK	GCAAAG	3320.10	3044	0.917	-0.087
AK	GCTAAA	2928.46	2022	0.690	-0.370
AK	GCGAAG	1559.29	765	0.491	-0.712
AK	GCTAAG	3792.68	1725	0.455	-0.788
AK	GCGAAA	1203.98	409	0.340	-1.080

AL	GCGCTG	2369.16	4619	1.950	0.668
AL	GCGCTC	1140.05	1765	1.548	0.437
AL	GCTTTG	1873.51	2601	1.388	0.328
AL	GCCCTG	8762.30	11409	1.302	0.264
AL	GCCTTG	2848.79	3695	1.297	0.260
AL	GCTTTA	1115.24	1385	1.242	0.217
AL	GCCCTC	4216.45	4499	1.067	0.065
AL	GCTCTT	1912.07	2038	1.066	0.064
AL	GCATTA	976.28	986	1.010	0.010
AL	GCTCTA	1031.16	940	0.912	-0.093
AL	GCACTT	1673.82	1444	0.863	-0.148
AL	GCAATTG	1640.07	1364	0.832	-0.184
AL	GCACTA	902.68	747	0.828	-0.189
AL	GCGCTA	423.94	342	0.807	-0.215
AL	GCCCTA	1567.95	1228	0.783	-0.244
AL	GCTCTG	5762.53	4505	0.782	-0.246
AL	GCCCTT	2907.42	2230	0.767	-0.265
AL	GCTCTC	2772.95	2036	0.734	-0.309
AL	GCCTTA	1695.80	1205	0.711	-0.342
AL	GCACTG	5044.51	3522	0.698	-0.359
AL	GCGTTG	770.26	476	0.618	-0.481
AL	GCGCTT	786.11	459	0.584	-0.538
AL	GCACTC	2427.43	1415	0.583	-0.540
AL	GCGTTA	458.51	169	0.369	-0.998
AM	GCCATG	4236.47	6521	1.539	0.431
AM	GCAATG	2438.96	1900	0.779	-0.250
AM	GCTATG	2786.11	1561	0.560	-0.579
AM	GCGATG	1145.46	625	0.546	-0.606
AN	GCCAAC	3190.28	5452	1.709	0.536
AN	GCAAAT	1667.60	2282	1.368	0.314
AN	GCCAAT	2896.62	3122	1.078	0.075
AN	GCAAAC	1836.66	1512	0.823	-0.195
AN	GCTAAT	1904.97	1356	0.712	-0.340
AN	GCTAAC	2098.09	925	0.441	-0.819
AN	GCGAAC	862.59	331	0.384	-0.958
AN	GCGAAT	783.19	260	0.332	-1.103
AP	GCGCCG	406.74	1172	2.881	1.058
AP	GCGCCC	1122.56	2271	2.023	0.705
AP	GCCCCG	1504.34	2335	1.552	0.440
AP	GCTCCA	2360.19	2463	1.044	0.043
AP	GCTCCT	2445.47	2548	1.042	0.041
AP	GCCCCC	4151.78	3957	0.953	-0.048
AP	GCACCT	2140.76	2028	0.947	-0.054
AP	GCCCCA	3588.82	3371	0.939	-0.063
AP	GCACCA	2066.10	1831	0.886	-0.121
AP	GCACCC	2390.20	2111	0.883	-0.124
AP	GCCCCT	3718.49	3269	0.879	-0.129
AP	GCTCCC	2730.42	2384	0.873	-0.136

AP	GCTCCG	989.33	773	0.781	-0.247
AP	GCGCCT	1005.41	778	0.774	-0.256
AP	GCACCG	866.06	571	0.659	-0.417
AP	GCGCCA	970.35	595	0.613	-0.489
AQ	GCCCAG	7143.67	9550	1.337	0.290
AQ	GCGCAG	1931.51	2101	1.088	0.084
AQ	GCACAA	1472.79	1416	0.961	-0.039
AQ	GCTCAA	1682.42	1522	0.905	-0.100
AQ	GCTCAG	4698.04	4141	0.881	-0.126
AQ	GCACAG	4112.65	3374	0.820	-0.198
AQ	GCCCAA	2558.23	1943	0.760	-0.275
AQ	GCGCAA	691.70	244	0.353	-1.042
AR	GCGCGC	580.17	1255	2.163	0.772
AR	GCGCGG	634.54	1175	1.852	0.616
AR	GCCCCG	2346.82	3946	1.681	0.520
AR	GCCCCG	2145.76	3135	1.461	0.379
AR	GCCAGG	2323.57	3242	1.395	0.333
AR	GCAAGA	1362.59	1559	1.144	0.135
AR	GCTCGA	836.64	943	1.127	0.120
AR	GCCCCA	1272.16	1418	1.115	0.109
AR	GCCCCG	918.67	935	1.018	0.018
AR	GCTCGT	604.17	595	0.985	-0.015
AR	GCCAGA	2366.81	2219	0.938	-0.064
AR	GCTCGG	1543.39	1295	0.839	-0.175
AR	GCGCGT	248.39	205	0.825	-0.192
AR	GCAAGG	1337.69	1089	0.814	-0.206
AR	GCGAGG	628.25	486	0.774	-0.257
AR	GCACGA	732.39	533	0.728	-0.318
AR	GCTCGC	1411.16	941	0.667	-0.405
AR	GCGCGA	343.97	226	0.657	-0.420
AR	GCACGT	528.89	338	0.639	-0.448
AR	GCACGG	1351.08	859	0.636	-0.453
AR	GCACGC	1235.33	619	0.501	-0.691
AR	GCTAGA	1556.53	714	0.459	-0.779
AR	GCGAGA	639.94	263	0.411	-0.889
AR	GCTAGG	1528.10	487	0.319	-1.144
AS	GCCTCG	963.41	1977	2.052	0.719
AS	GCGTCG	260.49	465	1.785	0.579
AS	GCCAGC	4127.58	6466	1.567	0.449
AS	GCCTCC	3643.21	5443	1.494	0.401
AS	GCTTCT	2084.25	2488	1.194	0.177
AS	GCCAGT	2604.12	3085	1.185	0.169
AS	GCATCT	1824.55	2154	1.181	0.166
AS	GCTTCA	1684.99	1932	1.147	0.137
AS	GCGTCC	985.05	1079	1.095	0.091
AS	GCATCA	1475.04	1531	1.038	0.037
AS	GCCTCT	3169.23	3235	1.021	0.021
AS	GCCTCA	2562.14	2514	0.981	-0.019

AS	GCTTCC	2395.96	2295	0.958	-0.043
AS	GCAAGT	1499.21	1307	0.872	-0.137
AS	GCTTCG	633.59	516	0.814	-0.205
AS	GCATCC	2097.42	1658	0.790	-0.235
AS	GCATCG	554.64	403	0.727	-0.319
AS	GCGTCT	856.90	521	0.608	-0.498
AS	GCGAGC	1116.02	595	0.533	-0.629
AS	GCGTCA	692.75	319	0.460	-0.775
AS	GCAAGC	2376.27	1080	0.454	-0.789
AS	GCTAGT	1712.60	737	0.430	-0.843
AS	GCGAGT	704.10	265	0.376	-0.977
AS	GCTAGC	2714.51	673	0.248	-1.395
AT	GCCACG	1262.40	2478	1.963	0.674
AT	GCCACC	3842.98	6598	1.717	0.541
AT	GCCACA	3111.04	4031	1.296	0.259
AT	GCCACT	2751.18	3205	1.165	0.153
AT	GCAACA	1791.05	1761	0.983	-0.017
AT	GCGACG	341.33	329	0.964	-0.037
AT	GCAACT	1583.87	1509	0.953	-0.048
AT	GCTACT	1809.31	1395	0.771	-0.260
AT	GCTACA	2045.98	1528	0.747	-0.292
AT	GCGACC	1039.07	601	0.578	-0.547
AT	GCAACC	2212.43	1259	0.569	-0.564
AT	GCTACC	2527.34	1364	0.540	-0.617
AT	GCAACG	726.77	384	0.528	-0.638
AT	GCTACG	830.22	363	0.437	-0.827
AT	GCGACT	743.87	308	0.414	-0.882
AT	GCGACA	841.17	347	0.413	-0.885
AV	GCTGTT	1736.99	3025	1.742	0.555
AV	GCTGTG	4399.56	7279	1.654	0.503
AV	GCTGTA	1127.89	1750	1.552	0.439
AV	GCTGTC	2223.90	3351	1.507	0.410
AV	GCAGTA	987.35	1401	1.419	0.350
AV	GCGGTG	1808.80	2487	1.375	0.318
AV	GCAGTT	1520.56	2087	1.373	0.317
AV	GCAGTG	3851.36	4349	1.129	0.122
AV	GCGGTC	914.32	883	0.966	-0.035
AV	GCAGTC	1946.80	1806	0.928	-0.075
AV	GCCGTG	6689.81	4322	0.646	-0.437
AV	GCGGTT	714.13	423	0.592	-0.524
AV	GCGGTA	463.71	270	0.582	-0.541
AV	GCCGTC	3381.59	1798	0.532	-0.632
AV	GCCGTT	2641.21	563	0.213	-1.546
AV	GCCGTA	1715.03	329	0.192	-1.651
AW	GCCTGG	2528.22	3848	1.522	0.420
AW	GCGTGG	683.58	558	0.816	-0.203
AW	GCTTGG	1662.69	1066	0.641	-0.445
AW	GCATGG	1455.51	858	0.589	-0.529

AY	GCCTAC	2643.77	4073	1.541	0.432
AY	GCCTAT	2148.26	2457	1.144	0.134
AY	GCTTAT	1412.81	1478	1.046	0.045
AY	GCATAT	1236.77	1244	1.006	0.006
AY	GCTTAC	1738.68	1139	0.655	-0.423
AY	GCGTAC	714.83	429	0.600	-0.511
AY	GCATAC	1522.04	868	0.570	-0.562
AY	GCGTAT	580.85	310	0.534	-0.628
CA	TGTGCT	1164.04	2021	1.736	0.552
CA	TGTGCC	1769.99	2992	1.690	0.525
CA	TGTGCA	1019.00	1708	1.676	0.517
CA	TGTGCG	478.57	477	0.997	-0.003
CA	TGCGCG	568.18	502	0.884	-0.124
CA	TGCGCC	2101.42	1313	0.625	-0.470
CA	TGCGCT	1382.00	368	0.266	-1.323
CA	TGCGCA	1209.80	312	0.258	-1.355
CC	TGCTGC	1534.17	2610	1.701	0.531
CC	TGCTGT	1292.21	1571	1.216	0.195
CC	TGTTGT	1088.41	529	0.486	-0.721
CC	TGTTGC	1292.21	497	0.385	-0.956
CD	TGTGAC	1920.20	3470	1.807	0.592
CD	TGTGAT	1699.87	2853	1.678	0.518
CD	TGCGAC	2279.75	1134	0.497	-0.698
CD	TGCGAT	2018.17	461	0.228	-1.477
CE	TGTGAA	1901.69	3636	1.912	0.648
CE	TGTGAG	2543.16	3935	1.547	0.437
CE	TGCGAG	3019.37	1709	0.566	-0.569
CE	TGCGAA	2257.78	442	0.196	-1.631
CF	TGCTTC	1891.74	2684	1.419	0.350
CF	TGCTTT	1652.78	1685	1.019	0.019
CF	TGTTTT	1392.11	1096	0.787	-0.239
CF	TGTTTC	1593.38	1065	0.668	-0.403
CG	TGTGGG	1594.78	3240	2.032	0.709
CG	TGTGGA	1633.57	2846	1.742	0.555
CG	TGTGGT	1057.61	1627	1.538	0.431
CG	TGTGGC	2214.90	3133	1.415	0.347
CG	TGCGGG	1893.40	1137	0.601	-0.510
CG	TGCGGC	2629.63	1461	0.556	-0.588
CG	TGCGGT	1255.64	344	0.274	-1.295
CG	TGCGGA	1939.46	431	0.222	-1.504
CH	TGCCAC	1618.50	2144	1.325	0.281
CH	TGCCAT	1173.68	1253	1.068	0.065
CH	TGTCAT	988.58	831	0.841	-0.174
CH	TGTCAC	1363.24	916	0.672	-0.398
CI	TGCATC	1821.04	2813	1.545	0.435
CI	TGCATT	1440.05	1579	1.096	0.092
CI	TGCATA	662.30	576	0.870	-0.140
CI	TGTATA	557.84	474	0.850	-0.163

CI	TGTATT	1212.94	927	0.764	-0.269
CI	TGTATC	1533.83	859	0.560	-0.580
CK	TGCAAG	2777.53	3348	1.205	0.187
CK	TGCAAA	2144.62	2441	1.138	0.129
CK	TGTAAA	1806.38	1770	0.980	-0.020
CK	TGTAAG	2339.47	1509	0.645	-0.438
CL	TGCCTC	1722.14	2468	1.433	0.360
CL	TGCCTG	3578.83	4525	1.264	0.235
CL	TGTTTA	583.38	704	1.207	0.188
CL	TGCCTT	1187.49	1384	1.165	0.153
CL	TGTTTG	980.04	1079	1.101	0.096
CL	TGCTTG	1163.55	1179	1.013	0.013
CL	TGTCTT	1000.21	940	0.940	-0.062
CL	TGCCTA	640.41	585	0.913	-0.090
CL	TGTCTA	539.40	481	0.892	-0.115
CL	TGCTTA	692.62	565	0.816	-0.204
CL	TGTCTC	1450.53	1010	0.696	-0.362
CL	TGTCTG	3014.39	1633	0.542	-0.613
CM	TGCATG	1518.22	1979	1.304	0.265
CM	TGTATG	1278.78	818	0.640	-0.447
CN	TGCAAC	1825.04	2351	1.288	0.253
CN	TGCAAT	1657.05	1636	0.987	-0.013
CN	TGTAAT	1395.71	1349	0.967	-0.034
CN	TGTAAC	1537.20	1079	0.702	-0.354
CP	TGCCCCG	687.28	978	1.423	0.353
CP	TGCCCC	1896.80	2279	1.201	0.184
CP	TGCCCA	1639.61	1728	1.054	0.053
CP	TGCCCT	1698.85	1690	0.995	-0.005
CP	TGTCCT	1430.91	1333	0.932	-0.071
CP	TGTCCA	1381.01	1263	0.915	-0.089
CP	TGTCCC	1597.65	1369	0.857	-0.154
CP	TGTCCG	578.88	271	0.468	-0.759
CQ	TGCCAG	3338.89	4321	1.294	0.258
CQ	TGCCAA	1195.69	1319	1.103	0.098
CQ	TGTCAA	1007.11	905	0.899	-0.107
CQ	TGTCAG	2812.30	1809	0.643	-0.441
CR	TGCCGC	1031.52	1860	1.803	0.590
CR	TGCCGG	1128.18	1543	1.368	0.313
CR	TGCAGG	1117.00	1450	1.298	0.261
CR	TGCCGT	441.63	541	1.225	0.203
CR	TGCCGA	611.56	742	1.213	0.193
CR	TGCAGA	1137.78	1252	1.100	0.096
CR	TGTCGA	515.11	458	0.889	-0.118
CR	TGTCGT	371.98	308	0.828	-0.189
CR	TGTAGA	958.34	570	0.595	-0.520
CR	TGTCGC	868.83	497	0.572	-0.559
CR	TGTCGG	950.24	463	0.487	-0.719
CR	TGTAGG	940.83	389	0.413	-0.883

CS	TGCAGC	1990.73	3150	1.582	0.459
CS	TGCTCC	1757.12	2397	1.364	0.311
CS	TGCAGT	1255.97	1701	1.354	0.303
CS	TGCTCG	464.65	571	1.229	0.206
CS	TGTTCT	1287.45	1184	0.920	-0.084
CS	TGCTCT	1528.52	1393	0.911	-0.093
CS	TGTTCA	1040.83	932	0.895	-0.110
CS	TGCTCA	1235.72	1079	0.873	-0.136
CS	TGTTCC	1479.99	1102	0.745	-0.295
CS	TGTAGT	1057.88	699	0.661	-0.414
CS	TGTTTCG	391.37	192	0.491	-0.712
CS	TGTAGC	1676.76	767	0.457	-0.782
CT	TGCACG	535.88	829	1.547	0.436
CT	TGCACC	1631.31	2321	1.423	0.353
CT	TGCACA	1320.60	1508	1.142	0.133
CT	TGCACT	1167.85	1185	1.015	0.015
CT	TGTACT	983.66	802	0.815	-0.204
CT	TGTACA	1112.32	830	0.746	-0.293
CT	TGTACC	1374.02	942	0.686	-0.377
CT	TGTACG	451.36	160	0.354	-1.037
CV	TGTGTC	1064.94	1821	1.710	0.536
CV	TGTGTT	831.78	1383	1.663	0.508
CV	TGTGTA	540.10	866	1.603	0.472
CV	TGTGTG	2106.78	3241	1.538	0.431
CV	TGCGTG	2501.27	1537	0.614	-0.487
CV	TGCGTC	1264.35	734	0.581	-0.544
CV	TGCGTT	987.53	219	0.222	-1.506
CV	TGCGTA	641.24	137	0.214	-1.543
CW	TGCTGG	1275.05	1842	1.445	0.368
CW	TGTTGG	1073.95	507	0.472	-0.751
CY	TGCTAC	1379.34	1995	1.446	0.369
CY	TGCTAT	1120.82	1170	1.044	0.043
CY	TGTTAT	944.05	653	0.692	-0.369
CY	TGTTAC	1161.80	788	0.678	-0.388
DA	GATGCT	2675.13	5292	1.978	0.682
DA	GATGCA	2341.80	3898	1.665	0.510
DA	GATGCC	4067.71	5983	1.471	0.386
DA	GACGCG	1242.39	1116	0.898	-0.107
DA	GATGCG	1099.83	972	0.884	-0.124
DA	GACGCC	4594.94	2668	0.581	-0.544
DA	GACGCA	2645.34	852	0.322	-1.133
DA	GACGCT	3021.87	908	0.300	-1.202
DC	GACTGC	2386.86	3465	1.452	0.373
DC	GACTGT	2010.41	2804	1.395	0.333
DC	GATTGT	1779.74	1163	0.653	-0.425
DC	GATTGC	2112.99	858	0.406	-0.901
DD	GATGAT	4271.42	7846	1.837	0.608
DD	GATGAC	4825.06	7181	1.488	0.398

DD	GACGAC	5450.46	2965	0.544	-0.609
DD	GACGAT	4825.06	1380	0.286	-1.252
DE	GATGAA	5114.33	10045	1.964	0.675
DE	GATGAG	6839.48	9573	1.400	0.336
DE	GACGAG	7725.97	4498	0.582	-0.541
DE	GACGAA	5777.22	1341	0.232	-1.461
DF	GACTTC	4696.28	6094	1.298	0.261
DF	GACTTT	4103.05	4250	1.036	0.035
DF	GATTTT	3632.26	3485	0.959	-0.041
DF	GATTTC	4157.42	2760	0.664	-0.410
DG	GATGGT	1910.36	3443	1.802	0.589
DG	GATGGA	2950.72	5133	1.740	0.554
DG	GATGGG	2880.65	4437	1.540	0.432
DG	GATGGC	4000.77	5419	1.354	0.303
DG	GACGGC	4519.33	2987	0.661	-0.414
DG	GACGGG	3254.02	1979	0.608	-0.497
DG	GACGGT	2157.97	723	0.335	-1.094
DG	GACGGA	3333.18	886	0.266	-1.325
DH	GACCAC	2653.74	3480	1.311	0.271
DH	GACCAT	1924.41	2014	1.047	0.046
DH	GATCAT	1703.60	1623	0.953	-0.048
DH	GATCAC	2349.25	1514	0.644	-0.439
DI	GACATC	4715.94	6532	1.385	0.326
DI	GACATT	3729.31	4087	1.096	0.092
DI	GATATT	3301.40	3271	0.991	-0.009
DI	GATATA	1518.36	1495	0.985	-0.016
DI	GACATA	1715.16	1565	0.912	-0.092
DI	GATATC	4174.83	2205	0.528	-0.638
DK	GACAAG	5562.52	7324	1.317	0.275
DK	GACAAA	4295.02	4794	1.116	0.110
DK	GATAAA	3802.20	3855	1.014	0.014
DK	GATAAG	4924.27	2611	0.530	-0.634
DL	GACCTC	3785.97	5029	1.328	0.284
DL	GACTTG	2557.95	3396	1.328	0.283
DL	GATTTA	1347.95	1740	1.291	0.255
DL	GACCTG	7867.71	9796	1.245	0.219
DL	GATTTG	2264.44	2687	1.187	0.171
DL	GACCTT	2610.58	2774	1.063	0.061
DL	GATCTT	2311.04	2416	1.045	0.044
DL	GACCTA	1407.87	1416	1.006	0.006
DL	GACCTA	1522.66	1403	0.921	-0.082
DL	GATCTA	1246.33	1020	0.818	-0.200
DL	GATCTC	3351.56	2214	0.661	-0.415
DL	GATCTG	6964.95	3348	0.481	-0.733
DM	GACATG	4089.63	5411	1.323	0.280
DM	GATATG	3620.37	2299	0.635	-0.454
DN	GACAAC	3511.00	4849	1.381	0.323
DN	GACAAT	3187.82	3349	1.051	0.049

DN	GATAAT	2822.05	2549	0.903	-0.102
DN	GATAAC	3108.14	1882	0.606	-0.502
DP	GACCCC	3732.11	5119	1.372	0.316
DP	GACCCG	1352.28	1692	1.251	0.224
DP	GACCCT	3342.62	3700	1.107	0.102
DP	GATCCT	2959.08	3111	1.051	0.050
DP	GACCCA	3226.05	3205	0.993	-0.007
DP	GATCCA	2855.89	2349	0.823	-0.195
DP	GATCCC	3303.88	2338	0.708	-0.346
DP	GATCCG	1197.11	455	0.380	-0.967
DQ	GACCAG	5250.37	6524	1.243	0.217
DQ	GACCAA	1880.22	2169	1.154	0.143
DQ	GATCAA	1664.48	1808	1.086	0.083
DQ	GATCAG	4647.93	2942	0.633	-0.457
DR	GACCGC	1807.77	2634	1.457	0.376
DR	GACAGA	1994.00	2869	1.439	0.364
DR	GACAGG	1957.57	2730	1.395	0.333
DR	GACCGT	773.97	1029	1.330	0.285
DR	GACCGG	1977.16	2568	1.299	0.261
DR	GACCGA	1071.78	1292	1.205	0.187
DR	GATCGA	948.80	923	0.973	-0.028
DR	GATCGT	685.16	626	0.914	-0.090
DR	GATAGA	1765.20	1123	0.636	-0.452
DR	GATCGG	1750.30	859	0.491	-0.712
DR	GATCGC	1600.34	754	0.471	-0.753
DR	GATAGG	1732.96	658	0.380	-0.968
DS	GACTCG	918.57	1527	1.662	0.508
DS	GACAGC	3935.48	6143	1.561	0.445
DS	GACAGT	2482.92	3657	1.473	0.387
DS	GATTCT	2675.01	2968	1.110	0.104
DS	GACTCC	3473.65	3800	1.094	0.090
DS	GATTCA	2162.59	2129	0.984	-0.016
DS	GACTCA	2442.89	2382	0.975	-0.025
DS	GACTCT	3021.73	2910	0.963	-0.038
DS	GATTCC	3075.07	2186	0.711	-0.341
DS	GATAGT	2198.02	1355	0.616	-0.484
DS	GATTCG	813.17	414	0.509	-0.675
DS	GATAGC	3483.91	1212	0.348	-1.056
DT	GACACG	1110.58	1842	1.659	0.506
DT	GACACC	3380.79	4666	1.380	0.322
DT	GACACA	2736.88	3538	1.293	0.257
DT	GACACT	2420.30	2688	1.111	0.105
DT	GATACT	2142.59	1731	0.808	-0.213
DT	GATACA	2422.85	1788	0.738	-0.304
DT	GATACC	2992.87	1586	0.530	-0.635
DT	GATACG	983.15	351	0.357	-1.030
DV	GATGTT	1957.96	3699	1.889	0.636
DV	GATGTA	1271.37	2214	1.741	0.555

DV	GATGTC	2506.81	3869	1.543	0.434
DV	GATGTG	4959.23	6668	1.345	0.296
DV	GACGTG	5602.02	3616	0.645	-0.438
DV	GACGTC	2831.73	1654	0.584	-0.538
DV	GACGTT	2211.73	672	0.304	-1.191
DV	GACGTA	1436.16	385	0.268	-1.316
DW	GACTGG	2619.27	3853	1.471	0.386
DW	GATTGG	2318.73	1085	0.468	-0.759
DY	GACTAC	3307.71	3930	1.188	0.172
DY	GATTAT	2379.36	2608	1.096	0.092
DY	GACTAT	2687.76	2853	1.061	0.060
DY	GATTAC	2928.18	1912	0.653	-0.426
EA	GAGGCG	2437.29	3179	1.304	0.266
EA	GAAGCA	3880.59	4844	1.248	0.222
EA	GAAGCT	4432.94	5143	1.160	0.149
EA	GAGGCC	9014.27	9805	1.088	0.084
EA	GAGGCT	5928.25	5314	0.896	-0.109
EA	GAGGCA	5189.57	4530	0.873	-0.136
EA	GAAGCC	6740.57	5649	0.838	-0.177
EA	GAAGCG	1822.52	982	0.539	-0.618
EC	GAATGT	2182.58	3541	1.622	0.484
EC	GAGTGT	2918.80	2792	0.957	-0.044
EC	GAGTGC	3465.35	2987	0.862	-0.149
EC	GAATGC	2591.27	1838	0.709	-0.343
ED	GAAGAT	6605.82	9691	1.467	0.383
ED	GAGGAC	9979.09	9684	0.970	-0.030
ED	GAAGAC	7462.02	6820	0.914	-0.090
ED	GAGGAT	8834.07	6686	0.757	-0.279
EE	GAAGAA	10747.11	14461	1.346	0.297
EE	GAGGAG	19220.31	21731	1.131	0.123
EE	GAAGAG	14372.29	11875	0.826	-0.191
EE	GAGGAA	14372.29	10645	0.741	-0.300
EF	GAATTT	3136.91	4237	1.351	0.301
EF	GAGTTC	4801.58	4739	0.987	-0.013
EF	GAGTTT	4195.05	4095	0.976	-0.024
EF	GAATTC	3590.46	2653	0.739	-0.303
EG	GAAGGA	3358.73	5032	1.498	0.404
EG	GAAGGT	2174.51	2839	1.306	0.267
EG	GAAGGG	3278.97	3559	1.085	0.082
EG	GAGGGC	6090.10	6505	1.068	0.066
EG	GAAGGC	4553.97	4340	0.953	-0.048
EG	GAGGGG	4385.02	3795	0.865	-0.145
EG	GAGGGT	2908.01	2378	0.818	-0.201
EG	GAGGGA	4491.69	2793	0.622	-0.475
EH	GAACAT	2017.28	2539	1.259	0.230
EH	GAGCAC	3720.16	4190	1.126	0.119
EH	GAGCAT	2697.74	2448	0.907	-0.097
EH	GAACAC	2781.81	2040	0.733	-0.310

EI	GAAATA	1687.78	3007	1.782	0.578
EI	GAAATT	3669.78	4788	1.305	0.266
EI	GAGATC	6206.03	6191	0.998	-0.002
EI	GAGATT	4907.66	3978	0.811	-0.210
EI	GAGATA	2257.09	1785	0.791	-0.235
EI	GAAATC	4640.66	3620	0.780	-0.248
EK	GAGAAG	12729.57	15133	1.189	0.173
EK	GAAAAA	7349.75	7522	1.023	0.023
EK	GAGAAA	9828.94	9127	0.929	-0.074
EK	GAAAAG	9518.74	7645	0.803	-0.219
EL	GAGCTG	10945.64	15625	1.428	0.356
EL	GAATTA	1584.03	2256	1.424	0.354
EL	GAACTA	1464.61	1830	1.249	0.223
EL	GAACCT	2715.79	3371	1.241	0.216
EL	GAGCTC	5267.08	5877	1.116	0.110
EL	GAGCTA	1958.64	2049	1.046	0.045
EL	GAATTG	2661.03	2335	0.877	-0.131
EL	GAGCTT	3631.87	3084	0.849	-0.164
EL	GAGTTG	3558.64	2719	0.764	-0.269
EL	GAAGTC	3938.54	2632	0.668	-0.403
EL	GAGTTA	2118.35	1357	0.641	-0.445
EL	GAAGTG	8184.78	4894	0.598	-0.514
EM	GAAATG	4983.92	5010	1.005	0.005
EM	GAGATG	6665.08	6639	0.996	-0.004
EN	GAAAAT	4791.73	6977	1.456	0.376
EN	GAGAAC	7057.70	6756	0.957	-0.044
EN	GAAAAC	5277.51	4930	0.934	-0.068
EN	GAGAAT	6408.07	4872	0.760	-0.274
EP	GAGCCG	1650.94	2438	1.477	0.390
EP	GAGCCC	4556.38	6270	1.376	0.319
EP	GAGCCT	4080.86	4236	1.038	0.037
EP	GAGCCA	3938.55	4067	1.033	0.032
EP	GAACCA	2945.12	2684	0.911	-0.093
EP	GAACCT	3051.53	2547	0.835	-0.181
EP	GAACCC	3407.10	2106	0.618	-0.481
EP	GAACCG	1234.52	517	0.419	-0.870
EQ	GAACAA	2579.50	3396	1.317	0.275
EQ	GAGCAG	9632.80	11185	1.161	0.149
EQ	GAGCAA	3449.61	3185	0.923	-0.080
EQ	GAACAG	7203.08	5099	0.708	-0.345
ER	GAAAGA	2650.27	3769	1.422	0.352
ER	GAGAGG	3479.50	4315	1.240	0.215
ER	GAGCGG	3514.32	4356	1.240	0.215
ER	GAGCGC	3213.23	3682	1.146	0.136
ER	GAAAGG	2601.85	2679	1.030	0.029
ER	GAGAGA	3544.25	3633	1.025	0.025
ER	GAGCGT	1375.70	1286	0.935	-0.067
ER	GAACGT	1028.70	894	0.869	-0.140

ER	GAACGA	1424.52	1188	0.834	-0.182
ER	GAGCGA	1905.04	1562	0.820	-0.199
ER	GAACGG	2627.88	1333	0.507	-0.679
ER	GAACGC	2402.74	1071	0.446	-0.808
ES	GAAAGT	2081.93	3138	1.507	0.410
ES	GAGAGC	4413.03	5786	1.311	0.271
ES	GAGAGT	2784.21	3237	1.163	0.151
ES	GAGTCG	1030.03	1174	1.140	0.131
ES	GAATCT	2533.73	2812	1.110	0.104
ES	GAATCA	2048.37	2131	1.040	0.040
ES	GAAAGC	3299.91	2880	0.873	-0.136
ES	GAGTCC	3895.16	3392	0.871	-0.138
ES	GAGTCT	3388.40	2799	0.826	-0.191
ES	GAGTCA	2739.33	2198	0.802	-0.220
ES	GAATCC	2912.67	1943	0.667	-0.405
ES	GAATCG	770.22	407	0.528	-0.638
ET	GAGACG	1658.42	2190	1.321	0.278
ET	GAAACA	3056.09	3851	1.260	0.231
ET	GAAACT	2702.59	3224	1.193	0.176
ET	GAGACC	5048.51	5514	1.092	0.088
ET	GAGACA	4086.97	3619	0.885	-0.122
ET	GAGACT	3614.21	3028	0.838	-0.177
ET	GAAACC	3775.11	2950	0.781	-0.247
ET	GAAACG	1240.11	806	0.650	-0.431
EV	GAAGTA	1580.16	2675	1.693	0.526
EV	GAAGTT	2433.50	3724	1.530	0.425
EV	GAGGTG	8242.83	9074	1.101	0.096
EV	GAAGTC	3115.66	2860	0.918	-0.086
EV	GAGGTC	4166.62	3741	0.898	-0.108
EV	GAAGTG	6163.71	5122	0.831	-0.185
EV	GAGGTT	3254.36	2359	0.725	-0.322
EV	GAGGTA	2113.17	1515	0.717	-0.333
EW	GAGTGG	3085.08	3238	1.050	0.048
EW	GAATGG	2306.92	2154	0.934	-0.069
EY	GAATAT	2307.55	3428	1.486	0.396
EY	GAGTAC	3797.72	3796	1.000	0.000
EY	GAGTAT	3085.93	2596	0.841	-0.173
EY	GAATAC	2839.80	2211	0.779	-0.250
FA	TTTGCA	1643.98	3299	2.007	0.696
FA	TTTGCT	1877.98	3746	1.995	0.690
FA	TTTGCC	2855.59	4348	1.523	0.420
FA	TTTGCG	772.10	622	0.806	-0.216
FA	TTCGCG	883.73	598	0.677	-0.391
FA	TTCGCC	3268.46	1802	0.551	-0.595
FA	TTCGCT	2149.50	516	0.240	-1.427
FA	TTCGCA	1881.67	402	0.214	-1.543
FC	TTCTGC	2058.60	3045	1.479	0.391
FC	TTCTGT	1733.93	2055	1.185	0.170

FC	TTTTGT	1514.90	1159	0.765	-0.268
FC	TTTTGC	1798.56	847	0.471	-0.753
FD	TTTGAT	2786.65	5380	1.931	0.658
FD	TTTGAC	3147.84	4737	1.505	0.409
FD	TTCGAC	3602.96	1746	0.485	-0.724
FD	TTCGAT	3189.55	864	0.271	-1.306
FE	TTTGAA	3016.02	6247	2.071	0.728
FE	TTTGAG	4033.37	6066	1.504	0.408
FE	TTCGAG	4616.53	2165	0.469	-0.757
FE	TTCGAA	3452.08	640	0.185	-1.685
FF	TTCTTC	3429.53	5168	1.507	0.410
FF	TTCTTT	2996.32	2989	0.998	-0.002
FF	TTTTTT	2617.83	1937	0.740	-0.301
FF	TTTTTC	2996.32	1946	0.649	-0.432
FG	TTTGGA	2068.21	4271	2.065	0.725
FG	TTTGGT	1339.00	2552	1.906	0.645
FG	TTTGGG	2019.09	3449	1.708	0.535
FG	TTTGGC	2804.20	3462	1.235	0.211
FG	TTCGGG	2311.02	1292	0.559	-0.581
FG	TTCGGC	3209.64	1648	0.513	-0.667
FG	TTCGGT	1532.60	419	0.273	-1.297
FG	TTCGGA	2367.24	558	0.236	-1.445
FH	TTCCAC	2463.48	3200	1.299	0.262
FH	TTTCAT	1560.78	1697	1.087	0.084
FH	TTCCAT	1786.44	1866	1.045	0.044
FH	TTTCAC	2152.30	1200	0.558	-0.584
FI	TTCATC	3454.46	5156	1.493	0.400
FI	TTCATT	2731.75	2953	1.081	0.078
FI	TTTATT	2386.67	2296	0.962	-0.039
FI	TTTATA	1097.66	950	0.865	-0.144
FI	TTCATA	1256.36	1035	0.824	-0.194
FI	TTTATC	3018.10	1555	0.515	-0.663
FK	TTCAAG	4090.45	5137	1.256	0.228
FK	TTCAAA	3158.38	3245	1.027	0.027
FK	TTTAAA	2759.42	2762	1.001	0.001
FK	TTTAAG	3573.75	2438	0.682	-0.382
FL	TTCTTC	3228.53	4426	1.371	0.315
FL	TTCTTG	6709.28	8734	1.302	0.264
FL	TTTTTA	1134.45	1334	1.176	0.162
FL	TTTCTT	1945.00	2267	1.166	0.153
FL	TTCTTA	1200.58	1280	1.066	0.064
FL	TTTCTA	1048.92	1087	1.036	0.036
FL	TTCTTG	2181.32	2239	1.026	0.026
FL	TTCTTT	2226.21	2150	0.966	-0.035
FL	TTTTTG	1905.78	1799	0.944	-0.058
FL	TTCTTA	1298.47	1144	0.881	-0.127
FL	TTTCTC	2820.70	1904	0.675	-0.393
FL	TTTCTG	5861.77	3197	0.545	-0.606

FM	TTCATG	2804.11	3662	1.306	0.267
FM	TTTATG	2449.89	1592	0.650	-0.431
FN	TTCAAC	2855.47	3919	1.372	0.317
FN	TTTAAT	2265.13	2185	0.965	-0.036
FN	TTCAAT	2592.63	2456	0.947	-0.054
FN	TTTAAC	2494.77	1648	0.661	-0.415
FP	TTCCCG	961.40	1205	1.253	0.226
FP	TTTCCT	2076.25	2539	1.223	0.201
FP	TTCCCC	2653.35	3099	1.168	0.155
FP	TTTCCA	2003.85	2141	1.068	0.066
FP	TTCCCA	2293.57	2310	1.007	0.007
FP	TTCCCT	2376.44	2379	1.001	0.001
FP	TTTCCC	2318.18	1529	0.660	-0.416
FP	TTTCCG	839.96	321	0.382	-0.962
FQ	TTCCAG	5468.69	7069	1.293	0.257
FQ	TTTCAA	1711.02	1803	1.054	0.052
FQ	TTCCAA	1958.40	1980	1.011	0.011
FQ	TTTCAG	4777.89	3064	0.641	-0.444
FR	TTCCGC	1531.47	2588	1.690	0.525
FR	TTCCGA	907.97	1410	1.553	0.440
FR	TTCCGG	1674.97	2451	1.463	0.381
FR	TTCCGT	655.68	893	1.362	0.309
FR	TTCAGA	1689.24	1852	1.096	0.092
FR	TTCAGG	1658.38	1810	1.091	0.087
FR	TTTCGA	793.28	850	1.072	0.069
FR	TTTCGT	572.85	490	0.855	-0.156
FR	TTTAGA	1475.86	947	0.642	-0.444
FR	TTTAGG	1448.90	691	0.477	-0.740
FR	TTTCGG	1463.39	688	0.470	-0.755
FR	TTTCGC	1338.02	540	0.404	-0.907
FS	TTCTCC	2990.83	4507	1.507	0.410
FS	TTCAGC	3388.47	4577	1.351	0.301
FS	TTCAGT	2137.80	2692	1.259	0.231
FS	TTCTCG	790.89	910	1.151	0.140
FS	TTTTCT	2273.08	2536	1.116	0.109
FS	TTCTCT	2601.73	2741	1.054	0.052
FS	TTTTCA	1837.65	1903	1.036	0.035
FS	TTCTCA	2103.34	1997	0.949	-0.052
FS	TTTTCC	2613.03	1872	0.716	-0.334
FS	TTTAGT	1867.76	1201	0.643	-0.442
FS	TTTTCG	690.99	258	0.373	-0.985
FS	TTTAGC	2960.44	1062	0.359	-1.025
FT	TTCACC	2909.29	4513	1.551	0.439
FT	TTCACG	955.69	1315	1.376	0.319
FT	TTCACT	2082.75	2494	1.197	0.180
FT	TTCACA	2355.18	2372	1.007	0.007
FT	TTTACT	1819.66	1622	0.891	-0.115
FT	TTTACA	2057.68	1485	0.722	-0.326

FT	TTTACC	2541.79	1495	0.588	-0.531
FT	TTTACG	834.97	261	0.313	-1.163
FV	TTTGTA	912.19	1711	1.876	0.629
FV	TTTGTT	1404.80	2620	1.865	0.623
FV	TTTGTC	1798.60	2635	1.465	0.382
FV	TTTGTG	3558.17	5206	1.463	0.381
FV	TTCGTG	4072.62	2589	0.636	-0.453
FV	TTCGTC	2058.64	1086	0.528	-0.640
FV	TTCGTT	1607.91	386	0.240	-1.427
FV	TTCGTA	1044.07	224	0.215	-1.539
FW	TTCTGG	2126.30	2834	1.333	0.287
FW	TTTTGG	1857.70	1150	0.619	-0.480
FY	TTCTAC	2720.70	3710	1.364	0.310
FY	TTTTAT	1931.51	2003	1.037	0.036
FY	TTCTAT	2210.77	2145	0.970	-0.030
FY	TTTTAC	2377.02	1382	0.581	-0.542
GA	GGTGCT	1531.20	2505	1.636	0.492
GA	GGGGCG	949.27	1433	1.510	0.412
GA	GGGGCC	3510.85	5061	1.442	0.366
GA	GGTGCC	2328.29	3109	1.335	0.289
GA	GGAGCA	2070.38	2678	1.293	0.257
GA	GGTGCA	1340.41	1715	1.279	0.246
GA	GGCGCG	1318.38	1659	1.258	0.230
GA	GGAGCT	2365.08	2975	1.258	0.229
GA	GGGGCT	2308.91	2850	1.234	0.211
GA	GGAGCC	3596.25	3845	1.069	0.067
GA	GGGGCA	2021.22	2074	1.026	0.026
GA	GGTGCG	629.52	501	0.796	-0.228
GA	GGAGCG	972.36	712	0.732	-0.312
GA	GGCGCC	4876.02	3121	0.640	-0.446
GA	GGCGCT	3206.72	906	0.283	-1.264
GA	GGCGCA	2807.15	688	0.245	-1.406
GC	GGCTGC	1888.96	4102	2.172	0.775
GC	GGCTGT	1591.04	2360	1.483	0.394
GC	GGTTGT	759.72	658	0.866	-0.144
GC	GGATGT	1173.45	793	0.676	-0.392
GC	GGTTGC	901.97	523	0.580	-0.545
GC	GGATGC	1393.18	655	0.470	-0.755
GC	GGGTGC	1360.09	628	0.462	-0.773
GC	GGGTGT	1145.59	495	0.432	-0.839
GD	GGGGAC	3126.50	4967	1.589	0.463
GD	GGTGAT	1835.49	2621	1.428	0.356
GD	GGTGAC	2073.40	2960	1.428	0.356
GD	GGAGAT	2835.09	3829	1.351	0.301
GD	GGAGAC	3202.56	4240	1.324	0.281
GD	GGGGAT	2767.76	2575	0.930	-0.072
GD	GGCGAC	4342.22	1955	0.450	-0.798
GD	GGCGAT	3843.98	880	0.229	-1.474

GE	GGAGAA	3433.99	5903	1.719	0.542
GE	GGGGAG	4483.27	6552	1.461	0.379
GE	GGTGAA	2223.23	3248	1.461	0.379
GE	GGAGAG	4592.33	5961	1.298	0.261
GE	GGTGAG	2973.17	2988	1.005	0.005
GE	GGGGAA	3352.44	3041	0.907	-0.098
GE	GGCGAG	6226.56	3530	0.567	-0.568
GE	GGCGAA	4656.01	718	0.154	-1.869
GF	GGCTTC	3466.22	6121	1.766	0.569
GF	GGATTT	2233.54	2666	1.194	0.177
GF	GGTTTT	1446.04	1665	1.151	0.141
GF	GGCTTT	3028.37	3201	1.057	0.055
GF	GGTTTC	1655.11	1548	0.935	-0.067
GF	GGATTC	2556.47	1534	0.600	-0.511
GF	GGGTTT	2180.50	1244	0.571	-0.561
GF	GGGTTC	2495.76	1083	0.434	-0.835
GG	GGTGGT	1061.28	2286	2.154	0.767
GG	GGTGGC	2222.59	3657	1.645	0.498
GG	GGTGGA	1639.25	2618	1.597	0.468
GG	GGAGGA	2531.97	3609	1.425	0.354
GG	GGTGGG	1600.32	2267	1.417	0.348
GG	GGGGGC	3351.47	4673	1.394	0.332
GG	GGAGGT	1639.25	2152	1.313	0.272
GG	GGAGGC	3433.00	3776	1.100	0.095
GG	GGCGGC	4654.67	4787	1.028	0.028
GG	GGGGGT	1600.32	1543	0.964	-0.036
GG	GGAGGG	2471.84	2351	0.951	-0.050
GG	GGGGGA	2471.84	1517	0.614	-0.488
GG	GGCGGG	3351.47	2001	0.597	-0.516
GG	GGGGGG	2413.14	1080	0.448	-0.804
GG	GGCGGT	2222.59	936	0.421	-0.865
GG	GGCGGA	3433.00	845	0.246	-1.402
GH	GGCCAC	2540.15	3679	1.448	0.370
GH	GGTCAT	879.57	1022	1.162	0.150
GH	GGACAT	1358.57	1438	1.058	0.057
GH	GGCCAT	1842.04	1679	0.911	-0.093
GH	GGGCAC	1828.97	1629	0.891	-0.116
GH	GGTCAC	1212.92	1008	0.831	-0.185
GH	GGACAC	1873.46	1479	0.789	-0.236
GH	GGGCAT	1326.31	928	0.700	-0.357
GI	GGCATC	3372.48	5474	1.623	0.484
GI	GGAATA	904.63	1338	1.479	0.391
GI	GGAATT	1966.96	2560	1.302	0.264
GI	GGCATT	2666.92	2670	1.001	0.001
GI	GGTATT	1273.45	1052	0.826	-0.191
GI	GGGATC	2428.27	1958	0.806	-0.215
GI	GGTATA	585.67	461	0.787	-0.239
GI	GGAATC	2487.34	1910	0.768	-0.264

GI	GGGATA	883.14	666	0.754	-0.282
GI	GGGATT	1920.24	1421	0.740	-0.301
GI	GGCATA	1226.55	885	0.722	-0.326
GI	GGTATC	1610.35	931	0.578	-0.548
GK	GGAAAA	3199.11	4553	1.423	0.353
GK	GGGAAG	4044.81	5674	1.403	0.338
GK	GGGAAA	3123.14	4119	1.319	0.277
GK	GGCAAG	5617.61	5712	1.017	0.017
GK	GGAAAG	4143.21	3706	0.894	-0.112
GK	GGCAAA	4337.55	3581	0.826	-0.192
GK	GGTAAA	2071.17	1334	0.644	-0.440
GK	GGTAAG	2682.40	540	0.201	-1.603
GL	GGCCTC	3017.19	4559	1.511	0.413
GL	GGTTTA	579.43	820	1.415	0.347
GL	GGTTTG	973.39	1294	1.329	0.285
GL	GGGCTG	4514.62	5878	1.302	0.264
GL	GGTCTT	993.42	1258	1.266	0.236
GL	GGCCTG	6270.10	7822	1.248	0.221
GL	GGGCTC	2172.45	2563	1.180	0.165
GL	GGATTA	894.98	991	1.107	0.102
GL	GGACTT	1534.44	1613	1.051	0.050
GL	GGCTTG	2038.53	2109	1.035	0.034
GL	GGCCTT	2080.48	2098	1.008	0.008
GL	GGACTA	827.51	799	0.966	-0.035
GL	GGGCTT	1497.99	1445	0.965	-0.036
GL	GGTCTC	1440.70	1365	0.947	-0.054
GL	GGTCTA	535.75	487	0.909	-0.095
GL	GGGCTA	807.86	726	0.899	-0.107
GL	GGCCTA	1121.99	968	0.863	-0.148
GL	GGCTTA	1213.47	935	0.771	-0.261
GL	GGACTC	2225.29	1656	0.744	-0.295
GL	GGATTG	1503.50	1062	0.706	-0.348
GL	GGTCTG	2993.96	2034	0.679	-0.387
GL	GGGTTG	1467.79	870	0.593	-0.523
GL	GGGTTA	873.73	467	0.534	-0.626
GL	GGACTG	4624.44	2384	0.516	-0.663
GM	GGCATG	3177.11	3953	1.244	0.219
GM	GGAATG	2343.24	2482	1.059	0.058
GM	GGGATG	2287.59	2247	0.982	-0.018
GM	GGTATG	1517.06	643	0.424	-0.858
GN	GGAAAT	2150.19	3332	1.550	0.438
GN	GGGAAC	2311.93	2816	1.218	0.197
GN	GGCAAC	3210.92	3701	1.153	0.142
GN	GGAAAC	2368.18	2679	1.131	0.123
GN	GGGAAT	2099.13	1823	0.868	-0.141
GN	GGCAAT	2915.36	2061	0.707	-0.347
GN	GGTAAT	1392.08	784	0.563	-0.574
GN	GGTAAC	1533.21	785	0.512	-0.669

GP	GGGCCC	2634.22	3947	1.498	0.404
GP	GGGCCG	954.47	1417	1.485	0.395
GP	GGCCCC	3658.52	4576	1.251	0.224
GP	GGCCCG	1325.61	1623	1.224	0.202
GP	GGTCCT	1564.62	1910	1.221	0.199
GP	GGGCCT	2359.31	2542	1.077	0.075
GP	GGTCCC	1746.93	1827	1.046	0.045
GP	GGCCCT	3276.71	2994	0.914	-0.090
GP	GGGCCA	2277.03	2003	0.880	-0.128
GP	GGTCCA	1510.06	1264	0.837	-0.178
GP	GGACCC	2698.30	2240	0.830	-0.186
GP	GGACCA	2332.42	1908	0.818	-0.201
GP	GGACCT	2416.70	1957	0.810	-0.211
GP	GGCCCA	3162.44	2548	0.806	-0.216
GP	GGTCCG	632.98	351	0.555	-0.590
GP	GGACCG	977.69	421	0.431	-0.843
GQ	GGACAA	1382.58	1677	1.213	0.193
GQ	GGGCAG	3769.06	4425	1.174	0.160
GQ	GGCCAG	5234.64	6081	1.162	0.150
GQ	GGTCAA	895.11	953	1.065	0.063
GQ	GGCCAA	1874.58	1593	0.850	-0.163
GQ	GGGCAA	1349.74	1124	0.833	-0.183
GQ	GGACAG	3860.75	3134	0.812	-0.209
GQ	GGTCAG	2499.53	1879	0.752	-0.285
GR	GGCCGC	1832.29	3615	1.973	0.680
GR	GGAAGA	1490.60	2294	1.539	0.431
GR	GGCCGG	2003.98	2892	1.443	0.367
GR	GGCCGT	784.47	1022	1.303	0.265
GR	GGTCGT	374.58	450	1.201	0.183
GR	GGCCGA	1086.32	1252	1.153	0.142
GR	GGGCGC	1319.29	1471	1.115	0.109
GR	GGTCGA	518.71	546	1.053	0.051
GR	GGCAGG	1984.13	2022	1.019	0.019
GR	GGGAGG	1428.62	1435	1.004	0.004
GR	GGGCGG	1442.91	1437	0.996	-0.004
GR	GGAAGG	1463.37	1370	0.936	-0.066
GR	GGGAGA	1455.20	1344	0.924	-0.079
GR	GGACGT	578.58	514	0.888	-0.118
GR	GGACGA	801.20	671	0.837	-0.177
GR	GGGCGT	564.84	471	0.834	-0.182
GR	GGCAGA	2021.05	1684	0.833	-0.182
GR	GGGCGA	782.17	626	0.800	-0.223
GR	GGTCGC	874.92	596	0.681	-0.384
GR	GGTCGG	956.90	555	0.580	-0.545
GR	GGTAGA	965.05	529	0.548	-0.601
GR	GGACGC	1351.39	729	0.539	-0.617
GR	GGACGG	1478.01	737	0.499	-0.696
GR	GGTAGG	947.42	244	0.258	-1.357

GS	GGCAGC	3581.32	6542	1.827	0.603
GS	GGCTCC	3161.05	5376	1.701	0.531
GS	GGCTCG	835.91	1323	1.583	0.459
GS	GGCAGT	2259.47	2875	1.272	0.241
GS	GGAAGT	1666.45	2085	1.251	0.224
GS	GGTTCT	1313.02	1563	1.190	0.174
GS	GGCTCT	2749.80	3087	1.123	0.116
GS	GGGAGC	2578.63	2566	0.995	-0.005
GS	GGTTCC	1509.39	1428	0.946	-0.055
GS	GGCTCA	2223.05	2101	0.945	-0.056
GS	GGTTCA	1061.50	981	0.924	-0.079
GS	GGAAGC	2641.36	2137	0.809	-0.212
GS	GGATCA	1639.59	1281	0.781	-0.247
GS	GGGAGT	1626.88	1267	0.779	-0.250
GS	GGATCT	2028.08	1470	0.725	-0.322
GS	GGGTCC	2276.03	1646	0.723	-0.324
GS	GGGTCT	1979.92	1280	0.646	-0.436
GS	GGGTCTG	601.87	379	0.630	-0.463
GS	GGTAGT	1078.89	646	0.599	-0.513
GS	GGATCC	2331.40	1342	0.576	-0.552
GS	GGGTCA	1600.65	887	0.554	-0.590
GS	GGTTCTG	399.14	209	0.524	-0.647
GS	GGATCTG	616.51	276	0.448	-0.804
GS	GGTAGC	1710.07	723	0.423	-0.861
GT	GGCACC	3271.07	4870	1.489	0.398
GT	GGCACG	1074.53	1368	1.273	0.241
GT	GGGACC	2355.25	2817	1.196	0.179
GT	GGAACA	1953.05	2290	1.173	0.159
GT	GGAACT	1727.13	1900	1.100	0.095
GT	GGGACG	773.69	838	1.083	0.080
GT	GGGACA	1906.66	1903	0.998	-0.002
GT	GGCACT	2341.75	2331	0.995	-0.005
GT	GGCACA	2648.06	2499	0.944	-0.058
GT	GGGACT	1686.11	1534	0.910	-0.095
GT	GGAACC	2412.54	1841	0.763	-0.270
GT	GGTACT	1118.18	840	0.751	-0.286
GT	GGTACC	1561.93	994	0.636	-0.452
GT	GGTACA	1264.44	780	0.617	-0.483
GT	GGAACG	792.51	445	0.562	-0.577
GT	GGTACG	513.09	150	0.292	-1.230
GV	GGTGTT	816.93	1802	2.206	0.791
GV	GGTGTC	1045.94	2070	1.979	0.683
GV	GGTGTA	530.46	957	1.804	0.590
GV	GGTGTCG	2069.18	3207	1.550	0.438
GV	GGAGTA	819.35	1225	1.495	0.402
GV	GGAGTT	1261.83	1841	1.459	0.378
GV	GGGGTC	1577.18	2150	1.363	0.310
GV	GGAGTC	1615.55	1839	1.138	0.130

GV	GGGGTT	1231.86	1123	0.912	-0.093
GV	GGGGTG	3120.14	2770	0.888	-0.119
GV	GGAGTG	3196.04	2641	0.826	-0.191
GV	GGGGTA	799.89	631	0.789	-0.237
GV	GGCGTC	2190.46	1653	0.755	-0.282
GV	GGCGTG	4333.39	2790	0.644	-0.440
GV	GGCGTT	1710.87	499	0.292	-1.232
GV	GGCGTA	1110.93	232	0.209	-1.566
GW	GGCTGG	2102.85	3748	1.782	0.578
GW	GGTTGG	1004.11	690	0.687	-0.375
GW	GGATGG	1550.94	1012	0.653	-0.427
GW	GGGTGG	1514.10	722	0.477	-0.741
GY	GGCTAC	2577.81	4581	1.777	0.575
GY	GGTTAT	1000.20	1309	1.309	0.269
GY	GGCTAT	2094.66	2528	1.207	0.188
GY	GGATAT	1544.90	1478	0.957	-0.044
GY	GGTTAC	1230.90	1074	0.873	-0.136
GY	GGATAC	1901.24	1052	0.553	-0.592
GY	GGGTAC	1856.09	982	0.529	-0.637
GY	GGGTAT	1508.21	710	0.471	-0.753
HA	CATGCT	1101.90	1959	1.778	0.575
HA	CATGCA	964.61	1670	1.731	0.549
HA	CATGCC	1675.52	2408	1.437	0.363
HA	CACGCG	624.72	681	1.090	0.086
HA	CATGCG	453.03	447	0.987	-0.013
HA	CACGCC	2310.52	1649	0.714	-0.337
HA	CACGCA	1330.18	617	0.464	-0.768
HA	CACGCT	1519.52	549	0.361	-1.018
HC	CACTGC	1778.65	2629	1.478	0.391
HC	CACTGT	1498.13	1717	1.146	0.136
HC	CATTGT	1086.40	673	0.619	-0.479
HC	CATTGC	1289.82	634	0.492	-0.710
HD	CATGAT	1329.76	2349	1.766	0.569
HD	CATGAC	1502.11	2329	1.550	0.439
HD	CACGAC	2071.40	1343	0.648	-0.433
HD	CACGAT	1833.73	716	0.390	-0.940
HE	CATGAA	1769.46	3512	1.985	0.686
HE	CATGAG	2366.33	3307	1.398	0.335
HE	CACGAG	3263.15	2230	0.683	-0.381
HE	CACGAA	2440.07	790	0.324	-1.128
HF	CACTTC	2538.66	3116	1.227	0.205
HF	CATTTT	1608.41	1806	1.123	0.116
HF	CACTTT	2217.98	1884	0.849	-0.163
HF	CATTTC	1840.95	1400	0.760	-0.274
HG	CATGGA	1246.72	2238	1.795	0.585
HG	CATGGT	807.15	1426	1.767	0.569
HG	CATGGG	1217.11	1849	1.519	0.418
HG	CATGGC	1690.37	2320	1.372	0.317

HG	CACGGC	2331.01	1680	0.721	-0.328
HG	CACGGG	1678.38	1184	0.705	-0.349
HG	CACGGT	1113.05	468	0.420	-0.866
HG	CACGGA	1719.21	638	0.371	-0.991
HH	CACCAC	2269.33	2795	1.232	0.208
HH	CATCAT	1193.37	1250	1.047	0.046
HH	CACCAT	1645.65	1453	0.883	-0.125
HH	CATCAC	1645.65	1256	0.763	-0.270
HI	CACATC	2433.52	3538	1.454	0.374
HI	CACATT	1924.40	1924	1.000	0.000
HI	CACATA	885.05	867	0.980	-0.021
HI	CATATT	1395.51	1260	0.903	-0.102
HI	CATATA	641.81	552	0.860	-0.151
HI	CATATC	1764.71	904	0.512	-0.669
HK	CACAAG	3102.81	3928	1.266	0.236
HK	CACAAA	2395.79	2432	1.015	0.015
HK	CATAAA	1737.35	1690	0.973	-0.028
HK	CATAAG	2250.06	1436	0.638	-0.449
HL	CATTTA	707.71	1053	1.488	0.397
HL	CATTTG	1188.90	1485	1.249	0.222
HL	CACCTG	5042.69	6030	1.196	0.179
HL	CACCTC	2426.56	2850	1.175	0.161
HL	CATCTT	1213.36	1409	1.161	0.149
HL	CACTTG	1639.48	1700	1.037	0.036
HL	CATCTA	654.36	649	0.992	-0.008
HL	CACCTT	1673.21	1499	0.896	-0.110
HL	CACCTA	902.35	761	0.843	-0.170
HL	CATCTC	1759.66	1422	0.808	-0.213
HL	CACTTA	975.93	781	0.800	-0.223
HL	CATCTG	3656.80	2202	0.602	-0.507
HM	CACATG	2348.18	3023	1.287	0.253
HM	CATATG	1702.82	1028	0.604	-0.505
HN	CACAAC	2031.88	2762	1.359	0.307
HN	CACAAT	1844.85	1832	0.993	-0.007
HN	CATAAT	1337.83	1225	0.916	-0.088
HN	CATAAC	1473.45	869	0.590	-0.528
HP	CACCCG	846.94	1341	1.583	0.460
HP	CATCCT	1518.15	1770	1.166	0.153
HP	CACCCC	2337.46	2530	1.082	0.079
HP	CATCCA	1465.21	1577	1.076	0.074
HP	CACCCA	2020.51	1919	0.950	-0.052
HP	CACCCT	2093.51	1859	0.888	-0.119
HP	CATCCC	1695.05	1265	0.746	-0.293
HP	CATCCG	614.18	330	0.537	-0.621
HQ	CATCAA	1143.96	1358	1.187	0.172
HQ	CACCAG	4405.09	4761	1.081	0.078
HQ	CATCAG	3194.43	2957	0.926	-0.077
HQ	CACCAA	1577.51	1245	0.789	-0.237

HR	CACAGG	1447.19	1936	1.338	0.291
HR	CACCGC	1336.44	1772	1.326	0.282
HR	CACAGA	1474.12	1788	1.213	0.193
HR	CACCGG	1461.67	1772	1.212	0.193
HR	CACCGT	572.18	667	1.166	0.153
HR	CATCGA	574.58	627	1.091	0.087
HR	CATCGT	414.93	452	1.089	0.086
HR	CACCGA	792.34	855	1.079	0.076
HR	CATCGG	1059.96	729	0.688	-0.374
HR	CATAGA	1068.98	635	0.594	-0.521
HR	CATCGC	969.15	565	0.583	-0.540
HR	CATAGG	1049.46	423	0.403	-0.909
HS	CACTCG	551.81	880	1.595	0.467
HS	CACAGC	2364.16	3726	1.576	0.455
HS	CACAGT	1491.56	1957	1.312	0.272
HS	CATTCA	1064.20	1307	1.228	0.206
HS	CATTCT	1316.36	1517	1.152	0.142
HS	CACTCC	2086.72	1964	0.941	-0.061
HS	CACTCA	1467.52	1318	0.898	-0.107
HS	CATTCC	1513.23	1219	0.806	-0.216
HS	CACTCT	1815.24	1231	0.678	-0.388
HS	CATAGT	1081.63	710	0.656	-0.421
HS	CATTCT	400.16	256	0.640	-0.447
HS	CATAGC	1714.41	782	0.456	-0.785
HT	CACACG	778.62	1526	1.960	0.673
HT	CACACT	1696.86	2036	1.200	0.182
HT	CACACA	1918.82	2255	1.175	0.161
HT	CACACC	2370.26	2537	1.070	0.068
HT	CATACT	1230.51	1306	1.061	0.060
HT	CATACA	1391.46	979	0.704	-0.352
HT	CATACC	1718.84	806	0.469	-0.757
HT	CATACG	564.63	225	0.398	-0.920
HV	CATGTT	869.32	1563	1.798	0.587
HV	CATGTA	564.48	880	1.559	0.444
HV	CATGTC	1113.00	1607	1.444	0.367
HV	CATGTG	2201.86	2797	1.270	0.239
HV	CACGTG	3036.34	2579	0.849	-0.163
HV	CACGTC	1534.82	1158	0.754	-0.282
HV	CACGTT	1198.78	434	0.362	-1.016
HV	CACGTA	778.41	279	0.358	-1.026
HW	CACTGG	1602.74	2197	1.371	0.315
HW	CATTGG	1162.26	568	0.489	-0.716
HY	CACTAC	1943.40	2385	1.227	0.205
HY	CATTAT	1145.15	1240	1.083	0.080
HY	CACTAT	1579.16	1378	0.873	-0.136
HY	CATTAC	1409.29	1074	0.762	-0.272
IA	ATTGCT	1886.56	3678	1.950	0.668
IA	ATAGCA	759.54	1446	1.904	0.644

IA	ATTGCA	1651.49	2818	1.706	0.534
IA	ATAGCT	867.65	1289	1.486	0.396
IA	ATTGCC	2868.63	3435	1.197	0.180
IA	ATAGCC	1319.32	1191	0.903	-0.102
IA	ATCGCG	980.82	708	0.722	-0.326
IA	ATCGCC	3627.56	2570	0.708	-0.345
IA	ATTGCG	775.62	494	0.637	-0.451
IA	ATAGCG	356.72	198	0.555	-0.589
IA	ATCGCA	2088.41	831	0.398	-0.922
IA	ATCGCT	2385.67	910	0.381	-0.964
IC	ATCTGC	2115.05	3055	1.444	0.368
IC	ATCTGT	1781.48	2074	1.164	0.152
IC	ATATGT	647.91	731	1.128	0.121
IC	ATTTGT	1408.77	1197	0.850	-0.163
IC	ATATGC	769.23	470	0.611	-0.493
IC	ATTTGC	1672.56	868	0.519	-0.656
ID	ATTGAT	2604.76	4341	1.667	0.511
ID	ATAGAT	1197.96	1947	1.625	0.486
ID	ATTGAC	2942.37	3938	1.338	0.291
ID	ATAGAC	1353.23	1476	1.091	0.087
ID	ATCGAC	3720.81	2270	0.610	-0.494
ID	ATCGAT	3293.87	1141	0.346	-1.060
IE	ATAGAA	1371.51	2939	2.143	0.762
IE	ATTGAA	2982.12	5518	1.850	0.615
IE	ATTGAG	3988.04	4634	1.162	0.150
IE	ATAGAG	1834.15	1898	1.035	0.034
IE	ATCGAG	5043.12	3007	0.596	-0.517
IE	ATCGAA	3771.07	994	0.264	-1.333
IF	ATATTT	1144.73	1929	1.685	0.522
IF	ATCTTC	3602.60	4836	1.342	0.294
IF	ATTTTT	2489.02	2226	0.894	-0.112
IF	ATCTTT	3147.52	2779	0.883	-0.125
IF	ATATTC	1310.24	886	0.676	-0.391
IF	ATTTTC	2848.89	1887	0.662	-0.412
IG	ATTGGT	1013.16	2102	2.075	0.730
IG	ATTGGA	1564.91	3151	2.014	0.700
IG	ATAGGA	719.72	1054	1.464	0.381
IG	ATTGGG	1527.75	2144	1.403	0.339
IG	ATAGGT	465.96	596	1.279	0.246
IG	ATTGGC	2121.81	2706	1.275	0.243
IG	ATAGGG	702.63	549	0.781	-0.247
IG	ATAGGC	975.84	700	0.717	-0.332
IG	ATCGGG	1931.93	1244	0.644	-0.440
IG	ATCGGC	2683.15	1619	0.603	-0.505
IG	ATCGGT	1281.20	498	0.389	-0.945
IG	ATCGGA	1978.93	604	0.305	-1.187
IH	ATTCAT	1622.93	2242	1.381	0.323
IH	ATCCAC	2830.09	3367	1.190	0.174

IH	ATACAT	746.40	760	1.018	0.018
IH	ATCCAT	2052.29	1814	0.884	-0.123
IH	ATTCAC	2238.00	1778	0.794	-0.230
IH	ATACAC	1029.28	558	0.542	-0.612
II	ATCATC	3797.03	5979	1.575	0.454
II	ATAATA	502.24	700	1.394	0.332
II	ATAATT	1092.04	1309	1.199	0.181
II	ATCATT	3002.64	3321	1.106	0.101
II	ATTATT	2374.46	2157	0.908	-0.096
II	ATCATA	1380.95	1183	0.857	-0.155
II	ATTATA	1092.04	921	0.843	-0.170
II	ATAATC	1380.95	715	0.518	-0.658
II	ATTATC	3002.64	1340	0.446	-0.807
IK	ATAAAA	1419.09	2244	1.581	0.458
IK	ATCAAG	5053.39	5884	1.164	0.152
IK	ATAAAG	1837.88	1943	1.057	0.056
IK	ATTAAA	3085.58	3107	1.007	0.007
IK	ATCAAA	3901.90	3830	0.982	-0.019
IK	ATTAAG	3996.16	2286	0.572	-0.559
IL	ATTTTA	977.08	1679	1.718	0.541
IL	ATATTA	449.37	723	1.609	0.476
IL	ATTTTG	1641.41	2339	1.425	0.354
IL	ATTCTT	1675.18	2271	1.356	0.304
IL	ATCCTC	3072.14	4017	1.308	0.268
IL	ATCCTG	6384.29	7754	1.215	0.194
IL	ATTCTA	903.41	1021	1.130	0.122
IL	ATCTTG	2075.66	2250	1.084	0.081
IL	ATCCTA	1142.42	1170	1.024	0.024
IL	ATACTA	415.49	416	1.001	0.001
IL	ATCCTT	2118.37	2058	0.972	-0.029
IL	ATATTG	754.90	717	0.950	-0.052
IL	ATACTT	770.44	726	0.942	-0.059
IL	ATCTTA	1235.57	1077	0.872	-0.137
IL	ATTCTC	2429.41	1918	0.789	-0.236
IL	ATTCTG	5048.62	3005	0.595	-0.519
IL	ATACTC	1117.32	458	0.410	-0.892
IL	ATACTG	2321.92	934	0.402	-0.911
IM	ATCATG	3206.80	4314	1.345	0.297
IM	ATAATG	1166.29	1196	1.025	0.025
IM	ATTATG	2535.90	1399	0.552	-0.595
IN	ATAAAT	1088.42	1649	1.515	0.415
IN	ATCAAC	3296.07	4599	1.395	0.333
IN	ATCAAT	2992.68	2890	0.966	-0.035
IN	ATAAAC	1198.76	1113	0.928	-0.074
IN	ATTAAT	2366.58	1967	0.831	-0.185
IN	ATTAAC	2606.49	1331	0.511	-0.672
IP	ATTCTT	2051.78	2787	1.358	0.306
IP	ATTCCA	1980.23	2644	1.335	0.289

IP	ATACCA	910.73	1047	1.150	0.139
IP	ATCCCC	2896.94	3229	1.115	0.109
IP	ATACCT	943.64	995	1.054	0.053
IP	ATCCCG	1049.66	1073	1.022	0.022
IP	ATCCCA	2504.13	2366	0.945	-0.057
IP	ATCCCT	2594.61	2451	0.945	-0.057
IP	ATTCCC	2290.86	1775	0.775	-0.255
IP	ATACCC	1053.60	610	0.579	-0.547
IP	ATTCCG	830.06	386	0.465	-0.766
IP	ATACCG	381.76	125	0.327	-1.116
IQ	ATACAA	765.47	950	1.241	0.216
IQ	ATTCAA	1664.38	2045	1.229	0.206
IQ	ATCCAG	5877.26	6881	1.171	0.158
IQ	ATTCAG	4647.67	3987	0.858	-0.153
IQ	ATCCAA	2104.71	1765	0.839	-0.176
IQ	ATACAG	2137.52	1569	0.734	-0.309
IR	ATCCGC	1552.18	2623	1.690	0.525
IR	ATTCGA	727.72	1142	1.569	0.451
IR	ATCCGA	920.25	1434	1.558	0.444
IR	ATCCGT	664.55	943	1.419	0.350
IR	ATAAGA	622.67	877	1.408	0.342
IR	ATCCGG	1697.63	2265	1.334	0.288
IR	ATTCGT	525.51	677	1.288	0.253
IR	ATCAGA	1712.09	1680	0.981	-0.019
IR	ATCAGG	1680.81	1513	0.900	-0.105
IR	ATAAGG	611.30	547	0.895	-0.111
IR	ATACGT	241.69	213	0.881	-0.126
IR	ATACGA	334.69	292	0.872	-0.136
IR	ATTCGG	1342.46	907	0.676	-0.392
IR	ATTAGA	1353.90	900	0.665	-0.408
IR	ATTCGC	1227.45	780	0.635	-0.453
IR	ATACGG	617.42	260	0.421	-0.865
IR	ATTAGG	1329.16	503	0.378	-0.972
IR	ATACGC	564.52	170	0.301	-1.200
IS	ATCTCC	2689.59	3743	1.392	0.330
IS	ATATCA	687.92	954	1.387	0.327
IS	ATCAGC	3047.17	3998	1.312	0.272
IS	ATTTCT	1850.19	2423	1.310	0.270
IS	ATTTCA	1495.77	1957	1.308	0.269
IS	ATCAGT	1922.48	2287	1.190	0.174
IS	ATATCT	850.92	1012	1.189	0.173
IS	ATCTCG	711.23	773	1.087	0.083
IS	ATAAGT	699.19	695	0.994	-0.006
IS	ATCTCT	2339.68	2317	0.990	-0.010
IS	ATCTCA	1891.49	1767	0.934	-0.068
IS	ATTTCC	2126.89	1795	0.844	-0.170
IS	ATATCC	978.18	703	0.719	-0.330
IS	ATTAGT	1520.28	906	0.596	-0.518

IS	ATAAGC	1108.24	636	0.574	-0.555
IS	ATATCG	258.67	132	0.510	-0.673
IS	ATTTCG	562.43	255	0.453	-0.791
IS	ATTAGC	2409.67	797	0.331	-1.106
IT	ATCACC	3094.94	4722	1.526	0.422
IT	ATCACG	1016.68	1306	1.285	0.250
IT	ATAACT	805.82	1009	1.252	0.225
IT	ATCACT	2215.66	2751	1.242	0.216
IT	ATCACA	2505.48	2989	1.193	0.176
IT	ATAACA	911.22	1079	1.184	0.169
IT	ATTACT	1752.12	1369	0.781	-0.247
IT	ATTACA	1981.30	1531	0.773	-0.258
IT	ATAACC	1125.61	741	0.658	-0.418
IT	ATAACG	369.76	204	0.552	-0.595
IT	ATTACC	2447.44	1083	0.443	-0.815
IT	ATTACG	803.98	246	0.306	-1.184
IV	ATTGTT	1261.28	2414	1.914	0.649
IV	ATTGTA	819.00	1478	1.805	0.590
IV	ATAGTA	376.67	645	1.712	0.538
IV	ATAGTT	580.08	877	1.512	0.413
IV	ATTGTC	1614.84	2315	1.434	0.360
IV	ATTGTG	3194.65	3762	1.178	0.163
IV	ATCGTC	2042.07	1679	0.822	-0.196
IV	ATAGTG	1469.26	1196	0.814	-0.206
IV	ATAGTC	742.69	575	0.774	-0.256
IV	ATCGTG	4039.83	2922	0.723	-0.324
IV	ATCGTA	1035.67	361	0.349	-1.054
IV	ATCGTT	1594.97	547	0.343	-1.070
IW	ATCTGG	1887.23	2427	1.286	0.252
IW	ATATGG	686.37	622	0.906	-0.098
IW	ATTTGG	1492.40	1017	0.681	-0.384
IY	ATCTAC	2708.47	3486	1.287	0.252
IY	ATATAT	800.43	953	1.191	0.174
IY	ATTTAT	1740.39	1984	1.140	0.131
IY	ATCTAT	2200.83	2196	0.998	-0.002
IY	ATTTAC	2141.83	1403	0.655	-0.423
IY	ATATAC	985.05	555	0.563	-0.574
KA	AAAGCA	3029.93	4322	1.426	0.355
KA	AAAGCT	3461.21	4262	1.231	0.208
KA	AAGGCC	6816.15	6676	0.979	-0.021
KA	AAGGCG	1842.96	1790	0.971	-0.029
KA	AAGGCA	3924.10	3654	0.931	-0.071
KA	AAAGCC	5262.99	4742	0.901	-0.104
KA	AAGGCT	4482.65	4032	0.899	-0.106
KA	AAAGCG	1423.01	765	0.538	-0.621
KC	AAATGT	1815.55	2671	1.471	0.386
KC	AAGTGT	2351.33	2267	0.964	-0.037
KC	AAGTGC	2791.62	2498	0.895	-0.111

KC	AAATGC	2155.50	1678	0.778	-0.250
KD	AAAGAT	4684.00	6115	1.306	0.267
KD	AAGGAC	6852.58	6836	0.998	-0.002
KD	AAGGAT	6066.30	5379	0.887	-0.120
KD	AAAGAC	5291.12	4564	0.863	-0.148
KE	AAAGAA	6989.41	9895	1.416	0.348
KE	AAGGAG	12105.47	12287	1.015	0.015
KE	AAGGAA	9052.06	8366	0.924	-0.079
KE	AAAGAG	9347.06	6946	0.743	-0.297
KF	AAATTT	2631.62	3140	1.193	0.177
KF	AAGTTT	3408.25	3638	1.067	0.065
KF	AAGTTC	3901.02	3950	1.013	0.012
KF	AAATTC	3012.11	2225	0.739	-0.303
KG	AAAGGA	2672.15	4509	1.687	0.523
KG	AAAGGT	1730.00	2402	1.388	0.328
KG	AAAGGC	3623.06	3435	0.948	-0.053
KG	AAAGGG	2608.69	2465	0.945	-0.057
KG	AAGGGC	4692.27	4309	0.918	-0.085
KG	AAGGGT	2240.55	1978	0.883	-0.125
KG	AAGGGG	3378.54	2740	0.811	-0.209
KG	AAGGGA	3460.73	2568	0.742	-0.298
KH	AAACAT	1929.29	2356	1.221	0.200
KH	AAGCAC	3445.60	3583	1.040	0.039
KH	AAGCAT	2498.64	2430	0.973	-0.028
KH	AAACAC	2660.47	2165	0.814	-0.206
KI	AAAATA	1547.96	2667	1.723	0.544
KI	AAAATT	3365.76	3894	1.157	0.146
KI	AAGATC	5512.26	5523	1.002	0.002
KI	AAGATA	2004.77	1943	0.969	-0.031
KI	AAGATT	4359.03	3732	0.856	-0.155
KI	AAAATC	4256.21	3287	0.772	-0.258
KK	AAGAAG	11070.03	13815	1.248	0.222
KK	AAGAAA	8547.55	10129	1.185	0.170
KK	AAAAAG	8547.55	6145	0.719	-0.330
KK	AAAAAA	6599.86	4676	0.708	-0.345
KL	AAATTA	1273.72	2084	1.636	0.492
KL	AAACTA	1177.70	1750	1.486	0.396
KL	AAACTT	2183.78	3014	1.380	0.322
KL	AAGCTG	8523.68	9600	1.126	0.119
KL	AAGCTA	1525.25	1660	1.088	0.085
KL	AAGCTC	4101.62	4076	0.994	-0.006
KL	AAATTG	2139.75	2113	0.987	-0.013
KL	AAGCTT	2828.24	2772	0.980	-0.020
KL	AAGTTA	1649.61	1459	0.884	-0.123
KL	AAACTC	3167.00	2653	0.838	-0.177
KL	AAGTTG	2771.21	2280	0.823	-0.195
KL	AAACTG	6581.43	4462	0.678	-0.389
KM	AAGATG	5479.27	5650	1.031	0.031

KM	AAAATG	4230.73	4060	0.960	-0.041
KN	AAAAAT	3683.47	4378	1.189	0.173
KN	AAGAAC	5254.13	5515	1.050	0.048
KN	AAGAAT	4770.51	4618	0.968	-0.032
KN	AAAAAC	4056.89	3254	0.802	-0.221
KP	AAACCA	2803.51	3370	1.202	0.184
KP	AAGCCC	4200.41	4673	1.113	0.107
KP	AAGCCA	3630.85	4035	1.111	0.106
KP	AAACCT	2904.80	3118	1.073	0.071
KP	AAGCCG	1521.96	1544	1.014	0.014
KP	AAGCCT	3762.04	3396	0.903	-0.102
KP	AAACCC	3243.28	2624	0.809	-0.212
KP	AAACCG	1175.16	482	0.410	-0.891
KQ	AAACAA	2178.87	3274	1.503	0.407
KQ	AAGCAA	2821.88	3177	1.126	0.119
KQ	AAGCAG	7879.90	8081	1.026	0.025
KQ	AAACAG	6084.35	4433	0.729	-0.317
KR	AAAAGA	2247.57	3147	1.400	0.337
KR	AAGAGG	2857.67	3975	1.391	0.330
KR	AAGAGA	2910.85	3511	1.206	0.187
KR	AAAAGG	2206.51	2325	1.054	0.052
KR	AAACGT	872.39	862	0.988	-0.012
KR	AAGCGG	2886.27	2828	0.980	-0.020
KR	AAGCGC	2638.99	2532	0.959	-0.041
KR	AAACGA	1208.07	1087	0.900	-0.106
KR	AAGCGT	1129.84	978	0.866	-0.144
KR	AAGCGA	1564.59	1325	0.847	-0.166
KR	AAACGG	2228.59	1178	0.529	-0.638
KR	AAACGC	2037.65	1041	0.511	-0.672
KS	AAATCA	1871.14	2533	1.354	0.303
KS	AAAAGT	1901.80	2389	1.256	0.228
KS	AAATCT	2314.50	2793	1.207	0.188
KS	AAGTCA	2423.33	2566	1.059	0.057
KS	AAGAGC	3903.97	4045	1.036	0.035
KS	AAGAGT	2463.04	2459	0.998	-0.002
KS	AAGTCG	911.22	904	0.992	-0.008
KS	AAGTCC	3445.84	3100	0.900	-0.106
KS	AAGTCT	2997.54	2675	0.892	-0.114
KS	AAATCC	2660.65	2304	0.866	-0.144
KS	AAAAGC	3014.39	2381	0.790	-0.236
KS	AAATCG	703.58	462	0.657	-0.421
KT	AAAACA	2831.74	3611	1.275	0.243
KT	AAGACG	1488.17	1790	1.203	0.185
KT	AAAACT	2504.18	2969	1.186	0.170
KT	AAGACC	4530.26	4475	0.988	-0.012
KT	AAGACA	3667.42	3574	0.975	-0.026
KT	AAGACT	3243.20	2876	0.887	-0.120
KT	AAAACC	3497.97	2854	0.816	-0.203

KT	AAAACG	1149.07	763	0.664	-0.409
KV	AAAGTA	1317.00	2214	1.681	0.519
KV	AAAGTT	2028.22	3042	1.500	0.405
KV	AAAGTC	2596.78	2642	1.017	0.017
KV	AAGGTG	6653.25	6512	0.979	-0.021
KV	AAGGTC	3363.11	3016	0.897	-0.109
KV	AAGGTT	2626.77	2294	0.873	-0.135
KV	AAAGTG	5137.21	4417	0.860	-0.151
KV	AAGGTA	1705.66	1291	0.757	-0.279
KW	AAGTGG	2598.56	2701	1.039	0.039
KW	AAATGG	2006.44	1904	0.949	-0.052
KY	AAATAT	2319.32	2982	1.286	0.251
KY	AAGTAC	3696.62	3603	0.975	-0.026
KY	AAATAC	2854.29	2763	0.968	-0.033
KY	AAGTAT	3003.78	2526	0.841	-0.173
LA	CTGGCG	2275.39	3643	1.601	0.471
LA	TTGGCA	1575.16	2350	1.492	0.400
LA	CTGGCC	8415.49	12456	1.480	0.392
LA	TTGGCT	1799.36	2643	1.469	0.384
LA	TTAGCA	937.64	1314	1.401	0.337
LA	CTTGCT	1836.39	2345	1.277	0.244
LA	CTAGCA	866.95	1107	1.277	0.244
LA	CTTGCA	1607.57	1861	1.158	0.146
LA	TTAGCT	1071.10	1239	1.157	0.146
LA	CTGGCT	5534.46	6333	1.144	0.135
LA	CTAGCT	990.35	1099	1.110	0.104
LA	CTGGCA	4844.85	5013	1.035	0.034
LA	TTGGCC	2736.04	2824	1.032	0.032
LA	TTGGCG	739.77	623	0.842	-0.172
LA	CTTGCC	2792.34	2201	0.788	-0.238
LA	CTAGCC	1505.89	1159	0.770	-0.262
LA	CTAGCG	407.16	253	0.621	-0.476
LA	TTAGCC	1628.68	941	0.578	-0.549
LA	CTTGCG	755.00	346	0.458	-0.780
LA	TTAGCG	440.36	198	0.450	-0.799
LA	CTCGCC	4049.56	1527	0.377	-0.975
LA	CTCGCG	1094.93	390	0.356	-1.032
LA	CTCGCT	2663.20	605	0.227	-1.482
LA	CTCGCA	2331.36	429	0.184	-1.693
LC	CTCTGC	1769.27	3523	1.991	0.689
LC	CTCTGT	1490.23	2145	1.439	0.364
LC	CTTTGT	1027.58	1155	1.124	0.117
LC	TTATGT	599.35	627	1.046	0.045
LC	CTGTGC	3676.77	3517	0.957	-0.044
LC	TTGTGT	1006.86	856	0.850	-0.162
LC	CTTTGC	1219.99	974	0.798	-0.225
LC	CTGTGT	3096.89	2370	0.765	-0.268
LC	CTATGT	554.17	417	0.752	-0.284

LC	TTGTGC	1195.39	722	0.604	-0.504
LC	TTATGC	711.58	368	0.517	-0.659
LC	CTATGC	657.93	332	0.505	-0.684
LD	TTGGAT	2174.51	3688	1.696	0.528
LD	TTAGAT	1294.41	1977	1.527	0.424
LD	CTGGAC	7555.23	10531	1.394	0.332
LD	CTAGAT	1196.83	1584	1.323	0.280
LD	TTGGAC	2456.35	2775	1.130	0.122
LD	CTTGAT	2219.25	2463	1.110	0.104
LD	CTGGAT	6688.33	6912	1.033	0.033
LD	CTAGAC	1351.95	1390	1.028	0.028
LD	CTTGAC	2506.90	1832	0.731	-0.314
LD	TTAGAC	1462.19	969	0.663	-0.411
LD	CTCGAC	3635.60	981	0.270	-1.310
LD	CTCGAT	3218.44	658	0.204	-1.587
LE	TTAGAA	1739.66	3085	1.773	0.573
LE	CTAGAA	1608.51	2701	1.679	0.518
LE	TTGGAA	2922.49	4652	1.592	0.465
LE	CTGGAG	12021.09	18044	1.501	0.406
LE	TTGGAG	3908.29	4774	1.222	0.200
LE	CTAGAG	2151.09	2515	1.169	0.156
LE	CTTGAA	2982.63	3161	1.060	0.058
LE	CTGGAA	8988.96	7642	0.850	-0.162
LE	TTAGAG	2326.48	1873	0.805	-0.217
LE	CTTGAG	3988.72	2484	0.623	-0.474
LE	CTCGAG	5784.58	1305	0.226	-1.489
LE	CTCGAA	4325.51	512	0.118	-2.134
LF	CTCTTC	2629.18	6495	2.470	0.904
LF	TTATTT	923.85	1405	1.521	0.419
LF	CTCTTT	2297.07	3446	1.500	0.406
LF	CTTTTT	1583.93	1937	1.223	0.201
LF	CTTTTC	1812.93	1936	1.068	0.066
LF	CTATTT	854.20	876	1.026	0.025
LF	TTGTTT	1551.99	1544	0.995	-0.005
LF	CTGTTT	4773.59	2957	0.619	-0.479
LF	CTGTTC	5463.77	3119	0.571	-0.561
LF	TTATTC	1057.42	583	0.551	-0.595
LF	TTGTTC	1776.38	940	0.529	-0.636
LF	CTATTC	977.70	464	0.475	-0.745
LG	CTTGGA	1534.14	2667	1.738	0.553
LG	CTTGGT	993.23	1579	1.590	0.464
LG	CTGGGC	6268.87	9794	1.562	0.446
LG	CTAGGA	827.35	1087	1.314	0.273
LG	CTTGGG	1497.70	1881	1.256	0.228
LG	TTAGGA	894.81	1114	1.245	0.219
LG	CTGGGG	4513.74	5602	1.241	0.216
LG	TTGGGT	973.20	1194	1.227	0.204
LG	TTGGGA	1503.20	1820	1.211	0.191

LG	CTAGGT	535.64	611	1.141	0.132
LG	TTAGGT	579.32	611	1.055	0.053
LG	TTGGGG	1467.50	1452	0.989	-0.011
LG	CTGGGT	2993.37	2947	0.985	-0.016
LG	CTTGGC	2080.08	2009	0.966	-0.035
LG	CTAGGG	807.70	766	0.948	-0.053
LG	TTGGGC	2038.13	1786	0.876	-0.132
LG	CTGGGA	4623.54	4034	0.872	-0.136
LG	CTAGGC	1121.77	940	0.838	-0.177
LG	TTAGGG	873.56	529	0.606	-0.502
LG	CTCGGG	2172.02	1076	0.495	-0.702
LG	CTCGGC	3016.60	1313	0.435	-0.832
LG	TTAGGC	1213.24	507	0.418	-0.873
LG	CTCGGT	1440.42	365	0.253	-1.373
LG	CTCGGA	2224.86	510	0.229	-1.473
LH	CTTCAT	1127.31	1980	1.756	0.563
LH	TTACAT	657.52	935	1.422	0.352
LH	CTACAT	607.95	741	1.219	0.198
LH	CTGCAC	4685.05	5459	1.165	0.153
LH	CTCCAC	2254.46	2204	0.978	-0.023
LH	CTTCAC	1554.55	1490	0.958	-0.042
LH	CTCCAT	1634.86	1521	0.930	-0.072
LH	CTACAC	838.36	777	0.927	-0.076
LH	TTGCAT	1104.58	1017	0.921	-0.083
LH	TTGCAC	1523.20	1140	0.748	-0.290
LH	CTGCAT	3397.45	2394	0.705	-0.350
LH	TTACAC	906.71	634	0.699	-0.358
LI	CTCATC	2602.42	6250	2.402	0.876
LI	TTAATA	380.66	798	2.096	0.740
LI	TTAATT	827.68	1290	1.559	0.444
LI	CTCATT	2057.96	3117	1.515	0.415
LI	CTAATA	351.96	516	1.466	0.383
LI	CTAATT	765.28	952	1.244	0.218
LI	CTTATT	1419.05	1761	1.241	0.216
LI	TTGATA	639.48	791	1.237	0.213
LI	TTGATT	1390.44	1468	1.056	0.054
LI	CTTATA	652.64	683	1.047	0.045
LI	CTCATA	946.48	919	0.971	-0.029
LI	CTTATC	1794.48	1189	0.663	-0.412
LI	TTGATC	1758.29	1135	0.646	-0.438
LI	CTGATC	5408.15	3356	0.621	-0.477
LI	CTGATT	4276.70	2639	0.617	-0.483
LI	CTGATA	1966.91	1193	0.607	-0.500
LI	TTAATC	1046.66	633	0.605	-0.503
LI	CTAATC	967.75	563	0.582	-0.542
LK	TTAAAA	1429.91	2557	1.788	0.581
LK	CTAAAA	1322.10	1842	1.393	0.332
LK	TTGAAA	2402.12	3193	1.329	0.285

LK	CTCAAG	4604.55	6048	1.313	0.273
LK	CTAAAG	1712.27	2078	1.214	0.194
LK	TTAAAG	1851.89	2128	1.149	0.139
LK	CTGAAG	9568.82	10212	1.067	0.065
LK	TTGAAG	3111.01	3222	1.036	0.035
LK	CTCAA	3555.33	2768	0.779	-0.250
LK	CTTAAA	2451.55	1850	0.755	-0.282
LK	CTGAAA	7388.42	5227	0.707	-0.346
LK	CTTAAG	3175.03	1448	0.456	-0.785
LL	TTATTA	500.55	802	1.602	0.471
LL	CTTCTA	793.49	1132	1.427	0.355
LL	CTTCTT	1471.36	2099	1.427	0.355
LL	CTTTTA	858.19	1203	1.402	0.338
LL	CTGCTG	13364.10	18236	1.365	0.311
LL	CTTTTG	1441.69	1945	1.349	0.299
LL	TTACTA	462.82	608	1.314	0.273
LL	CTCCTC	3094.54	3800	1.228	0.205
LL	CTCCTG	6430.85	7786	1.211	0.191
LL	TTACTT	858.19	1039	1.211	0.191
LL	TTGCTA	777.49	929	1.195	0.178
LL	CTGCTC	6430.85	7550	1.174	0.160
LL	CTACTA	427.93	474	1.108	0.102
LL	CTTCTC	2133.82	2292	1.074	0.072
LL	CTACTT	793.49	839	1.057	0.056
LL	CTCTTG	2090.79	2131	1.019	0.019
LL	TTGCTT	1441.69	1464	1.015	0.015
LL	TTATTG	840.89	818	0.973	-0.028
LL	CTCCTT	2133.82	2034	0.953	-0.048
LL	TTGTTA	840.89	771	0.917	-0.087
LL	TTGTTG	1412.62	1289	0.912	-0.092
LL	CTCCTA	1150.75	1034	0.899	-0.107
LL	TTGCTG	4344.93	3820	0.879	-0.129
LL	CTTCTG	4434.34	3837	0.865	-0.145
LL	CTGCTA	2391.41	1913	0.800	-0.223
LL	CTCTTA	1244.58	959	0.771	-0.261
LL	CTATTA	462.82	354	0.765	-0.268
LL	CTGCTT	4434.34	3148	0.710	-0.343
LL	TTGCTC	2090.79	1440	0.689	-0.373
LL	CTACTC	1150.75	792	0.688	-0.374
LL	CTATTG	777.49	532	0.684	-0.379
LL	CTACTG	2391.41	1583	0.662	-0.413
LL	CTGTTG	4344.93	2615	0.602	-0.508
LL	TTACTC	1244.58	657	0.528	-0.639
LL	TTACTG	2586.40	1358	0.525	-0.644
LL	CTGTTA	2586.40	953	0.368	-0.998
LM	CTCATG	2631.41	4030	1.531	0.426
LM	TTAATG	1058.32	1228	1.160	0.149
LM	CTAATG	978.53	1101	1.125	0.118

LM	TTGATG	1777.88	1763	0.992	-0.008
LM	CTGATG	5468.39	4470	0.817	-0.202
LM	CTTATG	1814.47	1137	0.627	-0.467
LN	TTAAAT	962.36	1926	2.001	0.694
LN	CTCAAC	2635.40	4681	1.776	0.574
LN	CTAAAT	889.81	1446	1.625	0.486
LN	TTGAAT	1616.68	2048	1.267	0.236
LN	CTCAAT	2392.82	2652	1.108	0.103
LN	CTAAAC	980.01	922	0.941	-0.061
LN	TTAAAC	1059.92	965	0.910	-0.094
LN	CTTAAT	1649.95	1441	0.873	-0.135
LN	TTGAAC	1780.58	1541	0.865	-0.145
LN	CTGAAC	5476.68	4308	0.787	-0.240
LN	CTGAAT	4972.58	3413	0.686	-0.376
LN	CTTAAC	1817.22	891	0.490	-0.713
LP	CTTCCT	1728.14	2795	1.617	0.481
LP	CTTCCA	1667.88	2369	1.420	0.351
LP	CTGCCC	5815.10	7856	1.351	0.301
LP	TTACCT	1007.96	1244	1.234	0.210
LP	CTGCCG	2107.02	2489	1.181	0.167
LP	TTACCA	972.81	1140	1.172	0.159
LP	CTCCCG	1013.90	1184	1.168	0.155
LP	TTGCCA	1634.25	1897	1.161	0.149
LP	CTACCT	931.97	1045	1.121	0.114
LP	TTGCCT	1693.30	1800	1.063	0.061
LP	CTTCCC	1929.51	1889	0.979	-0.021
LP	CTACCA	899.47	850	0.945	-0.057
LP	CTCCCA	2418.82	2126	0.879	-0.129
LP	CTGCCT	5208.23	4563	0.876	-0.132
LP	CTCCCT	2506.21	2192	0.875	-0.134
LP	CTACCC	1040.57	888	0.853	-0.159
LP	CTCCCC	2798.25	2369	0.847	-0.167
LP	TTGCCC	1890.60	1560	0.825	-0.192
LP	TTGCCG	685.03	478	0.698	-0.360
LP	CTGCCA	5026.60	3348	0.666	-0.406
LP	CTTCCG	699.13	451	0.645	-0.438
LP	TTACCC	1125.42	666	0.592	-0.525
LP	CTACCG	377.04	211	0.560	-0.580
LP	TTACCG	407.78	175	0.429	-0.846
LQ	TTACAA	864.28	1290	1.493	0.401
LQ	CTACAA	799.12	1188	1.487	0.397
LQ	CTTCAA	1481.79	2098	1.416	0.348
LQ	CTACAG	2231.48	2674	1.198	0.181
LQ	CTGCAG	12470.36	14508	1.163	0.151
LQ	CTTCAG	4137.79	4363	1.054	0.053
LQ	TTGCAA	1451.91	1467	1.010	0.010
LQ	CTCCAG	6000.78	5430	0.905	-0.100
LQ	TTACAG	2413.43	2107	0.873	-0.136

LQ	TTGCAG	4054.36	3177	0.784	-0.244
LQ	CTCCAA	2148.94	1524	0.709	-0.344
LQ	CTGCAA	4465.77	2694	0.603	-0.505
LR	CTTCGA	661.43	1365	2.064	0.725
LR	CTTCGT	477.64	784	1.641	0.496
LR	CTGCGG	3677.31	5467	1.487	0.397
LR	TTAAGA	717.74	1026	1.429	0.357
LR	CTGCGC	3362.26	4574	1.360	0.308
LR	CTCCGA	959.23	1289	1.344	0.295
LR	CTCCGG	1769.53	2229	1.260	0.231
LR	CTAAGA	663.63	821	1.237	0.213
LR	CTCAGG	1752.00	2047	1.168	0.156
LR	CTTCGG	1220.17	1415	1.160	0.148
LR	CTCCGT	692.69	771	1.113	0.107
LR	TTACGA	385.79	427	1.107	0.101
LR	CTAAGG	651.51	721	1.107	0.101
LR	CTCCGC	1617.93	1790	1.106	0.101
LR	TTGAGA	1205.75	1290	1.070	0.068
LR	CTACGT	257.59	275	1.068	0.065
LR	CTACGA	356.70	378	1.060	0.058
LR	CTGAGG	3640.88	3637	0.999	-0.001
LR	TTAAGG	704.63	678	0.962	-0.039
LR	TTACGT	278.59	264	0.948	-0.054
LR	CTGCGT	1439.50	1363	0.947	-0.055
LR	TTGAGG	1183.72	1080	0.912	-0.092
LR	CTACGG	658.03	577	0.877	-0.131
LR	CTCAGA	1784.60	1469	0.823	-0.195
LR	CTTCGC	1115.63	819	0.734	-0.309
LR	CTACGC	601.65	438	0.728	-0.317
LR	CTGCGA	1993.40	1399	0.702	-0.354
LR	TTGCGT	468.01	321	0.686	-0.377
LR	CTGAGA	3708.63	2486	0.670	-0.400
LR	TTGCGG	1195.56	772	0.646	-0.437
LR	TTGCGA	648.09	418	0.645	-0.439
LR	CTTAGA	1230.56	694	0.564	-0.573
LR	TTACGG	711.68	383	0.538	-0.620
LR	TTGCGC	1093.14	542	0.496	-0.702
LR	CTTAGG	1208.08	503	0.416	-0.876
LR	TTACGC	650.71	232	0.357	-1.031
LS	CTCAGC	2740.30	5167	1.886	0.634
LS	CTTTCT	1450.83	2502	1.725	0.545
LS	CTCTCC	2418.72	4070	1.683	0.520
LS	CTCTCG	639.61	1016	1.588	0.463
LS	CTCAGT	1728.87	2589	1.498	0.404
LS	TTATCA	684.12	963	1.408	0.342
LS	TTATCT	846.22	1175	1.389	0.328
LS	CTTTCA	1172.91	1626	1.386	0.327
LS	TTAAGT	695.33	886	1.274	0.242

LS	CTCTCT	2104.05	2553	1.213	0.193
LS	CTAAGT	642.91	770	1.198	0.180
LS	CTCTCA	1701.00	2003	1.178	0.163
LS	CTTTCC	1667.81	1819	1.091	0.087
LS	TTGTCA	1149.26	1210	1.053	0.052
LS	CTGTCTG	1329.18	1392	1.047	0.046
LS	TTGTCT	1421.58	1461	1.028	0.027
LS	CTGAGC	5694.68	5805	1.019	0.019
LS	CTGTCC	5026.41	4628	0.921	-0.083
LS	TTGAGT	1168.09	1035	0.886	-0.121
LS	TTGTCC	1634.18	1334	0.816	-0.203
LS	CTATCA	632.54	512	0.809	-0.211
LS	CTAAGC	1019.02	791	0.776	-0.253
LS	TTATCC	972.78	727	0.747	-0.291
LS	CTGAGT	3592.81	2665	0.742	-0.299
LS	CTTAGT	1192.13	856	0.718	-0.331
LS	CTATCT	782.42	557	0.712	-0.340
LS	CTGTCT	4372.48	2950	0.675	-0.394
LS	CTTTCTG	441.04	291	0.660	-0.416
LS	TTGTCTG	432.14	278	0.643	-0.441
LS	CTGTCA	3534.89	2228	0.630	-0.462
LS	TTGAGC	1851.45	1128	0.609	-0.496
LS	CTATCC	899.44	541	0.601	-0.508
LS	TTATCTG	257.24	152	0.591	-0.526
LS	TTAAGC	1102.11	551	0.500	-0.693
LS	CTATCTG	237.85	102	0.429	-0.847
LS	CTTAGC	1889.55	793	0.420	-0.868
LT	CTCACC	2534.19	4959	1.957	0.671
LT	CTCACG	832.47	1510	1.814	0.595
LT	TTAACA	825.09	1163	1.410	0.343
LT	CTCACT	1814.22	2521	1.390	0.329
LT	TTAACT	729.65	969	1.328	0.284
LT	CTAACT	674.64	817	1.211	0.191
LT	CTAACA	762.89	898	1.177	0.163
LT	CTCACA	2051.52	2374	1.157	0.146
LT	CTGACG	1729.98	1795	1.038	0.037
LT	TTGACT	1225.76	1259	1.027	0.027
LT	TTGACA	1386.09	1401	1.011	0.011
LT	CTTACT	1250.98	1259	1.006	0.006
LT	CTGACC	5266.36	5160	0.980	-0.020
LT	CTTACA	1414.61	1109	0.784	-0.243
LT	CTGACT	3770.17	2808	0.745	-0.295
LT	TTGACC	1712.20	1235	0.721	-0.327
LT	CTAACC	942.38	678	0.719	-0.329
LT	TTGACG	562.45	399	0.709	-0.343
LT	CTGACA	4263.32	3003	0.704	-0.350
LT	CTAACG	309.57	215	0.695	-0.365
LT	TTAACC	1019.22	687	0.674	-0.394

LT	CTTACC	1747.43	1104	0.632	-0.459
LT	TTAACG	334.81	164	0.490	-0.714
LT	CTTACG	574.02	247	0.430	-0.843
LV	CTTGTT	1029.60	1741	1.691	0.525
LV	TTAGTA	389.95	602	1.544	0.434
LV	TTGGTA	655.07	980	1.496	0.403
LV	CTTGTA	668.56	993	1.485	0.396
LV	CTGGTG	7859.41	11424	1.454	0.374
LV	CTAGTA	360.55	519	1.439	0.364
LV	TTGGTT	1008.84	1427	1.414	0.347
LV	CTTGTC	1318.22	1541	1.169	0.156
LV	TTAGTT	600.53	690	1.149	0.139
LV	CTGGTC	3972.81	4541	1.143	0.134
LV	TTGGTG	2555.25	2882	1.128	0.120
LV	CTAGTT	555.26	580	1.045	0.044
LV	TTGGTC	1291.64	1345	1.041	0.040
LV	CTTGTC	2607.83	2540	0.974	-0.026
LV	CTAGTG	1406.38	1272	0.904	-0.100
LV	CTGGTA	2014.87	1720	0.854	-0.158
LV	CTGGTT	3102.98	2576	0.830	-0.186
LV	CTAGTC	710.90	551	0.775	-0.255
LV	TTAGTG	1521.06	947	0.623	-0.474
LV	TTAGTC	768.87	416	0.541	-0.614
LV	CTCGTC	1911.73	1013	0.530	-0.635
LV	CTCGTG	3781.97	1691	0.447	-0.805
LV	CTCGTT	1493.16	373	0.250	-1.387
LV	CTCGTA	969.56	191	0.197	-1.625
LW	CTCTGG	1742.64	2796	1.604	0.473
LW	CTGTGG	3621.43	3365	0.929	-0.073
LW	CTTTGG	1201.63	1018	0.847	-0.166
LW	CTATGG	648.03	501	0.773	-0.257
LW	TTATGG	700.87	535	0.763	-0.270
LW	TTGTGG	1177.40	877	0.745	-0.295
LY	CTCTAC	2082.09	4204	2.019	0.703
LY	TTATAT	680.44	1022	1.502	0.407
LY	CTCTAT	1691.85	2487	1.470	0.385
LY	CTTTAT	1166.60	1591	1.364	0.310
LY	CTATAT	629.14	596	0.947	-0.054
LY	TTGTAT	1143.08	1063	0.930	-0.073
LY	CTGTAC	4326.84	3390	0.783	-0.244
LY	CTTTAC	1435.69	1069	0.745	-0.295
LY	TTGTAC	1406.74	1006	0.715	-0.335
LY	TTATAC	837.39	579	0.691	-0.369
LY	CTGTAT	3515.88	2202	0.626	-0.468
LY	CTATAC	774.26	481	0.621	-0.476
MA	ATGGCG	1645.46	2370	1.440	0.365
MA	ATGGCA	3503.58	3580	1.022	0.022
MA	ATGGCT	4002.27	4003	1.000	0.000

MA	ATGGCC	6085.70	5284	0.868	-0.141
MC	ATGTGT	1386.67	1448	1.044	0.043
MC	ATGTGC	1646.33	1585	0.963	-0.038
MD	ATGGAT	4467.48	4634	1.037	0.037
MD	ATGGAC	5046.52	4880	0.967	-0.034
ME	ATGGAG	8054.28	8223	1.021	0.021
ME	ATGGAA	6022.72	5854	0.972	-0.028
MF	ATGTTT	2565.53	2833	1.104	0.099
MF	ATGTTC	2936.47	2669	0.909	-0.096
MG	ATGGGC	3467.73	3533	1.019	0.019
MG	ATGGGT	1655.83	1675	1.012	0.012
MG	ATGGGA	2557.59	2526	0.988	-0.012
MG	ATGGGG	2496.85	2444	0.979	-0.021
MH	ATGCAT	1465.33	1478	1.009	0.009
MH	ATGCAC	2020.67	2008	0.994	-0.006
MI	ATGATT	2305.40	2382	1.033	0.033
MI	ATGATA	1060.28	1094	1.032	0.031
MI	ATGATC	2915.32	2805	0.962	-0.039
MK	ATGAAG	6107.32	6423	1.052	0.050
MK	ATGAAA	4715.68	4400	0.933	-0.069
ML	ATGCTG	5938.40	6536	1.101	0.096
ML	ATGCTA	1062.63	1122	1.056	0.054
ML	ATGTTG	1930.69	1922	0.995	-0.005
ML	ATGTTA	1149.28	1134	0.987	-0.013
ML	ATGCTT	1970.42	1887	0.958	-0.043
ML	ATGCTC	2857.58	2308	0.808	-0.214
MM	ATGATG	3925.00	3925	1.000	0.000
MN	ATGAAT	3249.30	3301	1.016	0.016
MN	ATGAAC	3578.70	3527	0.986	-0.015
MP	ATGCCC	2676.16	2752	1.028	0.028
MP	ATGCCA	2313.29	2313	1.000	0.000
MP	ATGCCT	2396.87	2372	0.990	-0.010
MP	ATGCCG	969.67	919	0.948	-0.054
MQ	ATGCAG	5141.70	5165	1.005	0.005
MQ	ATGCAA	1841.30	1818	0.987	-0.013
MR	ATGAGG	1626.37	2127	1.308	0.268
MR	ATGAGA	1656.63	1974	1.192	0.175
MR	ATGCGG	1642.64	1513	0.921	-0.082
MR	ATGCGT	643.02	531	0.826	-0.191
MR	ATGCGA	890.44	684	0.768	-0.264
MR	ATGCGC	1501.91	1132	0.754	-0.283
MS	ATGTCT	666.33	809	1.214	0.194
MS	ATGTCT	2191.95	2338	1.067	0.065
MS	ATGTCA	1772.07	1781	1.005	0.005
MS	ATGTCC	2519.77	2493	0.989	-0.011
MS	ATGAGT	1801.10	1770	0.983	-0.017
MS	ATGAGC	2854.78	2615	0.916	-0.088
MT	ATGACT	2098.83	2195	1.046	0.045

MT	ATGACC	2931.75	2927	0.998	-0.002
MT	ATGACA	2373.36	2337	0.985	-0.015
MT	ATGACG	963.07	908	0.943	-0.059
MV	ATGGTG	4813.46	5122	1.064	0.062
MV	ATGGTT	1900.41	1915	1.008	0.008
MV	ATGGTA	1234.00	1191	0.965	-0.035
MV	ATGGTC	2433.13	2153	0.885	-0.122
MW	ATGTGG	1876.00	1876	1.000	0.000
MY	ATGTAC	2354.66	2363	1.004	0.004
MY	ATGTAT	1913.34	1905	0.996	-0.004
NA	AATGCA	1705.68	3344	1.961	0.673
NA	AATGCT	1948.47	3458	1.775	0.574
NA	AATGCC	2962.77	4259	1.438	0.363
NA	AATGCG	801.08	624	0.779	-0.250
NA	AACGCG	882.29	661	0.749	-0.289
NA	AACGCC	3263.12	1899	0.582	-0.541
NA	AACGCA	1878.60	700	0.373	-0.987
NA	AACGCT	2146.00	643	0.300	-1.205
NC	AACTGC	1868.57	2826	1.512	0.414
NC	AACTGT	1573.86	2016	1.281	0.248
NC	AATTGT	1429.00	935	0.654	-0.424
NC	AATTGC	1696.57	791	0.466	-0.763
ND	AATGAT	2555.01	4420	1.730	0.548
ND	AATGAC	2886.18	4521	1.566	0.449
ND	AACGAC	3178.77	1654	0.520	-0.653
ND	AACGAT	2814.03	839	0.298	-1.210
NE	AATGAA	3381.19	7367	2.179	0.779
NE	AATGAG	4521.72	5796	1.282	0.248
NE	AACGAG	4980.12	2476	0.497	-0.699
NE	AACGAA	3723.97	968	0.260	-1.347
NF	AACTTC	3150.86	4259	1.352	0.301
NF	AACTTT	2752.85	2846	1.034	0.033
NF	AATTTT	2499.46	2350	0.940	-0.062
NF	AATTTT	2860.84	1809	0.632	-0.458
NG	AATGGA	2235.93	4484	2.005	0.696
NG	AATGGT	1447.59	2430	1.679	0.518
NG	AATGGG	2182.83	3202	1.467	0.383
NG	AATGGC	3031.62	4001	1.320	0.277
NG	AACGGG	2404.12	1508	0.627	-0.466
NG	AACGGC	3338.95	1752	0.525	-0.645
NG	AACGGA	2462.61	804	0.326	-1.119
NG	AACGGT	1594.34	517	0.324	-1.126
NH	AACCAC	2167.68	2776	1.281	0.247
NH	AACCAT	1571.93	1639	1.043	0.042
NH	AATCAT	1427.24	1456	1.020	0.020
NH	AATCAC	1968.15	1264	0.642	-0.443
NI	AACATC	3876.27	5487	1.416	0.348
NI	AACATT	3065.31	3184	1.039	0.038

NI	AATATA	1280.01	1309	1.023	0.022
NI	AACATA	1409.77	1384	0.982	-0.018
NI	AATATT	2783.16	2725	0.979	-0.021
NI	AATATC	3519.48	1845	0.524	-0.646
NK	AACAAG	4824.98	5918	1.227	0.204
NK	AACAAA	3725.54	4221	1.133	0.125
NK	AATAAA	3382.62	3607	1.066	0.064
NK	AATAAG	4380.86	2568	0.586	-0.534
NL	AATTTA	1025.31	1571	1.532	0.427
NL	AACCTC	2807.78	3954	1.408	0.342
NL	AAC TTG	1897.05	2429	1.280	0.247
NL	AACCTG	5834.92	6690	1.147	0.137
NL	AATTTG	1722.43	1947	1.130	0.123
NL	AATCTT	1757.88	1943	1.105	0.100
NL	AACCTA	1044.12	1135	1.087	0.083
NL	AACCTT	1936.08	2021	1.044	0.043
NL	AAC TTA	1129.25	1129	1.000	0.000
NL	AATCTA	948.01	893	0.942	-0.060
NL	AATCTC	2549.34	1713	0.672	-0.398
NL	AATCTG	5297.84	2525	0.477	-0.741
NM	AACATG	3351.76	4374	1.305	0.266
NM	AATATG	3043.24	2021	0.664	-0.409
NN	AACAAC	3150.02	4430	1.406	0.341
NN	AACAAT	2860.08	2830	0.989	-0.011
NN	AATAAT	2596.82	2424	0.933	-0.069
NN	AATAAC	2860.08	1783	0.623	-0.473
NP	AACCCC	2770.02	3474	1.254	0.226
NP	AATCCA	2174.02	2380	1.095	0.091
NP	AACCCA	2394.42	2612	1.091	0.087
NP	AATCCT	2252.58	2414	1.072	0.069
NP	AACCCG	1003.68	1048	1.044	0.043
NP	AACCCT	2480.94	2578	1.039	0.038
NP	AATCCC	2515.05	1641	0.652	-0.427
NP	AATCCG	911.29	355	0.390	-0.943
NQ	AATCAA	1516.57	1905	1.256	0.228
NQ	AACCAA	1670.31	1955	1.170	0.157
NQ	AACCAG	4664.22	5409	1.160	0.148
NQ	AATCAG	4234.90	2817	0.665	-0.408
NR	AACAGA	1511.98	2383	1.576	0.455
NR	AACCGC	1370.77	1966	1.434	0.361
NR	AACAGG	1484.36	1903	1.282	0.248
NR	AACCGA	812.69	998	1.228	0.205
NR	AACCGT	586.88	706	1.203	0.185
NR	AACCGG	1499.21	1779	1.187	0.171
NR	AATCGA	737.89	687	0.931	-0.071
NR	AATCGT	532.86	486	0.912	-0.092
NR	AATAGA	1372.81	1117	0.814	-0.206
NR	AATCGC	1244.60	602	0.484	-0.726

NR	AATAGG	1347.73	643	0.477	-0.740
NR	AATCGG	1361.22	593	0.436	-0.831
NS	AACAGC	2917.73	4490	1.539	0.431
NS	AACAGT	1840.81	2414	1.311	0.271
NS	AACTCG	681.02	821	1.206	0.187
NS	AATTCA	1644.43	1970	1.198	0.181
NS	AATTCT	2034.08	2383	1.172	0.158
NS	AACTCC	2575.33	2818	1.094	0.090
NS	AACTCA	1811.14	1783	0.984	-0.016
NS	AACTCT	2240.29	1981	0.884	-0.123
NS	AATAGT	1671.38	1193	0.714	-0.337
NS	AATTCC	2338.29	1655	0.708	-0.346
NS	AATAGC	2649.17	1273	0.481	-0.733
NS	AATTCG	618.33	241	0.390	-0.942
NT	AACACG	860.22	1238	1.439	0.364
NT	AACACA	2119.90	2783	1.313	0.272
NT	AACACC	2618.65	3278	1.252	0.225
NT	AACACT	1874.68	2099	1.120	0.113
NT	AATACT	1702.13	1540	0.905	-0.100
NT	AATACA	1924.77	1692	0.879	-0.129
NT	AATACC	2377.62	1312	0.552	-0.595
NT	AATACG	781.04	317	0.406	-0.902
NV	AATGTA	927.15	1710	1.844	0.612
NV	AATGTT	1427.85	2573	1.802	0.589
NV	AATGTC	1828.10	2877	1.574	0.453
NV	AATGTG	3616.54	4314	1.193	0.176
NV	AACGTG	3983.18	2772	0.696	-0.363
NV	AACGTC	2013.43	1341	0.666	-0.406
NV	AACGTT	1572.60	509	0.324	-1.128
NV	AACGTA	1021.14	294	0.288	-1.245
NW	AACTGG	1808.22	2595	1.435	0.361
NW	AATTGG	1641.78	855	0.521	-0.652
NY	AACTAC	2506.72	3191	1.273	0.241
NY	AACTAT	2036.89	2145	1.053	0.052
NY	AATTAT	1849.41	1795	0.971	-0.030
NY	AATTAC	2275.98	1538	0.676	-0.392
PA	CCGGCG	470.57	1166	2.478	0.907
PA	CCGGCC	1740.39	2666	1.532	0.426
PA	CCAGCA	2390.31	3368	1.409	0.343
PA	CCAGCT	2730.54	3622	1.326	0.283
PA	CCTGCT	2829.20	3750	1.325	0.282
PA	CCTGCA	2476.67	3178	1.283	0.249
PA	CCAGCC	4151.96	4942	1.190	0.174
PA	CCCGCG	1298.71	1528	1.177	0.163
PA	CCTGCC	4301.98	5000	1.162	0.150
PA	CCAGCG	1122.61	1078	0.960	-0.041
PA	CCTGCG	1163.17	1105	0.950	-0.051
PA	CCGGCT	1144.57	1013	0.885	-0.122

PA	CCGGCA	1001.95	777	0.775	-0.254
PA	CCCGCC	4803.25	2690	0.560	-0.580
PA	CCCGCA	2765.26	846	0.306	-1.184
PA	CCCGCT	3158.86	821	0.260	-1.347
PC	CCCTGC	1550.51	2870	1.851	0.616
PC	CCCTGT	1305.97	1577	1.208	0.189
PC	CCGTGC	561.80	630	1.121	0.115
PC	CCTTGT	1169.67	1001	0.856	-0.156
PC	CCATGT	1128.89	831	0.736	-0.306
PC	CCGTGT	473.20	340	0.719	-0.331
PC	CCTTGC	1388.69	937	0.675	-0.393
PC	CCATGC	1340.27	733	0.547	-0.603
PD	CCAGAT	2721.60	4165	1.530	0.425
PD	CCTGAT	2819.94	3781	1.341	0.293
PD	CCGGAC	1288.69	1659	1.287	0.253
PD	CCAGAC	3074.36	3766	1.225	0.203
PD	CCTGAC	3185.44	3646	1.145	0.135
PD	CCGGAT	1140.82	895	0.785	-0.243
PD	CCCGAC	3556.62	2215	0.623	-0.474
PD	CCCGAT	3148.53	809	0.257	-1.359
PE	CCAGAA	3999.86	5699	1.425	0.354
PE	CCTGAG	5542.36	7122	1.285	0.251
PE	CCGGAG	2242.20	2870	1.280	0.247
PE	CCAGAG	5349.08	6777	1.267	0.237
PE	CCTGAA	4144.39	5108	1.233	0.209
PE	CCCGAG	6188.17	4149	0.670	-0.400
PE	CCGGAA	1676.64	1032	0.616	-0.485
PE	CCCGAA	4627.30	1013	0.219	-1.519
PF	CCCTTC	2555.92	4301	1.683	0.520
PF	CCATTT	1930.27	2057	1.066	0.064
PF	CCTTTT	2000.01	1967	0.983	-0.017
PF	CCCTTT	2233.06	2159	0.967	-0.034
PF	CCTTTC	2289.18	2078	0.908	-0.097
PF	CCGTTC	926.10	662	0.715	-0.336
PF	CCATTC	2209.35	1290	0.584	-0.538
PF	CCGTTT	809.12	439	0.543	-0.611
PG	CCTGGG	2918.52	4310	1.477	0.390
PG	CCTGGA	2989.52	4317	1.444	0.367
PG	CCGGGC	1639.82	2353	1.435	0.361
PG	CCGGGG	1180.71	1657	1.403	0.339
PG	CCTGGT	1935.48	2673	1.381	0.323
PG	CCAGGA	2885.27	3897	1.351	0.301
PG	CCAGGG	2816.75	3472	1.233	0.209
PG	CCAGGT	1867.98	2259	1.209	0.190
PG	CCTGGC	4053.37	4622	1.140	0.131
PG	CCAGGC	3912.02	4106	1.050	0.048
PG	CCGGGT	783.01	661	0.844	-0.169
PG	CCGGGA	1209.43	963	0.796	-0.228

PG	CCCGGG	3258.60	2136	0.655	-0.422
PG	CCCGGC	4525.68	2555	0.565	-0.572
PG	CCCGGA	3337.86	968	0.290	-1.238
PG	CCCGGT	2161.00	526	0.243	-1.413
PH	CCGCAC	725.13	972	1.340	0.293
PH	CCCCAC	2001.25	2505	1.252	0.225
PH	CCTCAT	1299.79	1592	1.225	0.203
PH	CCACAT	1254.46	1222	0.974	-0.026
PH	CCCCAT	1451.24	1303	0.898	-0.108
PH	CCTCAC	1792.40	1531	0.854	-0.158
PH	CCACAC	1729.89	1366	0.790	-0.236
PH	CCGCAT	525.84	289	0.550	-0.599
PI	CCCATC	2119.04	4651	2.195	0.786
PI	CCCATT	1675.71	2102	1.254	0.227
PI	CCAATA	666.18	819	1.229	0.207
PI	CCCATA	770.68	776	1.007	0.007
PI	CCAATT	1448.49	1386	0.957	-0.044
PI	CCTATA	690.25	603	0.874	-0.135
PI	CCTATT	1500.83	1266	0.844	-0.170
PI	CCAATC	1831.71	939	0.513	-0.668
PI	CCTATC	1897.89	957	0.504	-0.685
PI	CCGATT	607.17	299	0.492	-0.708
PI	CCGATC	767.80	342	0.445	-0.809
PI	CCGATA	279.24	115	0.412	-0.887
PK	CCCAAG	3738.47	6383	1.707	0.535
PK	CCCAAA	2886.60	3787	1.312	0.271
PK	CCAAAA	2495.20	2489	0.998	-0.002
PK	CCAAAG	3231.55	3127	0.968	-0.033
PK	CCTAAA	2585.35	1840	0.712	-0.340
PK	CCGAAG	1354.58	940	0.694	-0.365
PK	CCTAAG	3348.32	1660	0.496	-0.702
PK	CCGAAA	1045.92	460	0.440	-0.821
PL	CCGCTG	1824.84	3343	1.832	0.605
PL	CCGCTC	878.12	1254	1.428	0.356
PL	CCTTTG	1466.52	2054	1.401	0.337
PL	CCTTTA	872.97	1195	1.369	0.314
PL	CCCTTG	1637.40	2122	1.296	0.259
PL	CCTCTT	1496.70	1827	1.221	0.199
PL	CCCCTG	5036.31	5760	1.144	0.134
PL	CCCCTC	2423.49	2646	1.092	0.088
PL	CCTCTA	807.16	871	1.079	0.076
PL	CCATTA	842.53	826	0.980	-0.020
PL	CCACTT	1444.51	1371	0.949	-0.052
PL	CCACTA	779.01	729	0.936	-0.066
PL	CCTCTC	2170.57	1934	0.891	-0.115
PL	CCTCTG	4510.71	3745	0.830	-0.186
PL	CCATTG	1415.38	1172	0.828	-0.189
PL	CCCCTT	1671.10	1324	0.792	-0.233

PL	CCGCTA	326.54	255	0.781	-0.247
PL	CCCCTA	901.21	689	0.765	-0.268
PL	CCACTG	4353.41	3218	0.739	-0.302
PL	CCCTTA	974.69	709	0.727	-0.318
PL	CCACTC	2094.88	1475	0.704	-0.351
PL	CCGTTG	593.29	402	0.678	-0.389
PL	CCGCTT	605.50	402	0.664	-0.410
PL	CCGTTA	353.17	157	0.445	-0.811
PM	CCCATG	2307.54	3923	1.700	0.531
PM	CCAATG	1994.65	1552	0.778	-0.251
PM	CCGATG	836.10	520	0.622	-0.475
PM	CCTATG	2066.72	1210	0.585	-0.535
PN	CCCAAC	2313.61	4255	1.839	0.609
PN	CCAAAT	1815.81	2453	1.351	0.301
PN	CCCAAT	2100.65	2296	1.093	0.089
PN	CCAAAC	1999.90	1735	0.868	-0.142
PN	CCTAAT	1881.42	1342	0.713	-0.338
PN	CCTAAC	2072.16	997	0.481	-0.732
PN	CCGAAT	761.14	340	0.447	-0.806
PN	CCGAAC	838.30	365	0.435	-0.831
PP	CCGCCG	608.57	2335	3.837	1.345
PP	CCGCCC	1679.58	2697	1.606	0.474
PP	CCCCCG	1679.58	2420	1.441	0.365
PP	CCTCCA	3588.72	4314	1.202	0.184
PP	CCTCCT	3718.39	4305	1.158	0.146
PP	CCACCA	3463.58	3850	1.112	0.106
PP	CCACCT	3588.72	3798	1.058	0.057
PP	CCCCCA	4006.89	4095	1.022	0.022
PP	CCACCC	4006.89	3595	0.897	-0.108
PP	CCGCCA	1451.84	1280	0.882	-0.126
PP	CCACCG	1451.84	1252	0.862	-0.148
PP	CCGCCT	1504.30	1286	0.855	-0.157
PP	CCTCCC	4151.67	3338	0.804	-0.218
PP	CCTCCG	1504.30	1152	0.766	-0.267
PP	CCCCCT	4151.67	3160	0.761	-0.273
PP	CCCCCC	4635.43	2315	0.499	-0.694
PQ	CCCCAG	5063.98	6421	1.268	0.237
PQ	CCGCAG	1834.86	2187	1.192	0.176
PQ	CCTCAA	1624.21	1752	1.079	0.076
PQ	CCTCAG	4535.49	4221	0.931	-0.072
PQ	CCACAA	1567.57	1405	0.896	-0.109
PQ	CCACAG	4377.33	3670	0.838	-0.176
PQ	CCCCAA	1813.47	1497	0.825	-0.192
PQ	CCGCAA	657.08	321	0.489	-0.716
PR	CCGCGC	563.43	1094	1.942	0.664
PR	CCGCGG	616.23	1113	1.806	0.591
PR	CCCAGG	1683.86	2927	1.738	0.553
PR	CCCCGG	1700.71	2608	1.533	0.428

PR	CCCCGC	1555.00	1979	1.273	0.241
PR	CCCCGA	921.92	1166	1.265	0.235
PR	CCTCGA	825.71	1015	1.229	0.206
PR	CCAAGA	1482.62	1608	1.085	0.081
PR	CCTCGT	596.27	644	1.080	0.077
PR	CCCAGA	1715.19	1801	1.050	0.049
PR	CCGAGG	610.12	636	1.042	0.042
PR	CCTCGG	1523.22	1511	0.992	-0.008
PR	CCCCGT	665.75	655	0.984	-0.016
PR	CCAAGG	1455.54	1347	0.925	-0.077
PR	CCACGA	796.91	632	0.793	-0.232
PR	CCGCGT	241.23	191	0.792	-0.233
PR	CCACGT	575.48	418	0.726	-0.320
PR	CCACGG	1470.10	1040	0.707	-0.346
PR	CCGCGA	334.04	226	0.677	-0.391
PR	CCTCGC	1392.72	838	0.602	-0.508
PR	CCACGC	1344.15	701	0.522	-0.651
PR	CCGAGA	621.48	308	0.496	-0.702
PR	CCTAGA	1536.19	692	0.450	-0.797
PR	CCTAGG	1508.13	586	0.389	-0.945
PS	CCCAGC	3196.25	6398	2.002	0.694
PS	CCCTCG	746.03	1385	1.856	0.619
PS	CCGTTCG	270.31	483	1.787	0.580
PS	CCCAGT	2016.53	2743	1.360	0.308
PS	CCTTCA	1776.97	2263	1.274	0.242
PS	CCTTCT	2198.02	2711	1.233	0.210
PS	CCCTCC	2821.16	3353	1.189	0.173
PS	CCATCA	1715.00	1819	1.061	0.059
PS	CCATCT	2121.37	2183	1.029	0.029
PS	CCTTCC	2526.74	2594	1.027	0.026
PS	CCGTCC	1022.21	1048	1.025	0.025
PS	CCCTCA	1984.02	1945	0.980	-0.020
PS	CCAAGT	1743.10	1582	0.908	-0.097
PS	CCCTCT	2454.14	2113	0.861	-0.150
PS	CCTTCG	668.17	552	0.826	-0.191
PS	CCATCC	2438.63	1995	0.818	-0.201
PS	CCGAGC	1158.11	885	0.764	-0.269
PS	CCATCG	644.87	475	0.737	-0.306
PS	CCAAGC	2762.85	1659	0.600	-0.510
PS	CCGTCT	889.22	523	0.588	-0.531
PS	CCGAGT	730.66	371	0.508	-0.678
PS	CCGTCA	718.88	364	0.506	-0.681
PS	CCTAGT	1806.08	860	0.476	-0.742
PS	CCTAGC	2862.68	968	0.338	-1.084
PT	CCCACG	829.55	1764	2.126	0.754
PT	CCCACC	2525.29	4586	1.816	0.597
PT	CCCACA	2044.32	2719	1.330	0.285
PT	CCCACT	1807.85	2282	1.262	0.233

PT	CCAACA	1767.12	1895	1.072	0.070
PT	CCAAC	1562.71	1593	1.019	0.019
PT	CCGACG	300.57	305	1.015	0.015
PT	CCTACT	1619.18	1252	0.773	-0.257
PT	CCAACC	2182.87	1514	0.694	-0.366
PT	CCTACA	1830.97	1241	0.678	-0.389
PT	CCGACC	915.00	592	0.647	-0.435
PT	CCAACG	717.06	463	0.646	-0.437
PT	CCTACC	2261.75	1251	0.553	-0.592
PT	CCGACT	655.05	342	0.522	-0.650
PT	CCGACA	740.73	352	0.475	-0.744
PT	CCTACG	742.97	352	0.474	-0.747
PV	CCTGTT	1493.79	2375	1.590	0.464
PV	CCTGTA	969.97	1482	1.528	0.424
PV	CCAGTA	936.15	1352	1.444	0.368
PV	CCTGTG	3783.57	5362	1.417	0.349
PV	CCAGTT	1441.70	2038	1.414	0.346
PV	CCTGTC	1912.53	2666	1.394	0.332
PV	CCGGTG	1530.67	1911	1.248	0.222
PV	CCAGTG	3651.63	3787	1.037	0.036
PV	CCAGTC	1845.84	1863	1.009	0.009
PV	CCGGTC	773.73	778	1.006	0.006
PV	CCCGTG	4224.44	2576	0.610	-0.495
PV	CCGGTT	604.32	351	0.581	-0.543
PV	CCGGTA	392.41	215	0.548	-0.602
PV	CCCGTC	2135.39	1084	0.508	-0.678
PV	CCCGTT	1667.85	391	0.234	-1.451
PV	CCCGTA	1083.00	216	0.199	-1.612
PW	CCCTGG	1769.80	2753	1.556	0.442
PW	CCGTGG	641.26	661	1.031	0.030
PW	CCATGG	1529.83	1060	0.693	-0.367
PW	CCTTGG	1585.10	1052	0.664	-0.410
PY	CCCTAC	2166.25	3378	1.559	0.444
PY	CCCTAT	1760.24	2097	1.191	0.175
PY	CCTTAT	1576.54	1702	1.080	0.077
PY	CCATAT	1521.56	1513	0.994	-0.006
PY	CCTTAC	1940.18	1485	0.765	-0.267
PY	CCGTAC	784.91	592	0.754	-0.282
PY	CCGTAT	637.80	429	0.673	-0.397
PY	CCATAC	1872.52	1064	0.568	-0.565
QA	CAAGCA	1597.87	2339	1.464	0.381
QA	CAAGCT	1825.31	2409	1.320	0.277
QA	CAGGCG	2095.55	2271	1.084	0.080
QA	CAGGCC	7750.37	7695	0.993	-0.007
QA	CAAGCC	2775.49	2655	0.957	-0.044
QA	CAGGCT	5097.04	4584	0.899	-0.106
QA	CAGGCA	4461.94	3943	0.884	-0.124
QA	CAAGCG	750.44	458	0.610	-0.494

QC	CAGTGT	2490.13	2791	1.121	0.114
QC	CAGTGC	2956.40	3260	1.103	0.098
QC	CAATGT	891.74	822	0.922	-0.081
QC	CAATGC	1058.72	524	0.495	-0.703
QD	CAAGAT	2128.42	3326	1.563	0.446
QD	CAAGAC	2404.29	2506	1.042	0.041
QD	CAGGAC	6713.82	6642	0.989	-0.011
QD	CAGGAT	5943.46	4716	0.793	-0.231
QE	CAAGAA	3247.03	5286	1.628	0.487
QE	CAGGAG	12125.58	12556	1.035	0.035
QE	CAAGAG	4342.30	4206	0.969	-0.032
QE	CAGGAA	9067.09	6734	0.743	-0.297
QF	CAGTTT	3509.26	4032	1.149	0.139
QF	CAGTTC	4016.64	4205	1.047	0.046
QF	CAATTT	1256.70	1156	0.920	-0.084
QF	CAATTC	1438.40	828	0.576	-0.552
QG	CAAGGA	1440.03	2837	1.970	0.678
QG	CAAGGT	932.30	1506	1.615	0.480
QG	CAAGGG	1405.83	1700	1.209	0.190
QG	CAAGGC	1952.47	2192	1.123	0.116
QG	CAGGGC	5452.14	5605	1.028	0.028
QG	CAGGGT	2603.39	2292	0.880	-0.127
QG	CAGGGA	4021.17	2871	0.714	-0.337
QG	CAGGGG	3925.67	2730	0.695	-0.363
QH	CAACAT	1067.82	1364	1.277	0.245
QH	CAGCAC	4111.88	4483	1.090	0.086
QH	CAGCAT	2981.80	2794	0.937	-0.065
QH	CAACAC	1472.51	993	0.674	-0.394
QI	CAAATA	656.37	1125	1.714	0.539
QI	CAAATT	1427.17	1667	1.168	0.155
QI	CAGATC	5039.60	5197	1.031	0.031
QI	CAGATA	1832.87	1802	0.983	-0.017
QI	CAGATT	3985.26	3693	0.927	-0.076
QI	CAAATC	1804.74	1262	0.699	-0.358
QK	CAGAAG	8990.94	9726	1.082	0.079
QK	CAAAAA	2486.09	2610	1.050	0.049
QK	CAGAAA	6942.22	6532	0.941	-0.061
QK	CAAAAG	3219.76	2771	0.861	-0.150
QL	CAGCTG	10304.18	12629	1.226	0.203
QL	CAACTA	660.31	798	1.209	0.189
QL	CAACTT	1224.39	1479	1.208	0.189
QL	CAGCTC	4958.40	5986	1.207	0.188
QL	CAGCTA	1843.86	2002	1.086	0.082
QL	CAGCTT	3419.03	3476	1.017	0.017
QL	CAATTA	714.15	642	0.899	-0.107
QL	CAGTTG	3350.09	2597	0.775	-0.255
QL	CAGTTA	1994.20	1518	0.761	-0.273
QL	CAACTC	1775.66	1279	0.720	-0.328

QL	CAACTG	3690.04	2093	0.567	-0.567
QL	CAATTG	1199.70	635	0.529	-0.636
QM	CAGATG	5587.91	5592	1.001	0.001
QM	CAAATG	2001.09	1997	0.998	-0.002
QN	CAAAAT	1720.47	2394	1.391	0.330
QN	CAGAAC	5291.34	5195	0.982	-0.018
QN	CAGAAT	4804.30	4430	0.922	-0.081
QN	CAAAAC	1894.89	1692	0.893	-0.113
QP	CAGCCG	1816.66	2237	1.231	0.208
QP	CAGCCC	5013.75	6143	1.225	0.203
QP	CAGCCT	4490.51	4526	1.008	0.008
QP	CAGCCA	4333.91	4235	0.977	-0.023
QP	CAACCA	1552.02	1441	0.928	-0.074
QP	CAACCT	1608.10	1304	0.811	-0.210
QP	CAACCC	1795.48	1132	0.630	-0.461
QP	CAACCG	650.57	243	0.374	-0.985
QQ	CAACAA	1545.49	1866	1.207	0.188
QQ	CAGCAG	12051.19	13131	1.090	0.086
QQ	CAGCAA	4315.66	4034	0.935	-0.067
QQ	CAACAG	4315.66	3197	0.741	-0.300
QR	CAAAGA	1214.45	1863	1.534	0.428
QR	CAGAGG	3329.32	4331	1.301	0.263
QR	CAAAGG	1192.27	1360	1.141	0.132
QR	CAGAGA	3391.27	3777	1.114	0.108
QR	CAGCGC	3074.54	3169	1.031	0.030
QR	CAGCGG	3362.63	3352	0.997	-0.003
QR	CAGCGT	1316.32	1215	0.923	-0.080
QR	CAGCGA	1822.82	1469	0.806	-0.216
QR	CAACGT	471.39	327	0.694	-0.366
QR	CAACGA	652.77	413	0.633	-0.458
QR	CAACGG	1204.20	453	0.376	-0.978
QR	CAACGC	1101.03	404	0.367	-1.003
QS	CAAAGT	904.91	1408	1.556	0.442
QS	CAGAGC	4005.17	5248	1.310	0.270
QS	CAGAGT	2526.89	2963	1.173	0.159
QS	CAAAGC	1434.30	1465	1.021	0.021
QS	CAGTCG	934.84	923	0.987	-0.013
QS	CAGTCA	2486.15	2379	0.957	-0.044
QS	CAGTCT	3075.24	2806	0.912	-0.092
QS	CAATCA	890.32	781	0.877	-0.131
QS	CAGTCC	3535.16	3051	0.863	-0.147
QS	CAATCT	1101.28	765	0.695	-0.364
QS	CAATCC	1265.98	587	0.464	-0.769
QS	CAATCG	334.78	119	0.355	-1.034
QT	CAAAC	1116.05	1463	1.311	0.271
QT	CAAACA	1262.03	1602	1.269	0.239
QT	CAGACG	1430.02	1665	1.164	0.152
QT	CAGACC	4353.25	4301	0.988	-0.012

QT	CAGACA	3524.12	3445	0.978	-0.023
QT	CAGACT	3116.48	2792	0.896	-0.110
QT	CAAACC	1558.95	1232	0.790	-0.235
QT	CAAACG	512.11	373	0.728	-0.317
QV	CAAGTA	657.01	1210	1.842	0.611
QV	CAAGTT	1011.82	1737	1.717	0.540
QV	CAAGTC	1295.45	1468	1.133	0.125
QV	CAAGTG	2562.79	2712	1.058	0.057
QV	CAGGTG	7156.41	7062	0.987	-0.013
QV	CAGGTC	3617.45	3213	0.888	-0.119
QV	CAGGTT	2825.43	2269	0.803	-0.219
QV	CAGGTA	1834.65	1290	0.703	-0.352
QW	CAGTGG	3057.92	3447	1.127	0.120
QW	CAATGG	1095.08	706	0.645	-0.439
QY	CAATAT	1029.01	1120	1.088	0.085
QY	CAGTAC	3536.21	3820	1.080	0.077
QY	CAGTAT	2873.43	2979	1.037	0.036
QY	CAATAC	1266.36	786	0.621	-0.477
RA	CGGGCG	659.18	1185	1.798	0.587
RA	CGGGCC	2437.97	3513	1.441	0.365
RA	AGAGCA	1415.51	1970	1.392	0.331
RA	CGCGCG	602.71	827	1.372	0.316
RA	CGTGCC	954.35	1266	1.327	0.283
RA	CGAGCA	760.84	970	1.275	0.243
RA	CGAGCT	869.13	1108	1.275	0.243
RA	CGAGCC	1321.57	1595	1.207	0.188
RA	AGAGCT	1616.99	1949	1.205	0.187
RA	CGTGCT	627.63	744	1.185	0.170
RA	CGGGCA	1403.55	1612	1.149	0.138
RA	CGTGCA	549.43	570	1.037	0.037
RA	CGTGCG	258.04	250	0.969	-0.032
RA	CGAGCG	357.33	341	0.954	-0.047
RA	AGGGCC	2413.81	2173	0.900	-0.105
RA	AGAGCC	2458.73	2202	0.896	-0.110
RA	CGGGCT	1603.33	1435	0.895	-0.111
RA	AGGGCA	1389.65	1242	0.894	-0.112
RA	AGGGCT	1587.45	1311	0.826	-0.191
RA	AGGGCG	652.65	524	0.803	-0.220
RA	CGCGCC	2229.09	1712	0.768	-0.264
RA	AGAGCG	664.79	384	0.578	-0.549
RA	CGCGCA	1283.30	331	0.258	-1.355
RA	CGCGCT	1465.97	369	0.252	-1.379
RC	CGCTGC	986.26	2873	2.913	1.069
RC	CGCTGT	830.71	1313	1.581	0.458
RC	CGTTGT	355.66	320	0.900	-0.106
RC	CGTTGC	422.25	372	0.881	-0.127
RC	AGATGT	916.29	806	0.880	-0.128
RC	CGATGT	492.51	421	0.855	-0.157

RC	AGGTGT	899.55	671	0.746	-0.293
RC	AGGTGC	1067.99	758	0.710	-0.343
RC	CGATGC	584.73	381	0.652	-0.428
RC	CGGTGC	1078.67	660	0.612	-0.491
RC	AGATGC	1087.86	642	0.590	-0.527
RC	CGGTGT	908.55	414	0.456	-0.786
RD	AGAGAT	2027.66	2952	1.456	0.376
RD	CGGGAC	2271.13	3231	1.423	0.353
RD	CGAGAT	1089.87	1500	1.376	0.319
RD	CGAGAC	1231.14	1693	1.375	0.319
RD	CGTGAC	889.05	1044	1.174	0.161
RD	AGAGAC	2290.48	2433	1.062	0.060
RD	CGTGAT	787.04	833	1.058	0.057
RD	AGGGAC	2248.63	2322	1.033	0.032
RD	AGGGAT	1990.62	1732	0.870	-0.139
RD	CGGGAT	2010.54	1606	0.799	-0.225
RD	CGCGAC	2076.56	1092	0.526	-0.643
RD	CGCGAT	1838.29	313	0.170	-1.770
RE	AGAGAA	2644.21	4195	1.586	0.462
RE	CGGGAG	3506.29	5344	1.524	0.421
RE	CGAGAG	1900.69	2475	1.302	0.264
RE	CGAGAA	1421.27	1844	1.297	0.260
RE	CGTGAG	1372.55	1453	1.059	0.057
RE	AGGGAG	3471.55	3469	0.999	-0.001
RE	AGAGAG	3536.15	3392	0.959	-0.042
RE	CGTGAA	1026.35	947	0.923	-0.080
RE	AGGGAA	2595.91	2343	0.903	-0.103
RE	CGGGAA	2621.88	2131	0.813	-0.207
RE	CGCGAG	3205.89	1839	0.574	-0.556
RE	CGCGAA	2397.25	268	0.112	-2.191
RF	CGCTTC	1446.49	3411	2.358	0.858
RF	CGTTTC	619.29	823	1.329	0.284
RF	CGTTTT	541.07	705	1.303	0.265
RF	AGATTT	1393.96	1531	1.098	0.094
RF	CGCTTT	1263.77	1366	1.081	0.078
RF	CGATTT	749.26	772	1.030	0.030
RF	AGGTTT	1368.50	1295	0.946	-0.055
RF	AGGTTC	1566.36	1192	0.761	-0.273
RF	CGATTC	857.59	632	0.737	-0.305
RF	CGGTTC	1582.03	951	0.601	-0.509
RF	AGATTC	1595.50	944	0.592	-0.525
RF	CGGTTT	1382.19	744	0.538	-0.619
RG	CGTGGT	370.38	685	1.849	0.615
RG	CGTGCG	558.50	980	1.755	0.562
RG	CGTGCC	775.66	1315	1.695	0.528
RG	CGAGGA	792.21	1266	1.598	0.469
RG	CGAGGG	773.39	1219	1.576	0.455
RG	AGAGGA	1473.87	2281	1.548	0.437

RG	CGAGGT	512.89	789	1.538	0.431
RG	CGGGGC	1981.48	2952	1.490	0.399
RG	CGTGGA	572.08	844	1.475	0.389
RG	CGAGGC	1074.12	1569	1.461	0.379
RG	AGAGGT	954.21	1128	1.182	0.167
RG	CGGGGT	946.15	918	0.970	-0.030
RG	CGCGGC	1811.72	1574	0.869	-0.141
RG	AGGGGC	1961.86	1660	0.846	-0.167
RG	AGAGGC	1998.36	1680	0.841	-0.174
RG	AGAGGG	1438.87	1203	0.836	-0.179
RG	AGGGGT	936.78	777	0.829	-0.187
RG	CGGGGG	1426.72	1146	0.803	-0.219
RG	CGGGGA	1461.42	1140	0.780	-0.248
RG	CGCGGG	1304.48	904	0.693	-0.367
RG	AGGGGA	1446.94	923	0.638	-0.450
RG	AGGGGG	1412.58	683	0.484	-0.727
RG	CGCGGT	865.09	248	0.287	-1.249
RG	CGCGGA	1336.22	302	0.226	-1.487
RH	CGCCAC	1288.00	1861	1.445	0.368
RH	CGGCAC	1408.69	1707	1.212	0.192
RH	AGACAT	1030.24	1201	1.166	0.153
RH	CGTCAT	399.89	447	1.118	0.111
RH	AGGCAT	1011.41	988	0.977	-0.023
RH	CGACAT	553.75	530	0.957	-0.044
RH	AGGCAC	1394.73	1292	0.926	-0.077
RH	AGACAC	1420.69	1212	0.853	-0.159
RH	CGTCAC	551.44	468	0.849	-0.164
RH	CGACAC	763.62	614	0.804	-0.218
RH	CGCCAT	934.02	728	0.779	-0.249
RH	CGGCAT	1021.53	730	0.715	-0.336
RI	CGCATC	1625.56	2948	1.814	0.595
RI	AGAATA	652.11	1175	1.802	0.589
RI	AGAATT	1417.90	2185	1.541	0.432
RI	AGGATA	640.20	804	1.256	0.228
RI	CGAATA	350.51	439	1.252	0.225
RI	CGAATT	762.13	850	1.115	0.109
RI	AGGATT	1392.00	1366	0.981	-0.019
RI	AGGATC	1760.27	1662	0.944	-0.057
RI	CGAATC	963.75	802	0.832	-0.184
RI	CGGATC	1777.88	1479	0.832	-0.184
RI	AGAATC	1793.03	1389	0.775	-0.255
RI	CGTATT	550.36	408	0.741	-0.299
RI	CGCATT	1285.48	913	0.710	-0.342
RI	CGGATA	646.60	451	0.697	-0.360
RI	CGTATC	695.96	440	0.632	-0.459
RI	CGTATA	253.12	152	0.601	-0.510
RI	CGGATT	1405.93	825	0.587	-0.533
RI	CGCATA	591.21	276	0.467	-0.762

RK	AGGAAG	3199.71	4856	1.518	0.417
RK	AGGAAA	2470.61	3737	1.513	0.414
RK	AGAAAA	2516.58	3482	1.384	0.325
RK	CGCAAG	2954.85	2981	1.009	0.009
RK	CGGAAG	3231.73	3225	0.998	-0.002
RK	AGAAAG	3259.25	2909	0.893	-0.114
RK	CGAAAA	1352.67	1189	0.879	-0.129
RK	CGGAAA	2495.33	1834	0.735	-0.308
RK	CGAAAG	1751.85	1265	0.722	-0.326
RK	CGTAAA	976.81	566	0.579	-0.546
RK	CGCAAA	2281.54	1209	0.530	-0.635
RK	CGTAAG	1265.08	503	0.398	-0.922
RL	CGCCTC	1491.12	2511	1.684	0.521
RL	CGCCTG	3098.73	4809	1.552	0.439
RL	CGGCTG	3389.08	5029	1.484	0.395
RL	CGGCTC	1630.84	2301	1.411	0.344
RL	CGTTTA	256.76	337	1.313	0.272
RL	AGATTA	661.49	862	1.303	0.265
RL	CGTCTT	440.20	562	1.277	0.244
RL	CGTCTA	237.40	296	1.247	0.221
RL	CGTTTG	431.33	526	1.219	0.198
RL	CGTCTC	638.40	723	1.133	0.124
RL	AGGCTA	600.44	669	1.114	0.108
RL	AGACTT	1134.11	1227	1.082	0.079
RL	AGGCTG	3355.51	3531	1.052	0.051
RL	AGACTA	611.62	617	1.009	0.009
RL	AGGCTT	1113.39	1104	0.992	-0.008
RL	CGACTA	328.75	324	0.986	-0.015
RL	CGGCTA	606.45	593	0.978	-0.022
RL	CGTCTG	1326.68	1281	0.966	-0.035
RL	AGGCTC	1614.68	1540	0.954	-0.047
RL	CGATTA	355.55	337	0.948	-0.054
RL	CGACTT	609.59	576	0.945	-0.057
RL	CGCCTA	554.49	501	0.904	-0.101
RL	AGGTTA	649.40	586	0.902	-0.103
RL	CGCCTT	1028.19	862	0.838	-0.176
RL	CGCTTG	1007.46	804	0.798	-0.226
RL	CGGCTT	1124.53	866	0.770	-0.261
RL	AGATTG	1111.24	839	0.755	-0.281
RL	CGACTC	884.04	663	0.750	-0.288
RL	AGGTTG	1090.94	774	0.709	-0.343
RL	AGACTC	1644.73	1142	0.694	-0.365
RL	CGATTG	597.29	408	0.683	-0.381
RL	CGACTG	1837.15	1128	0.614	-0.488
RL	CGCTTA	599.71	345	0.575	-0.553
RL	CGGTTG	1101.86	566	0.514	-0.666
RL	AGACTG	3417.95	1701	0.498	-0.698
RL	CGGTTA	655.90	297	0.453	-0.792

RM	CGCATG	1558.32	1961	1.258	0.230
RM	AGGATG	1687.45	1974	1.170	0.157
RM	CGAATG	923.88	932	1.009	0.009
RM	AGAATG	1718.85	1690	0.983	-0.017
RM	CGGATG	1704.33	1374	0.806	-0.215
RM	CGTATG	667.17	329	0.493	-0.707
RN	AGAAAT	1568.88	2627	1.674	0.515
RN	AGGAAC	1696.37	2200	1.297	0.260
RN	AGGAAT	1540.22	1796	1.166	0.154
RN	AGAAAC	1727.93	1949	1.128	0.120
RN	CGAAAT	843.28	930	1.103	0.098
RN	CGCAAC	1566.55	1575	1.005	0.005
RN	CGGAAC	1713.34	1621	0.946	-0.055
RN	CGAAAC	928.77	784	0.844	-0.169
RN	CGGAAT	1555.63	1002	0.644	-0.440
RN	CGTAAT	608.96	340	0.558	-0.583
RN	CGCAAT	1422.36	711	0.500	-0.693
RN	CGTAAC	670.70	308	0.459	-0.778
RP	CGGCCG	587.88	1226	2.085	0.735
RP	CGGCCC	1622.47	2939	1.811	0.594
RP	CGCCCG	537.51	717	1.334	0.288
RP	AGGCCC	1606.39	1982	1.234	0.210
RP	AGGCCG	582.05	666	1.144	0.135
RP	AGGCCT	1438.75	1642	1.141	0.132
RP	AGGCCA	1388.57	1511	1.088	0.084
RP	CGTCCT	568.84	589	1.035	0.035
RP	AGACCA	1414.41	1387	0.981	-0.020
RP	CGGCCT	1453.14	1390	0.957	-0.044
RP	AGACCT	1465.52	1398	0.954	-0.047
RP	CGTCCC	635.12	582	0.916	-0.087
RP	CGGCCA	1402.47	1285	0.916	-0.087
RP	CGCCCC	1483.46	1320	0.890	-0.117
RP	CGTCCA	549.00	487	0.887	-0.120
RP	AGACCC	1636.29	1283	0.784	-0.243
RP	CGACCA	760.25	591	0.777	-0.252
RP	CGACCC	879.51	671	0.763	-0.271
RP	CGACCT	787.72	580	0.736	-0.306
RP	CGCCCA	1282.31	887	0.692	-0.369
RP	CGTCCG	230.13	159	0.691	-0.370
RP	CGCCCT	1328.65	830	0.625	-0.470
RP	CGACCG	318.68	184	0.577	-0.549
RP	AGACCG	592.88	246	0.415	-0.880
RQ	AGACAA	1054.78	1456	1.380	0.322
RQ	CGGCAG	2920.52	3950	1.352	0.302
RQ	CGCCAG	2670.31	3160	1.183	0.168
RQ	AGGCAA	1035.51	1177	1.137	0.128
RQ	AGGCAG	2891.59	3013	1.042	0.041
RQ	CGACAA	566.95	522	0.921	-0.083

RQ	CGTCAG	1143.25	953	0.834	-0.182
RQ	CGTCAA	409.41	327	0.799	-0.225
RQ	CGACAG	1583.16	1249	0.789	-0.237
RQ	CGGCAA	1045.87	763	0.730	-0.315
RQ	AGACAG	2945.39	2062	0.700	-0.357
RQ	CGCCAA	956.27	591	0.618	-0.481
RR	CGCCGC	1172.08	2232	1.904	0.644
RR	CGGCGG	1402.02	2316	1.652	0.502
RR	AGAAGA	1426.00	2307	1.618	0.481
RR	CGGCGC	1281.90	2064	1.610	0.476
RR	AGGAGG	1374.38	1973	1.436	0.362
RR	CGCCGG	1281.90	1679	1.310	0.270
RR	CGAAGA	766.48	987	1.288	0.253
RR	AGGAGA	1399.95	1758	1.256	0.228
RR	CGCAGG	1269.20	1565	1.233	0.209
RR	CGGAGG	1388.13	1670	1.203	0.185
RR	CGTCGT	214.84	228	1.061	0.059
RR	CGAAGG	752.48	770	1.023	0.023
RR	CGCCGT	501.81	502	1.000	0.000
RR	AGAAGG	1399.95	1325	0.946	-0.055
RR	CGGCGT	548.83	498	0.907	-0.097
RR	CGTCGA	297.51	265	0.891	-0.116
RR	CGGCGA	760.01	675	0.888	-0.119
RR	CGTCGC	501.81	438	0.873	-0.136
RR	AGGCGG	1388.13	1177	0.848	-0.165
RR	CGTCGG	548.83	450	0.820	-0.199
RR	CGACGT	297.51	241	0.810	-0.211
RR	CGCCGA	694.89	547	0.787	-0.239
RR	AGGCGA	752.48	570	0.757	-0.278
RR	CGGAGA	1413.96	1068	0.755	-0.281
RR	AGACGA	766.48	557	0.727	-0.319
RR	AGGCGT	543.39	383	0.705	-0.350
RR	AGGCGC	1269.20	889	0.700	-0.356
RR	AGACGT	553.50	376	0.679	-0.387
RR	CGACGA	411.98	272	0.660	-0.415
RR	CGCAGA	1292.82	771	0.596	-0.517
RR	CGACGG	760.01	411	0.541	-0.615
RR	CGACGC	694.89	368	0.530	-0.636
RR	CGTAGA	553.50	271	0.490	-0.714
RR	CGTAGG	543.39	235	0.432	-0.838
RR	AGACGC	1292.82	524	0.405	-0.903
RR	AGACGG	1413.96	569	0.402	-0.910
RS	CGCTCG	332.61	817	2.456	0.899
RS	CGCAGC	1425.00	2853	2.002	0.694
RS	CGCTCC	1257.78	2184	1.736	0.552
RS	AGAAGT	991.66	1532	1.545	0.435
RS	CGTTCT	468.44	687	1.467	0.383
RS	CGAAGT	533.02	728	1.366	0.312

RS	CGTTCC	538.50	707	1.313	0.272
RS	AGGAGC	1543.09	1992	1.291	0.255
RS	CGTTCA	378.71	471	1.244	0.218
RS	CGGAGC	1558.53	1856	1.191	0.175
RS	AGGAGT	973.54	1071	1.100	0.095
RS	AGAAGC	1571.80	1628	1.036	0.035
RS	AGATCA	975.67	1000	1.025	0.025
RS	CGAAGC	844.85	859	1.017	0.017
RS	CGCTCA	884.55	860	0.972	-0.028
RS	CGCAGT	899.04	853	0.949	-0.053
RS	AGATCT	1206.86	1106	0.916	-0.087
RS	CGCTCT	1094.14	942	0.861	-0.150
RS	CGTTCT	142.40	121	0.850	-0.163
RS	AGGTCA	957.85	808	0.844	-0.170
RS	CGATCA	524.43	416	0.793	-0.232
RS	AGGTCT	1184.81	939	0.793	-0.233
RS	AGGTCT	360.17	284	0.789	-0.238
RS	CGATCT	648.69	497	0.766	-0.266
RS	AGGTCC	1362.00	1036	0.761	-0.274
RS	CGGAGT	983.28	745	0.758	-0.278
RS	CGTAGT	384.91	278	0.722	-0.325
RS	CGGTCT	363.77	235	0.646	-0.437
RS	CGATCC	745.70	455	0.610	-0.494
RS	AGATCC	1387.35	830	0.598	-0.514
RS	CGGTCC	1375.63	821	0.597	-0.516
RS	CGATCG	197.19	107	0.543	-0.611
RS	CGGTCA	967.43	507	0.524	-0.646
RS	CGTAGC	610.09	317	0.520	-0.655
RS	AGATCG	366.87	177	0.482	-0.729
RS	CGGTCT	1196.66	518	0.433	-0.837
RT	CGCACG	450.78	858	1.903	0.644
RT	AGAACT	1083.61	1467	1.354	0.303
RT	CGCACC	1372.27	1821	1.327	0.283
RT	AGGACG	488.14	646	1.323	0.280
RT	AGGACT	1063.81	1389	1.306	0.267
RT	AGAACA	1225.34	1575	1.285	0.251
RT	AGGACA	1202.96	1523	1.266	0.236
RT	AGGACC	1485.98	1773	1.193	0.177
RT	CGGACG	493.02	537	1.089	0.085
RT	CGAACA	658.62	661	1.004	0.004
RT	CGAACT	582.44	556	0.955	-0.046
RT	CGGACC	1500.85	1408	0.938	-0.064
RT	CGCACA	1110.90	984	0.886	-0.121
RT	CGGACA	1215.00	949	0.781	-0.247
RT	AGAACC	1513.63	1166	0.770	-0.261
RT	CGTACT	420.60	313	0.744	-0.295
RT	CGAACC	813.58	599	0.736	-0.306
RT	CGGACT	1074.45	712	0.663	-0.411

RT	CGCACT	982.40	638	0.649	-0.432
RT	CGTACC	587.52	361	0.614	-0.487
RT	AGAACG	497.22	302	0.607	-0.499
RT	CGTACA	475.62	288	0.606	-0.502
RT	CGAACG	267.26	154	0.576	-0.551
RT	CGTACG	193.00	79	0.409	-0.893
RV	CGTGTG	889.90	1699	1.909	0.647
RV	CGTGTC	449.83	826	1.836	0.608
RV	CGAGTA	315.92	562	1.779	0.576
RV	CGTGTA	228.14	391	1.714	0.539
RV	CGTGTT	351.34	565	1.608	0.475
RV	AGAGTT	905.17	1350	1.491	0.400
RV	AGAGTA	587.76	876	1.490	0.399
RV	CGAGTC	622.91	914	1.467	0.383
RV	CGAGTT	486.53	681	1.400	0.336
RV	CGAGTG	1232.31	1576	1.279	0.246
RV	CGGGTC	1149.12	1310	1.140	0.131
RV	AGGGTC	1137.73	1221	1.073	0.071
RV	CGGGTG	2273.30	2328	1.024	0.024
RV	AGAGTC	1158.91	1154	0.996	-0.004
RV	CGCGTG	2078.54	1725	0.830	-0.186
RV	AGGGTA	577.02	471	0.816	-0.203
RV	AGAGTG	2292.67	1750	0.763	-0.270
RV	CGGGTA	582.79	438	0.752	-0.286
RV	AGGGTG	2250.78	1658	0.737	-0.306
RV	CGCGTC	1050.67	763	0.726	-0.320
RV	AGGGTT	888.63	645	0.726	-0.320
RV	CGGGTT	897.52	548	0.611	-0.493
RV	CGCGTA	532.86	132	0.248	-1.395
RV	CGCGTT	820.63	178	0.217	-1.528
RW	CGCTGG	1038.00	2199	2.118	0.751
RW	CGTTGG	444.40	380	0.855	-0.157
RW	AGGTGG	1124.01	876	0.779	-0.249
RW	CGATGG	615.40	466	0.757	-0.278
RW	AGATGG	1144.93	804	0.702	-0.353
RW	CGGTGG	1135.26	777	0.684	-0.379
RY	CGCTAC	1173.12	2612	2.227	0.800
RY	CGCTAT	953.25	1198	1.257	0.229
RY	CGTTAC	502.25	565	1.125	0.118
RY	CGTTAT	408.12	459	1.125	0.117
RY	AGATAT	1051.45	1018	0.968	-0.032
RY	AGATAC	1293.97	1239	0.958	-0.043
RY	CGATAT	565.15	509	0.901	-0.105
RY	CGATAC	695.51	584	0.840	-0.175
RY	AGGTAC	1270.33	1007	0.793	-0.232
RY	AGGTAT	1032.24	769	0.745	-0.294
RY	CGGTAC	1283.04	856	0.667	-0.405
RY	CGGTAT	1042.57	455	0.436	-0.829

SA	TCGGCG	241.39	778	3.223	1.170
SA	TCGGCC	892.76	1976	2.213	0.795
SA	TCAGCA	1366.87	2526	1.848	0.614
SA	TCTGCA	1690.75	3035	1.795	0.585
SA	TCTGCT	1931.41	3350	1.734	0.551
SA	TCAGCT	1561.43	2630	1.684	0.521
SA	AGTGCT	1587.01	2487	1.567	0.449
SA	AGTGCA	1389.27	2040	1.468	0.384
SA	AGTGCC	2413.15	3437	1.424	0.354
SA	TCAGCC	2374.25	3294	1.387	0.327
SA	TCGGCT	587.12	808	1.376	0.319
SA	TCTGCC	2936.83	3480	1.185	0.170
SA	TCGGCA	513.97	598	1.163	0.151
SA	TCTGCG	794.06	745	0.938	-0.064
SA	TCAGCG	641.95	584	0.910	-0.095
SA	AGTGCG	652.47	532	0.815	-0.204
SA	AGCGCG	1034.18	802	0.775	-0.254
SA	AGCGCC	3824.90	2428	0.635	-0.454
SA	TCCGCG	912.82	577	0.632	-0.459
SA	TCCGCC	3376.05	1230	0.364	-1.010
SA	AGCGCT	2515.45	709	0.282	-1.266
SA	AGCGCA	2202.02	601	0.273	-1.299
SA	TCCGCA	1943.61	476	0.245	-1.407
SA	TCCGCT	2220.26	481	0.217	-1.530
SC	TCCTGC	1640.34	2828	1.724	0.545
SC	AGCTGC	1858.43	3034	1.633	0.490
SC	TCCTGT	1381.63	1779	1.288	0.253
SC	AGCTGT	1565.33	1922	1.228	0.205
SC	TCGTGC	433.77	361	0.832	-0.184
SC	TCTTGT	1201.89	941	0.783	-0.245
SC	AGTTGT	987.57	698	0.707	-0.347
SC	TCGTGT	365.36	225	0.616	-0.485
SC	TCATGT	971.65	584	0.601	-0.509
SC	TCTTGC	1426.94	758	0.531	-0.633
SC	TCATGC	1153.59	525	0.455	-0.787
SC	AGTTGC	1172.49	504	0.430	-0.844
SD	TCAGAT	1978.63	3706	1.873	0.628
SD	AGTGAT	2011.05	3683	1.831	0.605
SD	AGTGAC	2271.71	4040	1.778	0.576
SD	TCGGAC	840.43	1438	1.711	0.537
SD	TCTGAT	2447.46	3578	1.462	0.380
SD	TCAGAC	2235.09	2906	1.300	0.262
SD	TCGGAT	744.00	840	1.129	0.121
SD	TCTGAC	2764.69	2949	1.067	0.065
SD	AGCGAC	3600.71	2017	0.560	-0.580
SD	TCCGAC	3178.17	1336	0.420	-0.867
SD	AGCGAT	3187.56	920	0.289	-1.243
SD	TCCGAT	2813.50	660	0.235	-1.450

SE	TCAGAA	2420.84	4815	1.989	0.688
SE	AGTGAA	2460.50	4686	1.904	0.644
SE	TCGGAG	1217.33	2184	1.794	0.584
SE	TCTGAA	2994.45	4621	1.543	0.434
SE	TCAGAG	3237.43	4683	1.447	0.369
SE	AGTGAG	3290.47	4410	1.340	0.293
SE	TCTGAG	4004.54	4891	1.221	0.200
SE	TCGGAA	910.28	879	0.966	-0.035
SE	AGCGAG	5215.47	2961	0.568	-0.566
SE	TCCGAG	4603.44	2005	0.436	-0.831
SE	AGCGAA	3899.95	847	0.217	-1.527
SE	TCCGAA	3442.29	715	0.208	-1.572
SF	TCCTTC	2645.79	4407	1.666	0.510
SF	AGCTTC	2997.56	3942	1.315	0.274
SF	TCATTT	1625.65	1773	1.091	0.087
SF	TCCTTT	2311.58	2487	1.076	0.073
SF	AGTTTT	1652.29	1695	1.026	0.026
SF	AGCTTT	2618.91	2370	0.905	-0.100
SF	TCTTTT	2010.85	1809	0.900	-0.106
SF	TCTTTC	2301.58	1728	0.751	-0.287
SF	AGTTTC	1891.18	1353	0.715	-0.335
SF	TCGTTT	611.27	342	0.559	-0.581
SF	TCATTC	1860.69	991	0.533	-0.630
SF	TCGTTC	699.65	330	0.472	-0.751
SG	AGTGGT	1051.00	2094	1.992	0.689
SG	TCGGGG	586.31	1117	1.905	0.645
SG	TCGGGC	814.29	1487	1.826	0.602
SG	AGTGGA	1623.36	2932	1.806	0.591
SG	TCAGGA	1597.19	2760	1.728	0.547
SG	TCTGGA	1975.64	3391	1.716	0.540
SG	AGTGGG	1584.81	2584	1.630	0.489
SG	TCTGGG	1928.73	2974	1.542	0.433
SG	AGTGGC	2201.05	3314	1.506	0.409
SG	TCTGGT	1279.07	1902	1.487	0.397
SG	TCAGGG	1559.26	2161	1.386	0.326
SG	TCAGGT	1034.06	1351	1.307	0.267
SG	TCGGGA	600.57	684	1.139	0.130
SG	TCGGGT	388.82	410	1.054	0.053
SG	TCTGGC	2678.70	2734	1.021	0.020
SG	TCAGGC	2165.57	2114	0.976	-0.024
SG	AGCGGC	3488.72	2475	0.709	-0.343
SG	AGCGGG	2511.96	1464	0.583	-0.540
SG	TCCGGG	2217.18	1117	0.504	-0.686
SG	TCCGGC	3079.31	1163	0.378	-0.974
SG	AGCGGT	1665.85	536	0.322	-1.134
SG	AGCGGA	2573.06	663	0.258	-1.356
SG	TCCGGA	2271.11	560	0.247	-1.400
SG	TCCGGT	1470.37	359	0.244	-1.410

SH	AGCCAC	2202.27	3210	1.458	0.377
SH	TCTCAT	1226.22	1426	1.163	0.151
SH	TCCCAC	1943.83	2233	1.149	0.139
SH	AGTCAT	1007.57	1082	1.074	0.071
SH	AGCCAT	1597.01	1606	1.006	0.006
SH	TCGCAC	514.03	512	0.996	-0.004
SH	TCCCAT	1409.60	1349	0.957	-0.044
SH	TCACAT	991.32	929	0.937	-0.065
SH	AGTCAC	1389.42	1077	0.775	-0.255
SH	TCACAC	1367.03	956	0.699	-0.358
SH	TCTCAC	1690.94	1158	0.685	-0.379
SH	TCGCAT	372.75	174	0.467	-0.762
SI	TCCATC	2374.96	4526	1.906	0.645
SI	AGCATC	2690.72	4471	1.662	0.508
SI	TCCATT	1878.09	2383	1.269	0.238
SI	AGCATT	2127.79	2384	1.120	0.114
SI	TCCATA	863.76	963	1.115	0.109
SI	AGTATA	617.40	640	1.037	0.036
SI	TCAATA	607.45	618	1.017	0.017
SI	AGTATT	1342.43	1299	0.968	-0.033
SI	AGCATA	978.60	943	0.964	-0.037
SI	TCTATA	751.38	658	0.876	-0.133
SI	TCTATT	1633.75	1215	0.744	-0.296
SI	TCAATT	1320.79	957	0.725	-0.322
SI	AGTATC	1697.59	924	0.544	-0.608
SI	TCGATA	228.41	109	0.477	-0.740
SI	TCTATC	2065.98	958	0.464	-0.769
SI	TCGATT	496.64	185	0.373	-0.988
SI	TCAATC	1670.22	557	0.333	-1.098
SI	TCGATC	628.03	184	0.293	-1.228
SK	TCCAAG	3563.99	5021	1.409	0.343
SK	TCCAAA	2751.88	3634	1.321	0.278
SK	AGCAAG	4037.83	5128	1.270	0.239
SK	AGCAAA	3117.75	3736	1.198	0.181
SK	TCAAAA	1935.30	2282	1.179	0.165
SK	AGTAAA	1967.01	2149	1.093	0.088
SK	TCAAAG	2506.42	2082	0.831	-0.186
SK	TCTAAA	2393.86	1838	0.768	-0.264
SK	TCGAAG	942.46	522	0.554	-0.591
SK	AGTAAG	2547.49	1300	0.510	-0.673
SK	TCTAAG	3100.32	1569	0.506	-0.681
SK	TCGAAA	727.71	331	0.455	-0.788
SL	AGTTTA	709.05	1103	1.556	0.442
SL	TCGCTG	1355.42	2104	1.552	0.440
SL	TCCTTG	1666.44	2462	1.477	0.390
SL	TCTTTA	862.92	1267	1.468	0.384
SL	AGCCTC	2794.39	4013	1.436	0.362
SL	TCTTTG	1449.64	2009	1.386	0.326

SL	TCATTA	697.62	862	1.236	0.212
SL	AGCCTG	5807.08	7014	1.208	0.189
SL	AGTTTG	1191.15	1427	1.198	0.181
SL	TCGCTC	652.23	777	1.191	0.175
SL	TCTCTA	797.87	950	1.191	0.175
SL	TCTCTT	1479.47	1750	1.183	0.168
SL	TCCCTG	5125.62	6034	1.177	0.163
SL	TCCCTC	2466.46	2805	1.137	0.129
SL	TCCTTA	991.98	1076	1.085	0.081
SL	AGTCTT	1215.66	1242	1.022	0.021
SL	AGCCTT	1926.85	1959	1.017	0.017
SL	TCACTA	645.03	630	0.977	-0.024
SL	AGCTTG	1888.00	1786	0.946	-0.056
SL	TCACTT	1196.06	1111	0.929	-0.074
SL	TCCCTT	1700.73	1545	0.908	-0.096
SL	TCCCTA	917.19	810	0.883	-0.124
SL	AGTCTA	655.60	569	0.868	-0.142
SL	TCATTG	1171.95	1015	0.866	-0.144
SL	AGCCTA	1039.14	875	0.842	-0.172
SL	TCTCTC	2145.58	1760	0.820	-0.198
SL	TCTCTG	4458.78	3418	0.767	-0.266
SL	AGCTTA	1123.86	758	0.674	-0.394
SL	AGTCTC	1763.00	1158	0.657	-0.420
SL	TCGTTG	440.67	280	0.635	-0.454
SL	TCACTC	1734.58	1100	0.634	-0.455
SL	TCACTG	3604.66	2254	0.625	-0.470
SL	TCGCTT	449.74	279	0.620	-0.477
SL	TCGCTA	242.54	143	0.590	-0.528
SL	TCGTTA	262.32	140	0.534	-0.628
SL	AGTCTG	3663.72	1808	0.493	-0.706
SM	TCCATG	2282.65	3908	1.712	0.538
SM	AGCATG	2586.13	3300	1.276	0.244
SM	TCAATG	1605.31	1129	0.703	-0.352
SM	TCGATG	603.62	365	0.605	-0.503
SM	AGTATG	1631.61	966	0.592	-0.524
SM	TCTATG	1985.68	1027	0.517	-0.659
SN	AGCAAC	2539.42	3717	1.464	0.381
SN	TCCAAC	2241.42	3216	1.435	0.361
SN	TCAAAT	1431.22	1883	1.316	0.274
SN	AGCAAT	2305.68	2513	1.090	0.086
SN	TCCAAT	2035.11	2000	0.983	-0.017
SN	AGTAAT	1454.67	1425	0.980	-0.021
SN	AGTAAC	1602.14	1339	0.836	-0.179
SN	TCAAAC	1576.31	1194	0.757	-0.278
SN	TCTAAT	1770.34	1297	0.733	-0.311
SN	TCTAAC	1949.81	955	0.490	-0.714
SN	TCGAAT	538.16	258	0.479	-0.735
SN	TCGAAC	592.72	240	0.405	-0.904

SP	TCGCCG	282.21	549	1.945	0.665
SP	TCGCCC	778.87	1221	1.568	0.450
SP	TCCCCG	1067.21	1621	1.519	0.418
SP	TCTCCA	2214.76	3119	1.408	0.342
SP	AGCCCC	3336.96	4654	1.395	0.333
SP	TCTCCT	2294.78	2888	1.259	0.230
SP	AGCCCG	1209.10	1432	1.184	0.169
SP	TCCCCA	2545.99	2968	1.166	0.153
SP	TCACCA	1790.50	1869	1.044	0.043
SP	AGCCCT	2988.71	3086	1.033	0.032
SP	AGTCCT	1885.59	1904	1.010	0.010
SP	TCACCT	1855.20	1752	0.944	-0.057
SP	AGCCCA	2884.48	2607	0.904	-0.101
SP	TCCCCT	2637.98	2238	0.848	-0.164
SP	AGTCCA	1819.84	1473	0.809	-0.211
SP	TCGCCT	697.59	562	0.806	-0.216
SP	TCGCCA	673.26	541	0.804	-0.219
SP	TCTCCC	2562.18	2036	0.795	-0.230
SP	TCACCC	2071.37	1568	0.757	-0.278
SP	AGTCCC	2105.31	1534	0.729	-0.317
SP	TCTCCG	928.37	664	0.715	-0.335
SP	TCCCCC	2945.37	2058	0.699	-0.358
SP	TCACCG	750.53	426	0.568	-0.566
SP	AGTCCG	762.83	319	0.418	-0.872
SQ	TCCCAG	4427.95	5592	1.263	0.233
SQ	AGCCAG	5016.65	6041	1.204	0.186
SQ	TCTCAA	1379.40	1644	1.192	0.175
SQ	AGTCAA	1133.44	1293	1.141	0.132
SQ	TCACAA	1115.16	1196	1.072	0.070
SQ	AGCCAA	1796.52	1819	1.013	0.012
SQ	TCCCAA	1585.70	1474	0.930	-0.073
SQ	TCTCAG	3851.88	3430	0.890	-0.116
SQ	TCGCAG	1170.92	1015	0.867	-0.143
SQ	TCACAG	3114.02	2271	0.729	-0.316
SQ	AGTCAG	3165.04	2215	0.700	-0.357
SQ	TCGCAA	419.32	186	0.444	-0.813
SR	AGCCGC	1540.23	2828	1.836	0.608
SR	TCCAGG	1472.14	2309	1.568	0.450
SR	AGCCGG	1684.56	2353	1.397	0.334
SR	TCCCCG	1486.87	1976	1.329	0.284
SR	AGCAGG	1667.87	2186	1.311	0.271
SR	AGCCGT	659.43	857	1.300	0.262
SR	TCGCGC	359.50	446	1.241	0.216
SR	TCCAGA	1499.54	1850	1.234	0.210
SR	TCAAGA	1054.57	1294	1.227	0.205
SR	TCGCGG	393.19	481	1.223	0.202
SR	TCCCCG	1359.49	1605	1.181	0.166
SR	TCTCGA	701.14	826	1.178	0.164

SR	AGTCGT	416.04	484	1.163	0.151
SR	TCCCGA	806.00	937	1.163	0.151
SR	AGCAGA	1698.90	1925	1.133	0.125
SR	AGCCGA	913.16	1020	1.117	0.111
SR	TCTCGT	506.32	493	0.974	-0.027
SR	AGTCGA	576.12	553	0.960	-0.041
SR	TCCCGT	582.04	553	0.950	-0.051
SR	TCAAGG	1035.31	922	0.891	-0.116
SR	TCGAGG	389.29	324	0.832	-0.184
SR	TCTCGG	1293.43	1062	0.821	-0.197
SR	TCACGT	409.33	323	0.789	-0.237
SR	AGTAGA	1071.85	746	0.696	-0.362
SR	TCGCGT	153.92	102	0.663	-0.411
SR	AGTCGG	1062.80	675	0.635	-0.454
SR	AGTCGC	971.74	591	0.608	-0.497
SR	TCACGA	566.83	344	0.607	-0.499
SR	TCGAGA	396.54	240	0.605	-0.502
SR	TCTAGA	1304.45	750	0.575	-0.553
SR	TCGCGA	213.14	115	0.540	-0.617
SR	TCTCGC	1182.62	636	0.538	-0.620
SR	TCACGG	1045.66	534	0.511	-0.672
SR	TCTAGG	1280.62	574	0.448	-0.802
SR	TCACGC	956.08	406	0.425	-0.856
SR	AGTAGG	1052.27	443	0.421	-0.865
SS	AGCAGC	3919.72	7160	1.827	0.602
SS	TCGTTCG	213.54	376	1.761	0.566
SS	TCCTCG	807.53	1302	1.612	0.478
SS	TCCAGC	3459.74	4832	1.397	0.334
SS	TCTTCA	1868.19	2596	1.390	0.329
SS	AGCAGT	2472.97	3417	1.382	0.323
SS	TCCTCC	3053.74	4162	1.363	0.310
SS	TCTTCT	2310.85	2896	1.253	0.226
SS	TCCAGT	2182.77	2691	1.233	0.209
SS	TCATCA	1510.32	1795	1.188	0.173
SS	AGCTCC	3459.74	4024	1.163	0.151
SS	TCATCT	1868.19	2118	1.134	0.126
SS	TCCTCA	2147.58	2413	1.124	0.117
SS	AGCTCG	914.89	1001	1.094	0.090
SS	TCCTCT	2656.45	2744	1.033	0.032
SS	TCGTCC	807.53	818	1.013	0.013
SS	TCTTCC	2656.45	2600	0.979	-0.021
SS	AGTTCT	1898.79	1856	0.977	-0.023
SS	AGTTCA	1535.06	1498	0.976	-0.024
SS	TCAAGT	1535.06	1404	0.915	-0.089
SS	AGCTCA	2433.11	2075	0.853	-0.159
SS	AGCTCT	3009.63	2465	0.819	-0.200
SS	TCTTTCG	702.47	556	0.791	-0.234
SS	TCATCC	2147.58	1632	0.760	-0.275

SS	AGTAGT	1560.21	1030	0.660	-0.415
SS	AGTTCC	2182.77	1405	0.644	-0.441
SS	TCGTCT	702.47	434	0.618	-0.482
SS	TCATCG	567.91	343	0.604	-0.504
SS	TCGTCA	567.91	313	0.551	-0.596
SS	TCTAGT	1898.79	957	0.504	-0.685
SS	TCGAGC	914.89	440	0.481	-0.732
SS	AGTAGC	2472.97	1158	0.468	-0.759
SS	TCAAGC	2433.11	1117	0.459	-0.779
SS	TCGAGT	577.21	259	0.449	-0.801
SS	AGTTCG	577.21	251	0.435	-0.833
SS	TCTAGC	3009.63	899	0.299	-1.208
ST	TCCACG	785.52	1434	1.826	0.602
ST	AGCACC	2709.18	4149	1.531	0.426
ST	TCCACC	2391.25	3527	1.475	0.389
ST	AGCACG	889.95	1180	1.326	0.282
ST	AGCACA	2193.18	2692	1.227	0.205
ST	TCCACA	1935.81	2329	1.203	0.185
ST	TCCACT	1711.89	1937	1.131	0.124
ST	AGCACT	1939.49	2193	1.131	0.123
ST	TCAACA	1361.39	1485	1.091	0.087
ST	TCAACT	1203.91	1270	1.055	0.053
ST	TCTACT	1489.18	1390	0.933	-0.069
ST	TCTACA	1683.97	1461	0.868	-0.142
ST	AGTACT	1223.64	1036	0.847	-0.166
ST	AGTACA	1383.69	1061	0.767	-0.266
ST	TCGACG	207.72	145	0.698	-0.359
ST	TCTACC	2080.15	1218	0.586	-0.535
ST	TCGACC	632.34	365	0.577	-0.550
ST	AGTACC	1709.24	976	0.571	-0.560
ST	TCGACT	452.69	240	0.530	-0.635
ST	TCAACC	1681.68	873	0.519	-0.656
ST	TCAACG	552.43	275	0.498	-0.698
ST	TCGACA	511.90	236	0.461	-0.774
ST	TCTACG	683.32	302	0.442	-0.817
ST	AGTACG	561.48	201	0.358	-1.027
SV	TCGGTG	935.47	1822	1.948	0.667
SV	TCTGTA	788.92	1398	1.772	0.572
SV	TCTGTT	1214.96	2136	1.758	0.564
SV	TCAGTA	637.79	1121	1.758	0.564
SV	AGTGTT	998.32	1719	1.722	0.543
SV	TCAGTT	982.23	1591	1.620	0.482
SV	TCTGTC	1555.54	2367	1.522	0.420
SV	AGTGTC	1278.17	1943	1.520	0.419
SV	TCTGTG	3077.33	4672	1.518	0.418
SV	AGTGTA	648.24	976	1.506	0.409
SV	TCGGTC	472.87	683	1.444	0.368
SV	TCAGTG	2487.84	2925	1.176	0.162

SV	AGTGTG	2528.60	2901	1.147	0.137
SV	TCAGTC	1257.56	1351	1.074	0.072
SV	TCGGTA	239.82	231	0.963	-0.037
SV	TCGGTT	369.33	266	0.720	-0.328
SV	AGCGTC	2025.93	1298	0.641	-0.445
SV	TCCGTG	3537.57	2065	0.584	-0.538
SV	AGCGTG	4007.89	2221	0.554	-0.590
SV	TCCGTC	1788.18	829	0.464	-0.769
SV	AGCGTT	1582.36	446	0.282	-1.266
SV	TCCGTA	906.91	239	0.264	-1.334
SV	TCCGTT	1396.67	329	0.236	-1.446
SV	AGCGTA	1027.48	217	0.211	-1.555
SW	TCCTGG	1756.97	2825	1.608	0.475
SW	AGCTGG	1990.56	2404	1.208	0.189
SW	TCGTGG	464.61	444	0.956	-0.045
SW	TCTTGG	1528.39	1137	0.744	-0.296
SW	TCATGG	1235.61	778	0.630	-0.463
SW	AGTTGG	1255.86	644	0.513	-0.668
SY	TCCTAC	1871.53	3038	1.623	0.484
SY	AGCTAC	2120.35	2864	1.351	0.301
SY	TCCTAT	1520.75	1869	1.229	0.206
SY	AGCTAT	1722.94	1609	0.934	-0.068
SY	AGTTAT	1087.01	1010	0.929	-0.073
SY	AGTTAC	1337.74	1153	0.862	-0.149
SY	TCATAT	1069.49	897	0.839	-0.176
SY	TCTTAT	1322.91	1100	0.832	-0.185
SY	TCTTAC	1628.04	1204	0.740	-0.302
SY	TCGTAC	494.91	304	0.614	-0.487
SY	TCGTAT	402.15	204	0.507	-0.679
SY	TCATAC	1316.18	642	0.488	-0.718
TA	ACGGCG	348.71	734	2.105	0.744
TA	ACAGCA	1829.79	3283	1.794	0.585
TA	ACGGCC	1289.71	2090	1.621	0.483
TA	ACTGCA	1618.13	2557	1.580	0.458
TA	ACAGCT	2090.24	3295	1.576	0.455
TA	ACTGCT	1848.45	2764	1.495	0.402
TA	ACAGCC	3178.34	3912	1.231	0.208
TA	ACGGCA	742.49	804	1.083	0.080
TA	ACTGCC	2810.69	3015	1.073	0.070
TA	ACGGCT	848.18	804	0.948	-0.053
TA	ACAGCG	859.36	803	0.934	-0.068
TA	ACTGCG	759.96	623	0.820	-0.199
TA	ACCGCG	1061.55	584	0.550	-0.598
TA	ACCGCC	3926.11	1648	0.420	-0.868
TA	ACCGCA	2260.29	561	0.248	-1.394
TA	ACCGCT	2582.01	577	0.223	-1.498
TC	ACCTGC	1892.82	3247	1.715	0.540
TC	ACCTGT	1594.30	1994	1.251	0.224

TC	ACGTGC	621.78	691	1.111	0.106
TC	ACGTGT	523.72	484	0.924	-0.079
TC	ACTTGT	1141.35	1033	0.905	-0.100
TC	ACATGT	1290.64	938	0.727	-0.319
TC	ACTTGC	1355.07	815	0.601	-0.508
TC	ACATGC	1532.31	750	0.489	-0.714
TD	ACAGAT	2415.25	4195	1.737	0.552
TD	ACAGAC	2728.31	3765	1.380	0.322
TD	ACTGAT	2135.87	2913	1.364	0.310
TD	ACGGAC	1107.10	1446	1.306	0.267
TD	ACTGAC	2412.71	2615	1.084	0.081
TD	ACGGAT	980.07	922	0.941	-0.061
TD	ACCGAC	3370.20	1547	0.459	-0.779
TD	ACCGAT	2983.49	730	0.245	-1.408
TE	ACAGAA	3127.33	5307	1.697	0.529
TE	ACGGAG	1697.07	2517	1.483	0.394
TE	ACTGAA	2765.58	4093	1.480	0.392
TE	ACAGAG	4182.23	5419	1.296	0.259
TE	ACTGAG	3698.46	4124	1.115	0.109
TE	ACGGAA	1269.01	1080	0.851	-0.161
TE	ACCGAG	5166.20	2450	0.474	-0.746
TE	ACCGAA	3863.10	779	0.202	-1.601
TF	ACCTTC	3026.54	4955	1.637	0.493
TF	ACATTT	2140.61	2275	1.063	0.061
TF	ACTTTT	1893.00	1904	1.006	0.006
TF	ACCTTT	2644.23	2518	0.952	-0.049
TF	ACTTTC	2166.69	1822	0.841	-0.173
TF	ACGTTT	868.62	650	0.748	-0.290
TF	ACGTTC	994.21	666	0.670	-0.401
TF	ACATTC	2450.10	1394	0.569	-0.564
TG	ACTGGA	1710.74	3660	2.139	0.761
TG	ACTGGT	1107.57	1887	1.704	0.533
TG	ACAGGA	1934.51	2970	1.535	0.429
TG	ACGGGC	1064.34	1583	1.487	0.397
TG	ACTGGG	1670.12	2322	1.390	0.330
TG	ACGGGG	766.35	1049	1.369	0.314
TG	ACAGGT	1252.44	1694	1.353	0.302
TG	ACAGGG	1888.57	2148	1.137	0.129
TG	ACTGGC	2319.53	2620	1.130	0.122
TG	ACAGGC	2622.93	2664	1.016	0.016
TG	ACGGGT	508.22	484	0.952	-0.049
TG	ACGGGA	784.99	710	0.904	-0.100
TG	ACCGGG	2332.90	1093	0.469	-0.758
TG	ACCGGC	3240.03	1373	0.424	-0.859
TG	ACCGGT	1547.11	355	0.229	-1.472
TG	ACCGGA	2389.65	528	0.221	-1.510
TH	ACTCAT	1054.95	1291	1.224	0.202
TH	ACCCAC	2032.09	2408	1.185	0.170

TH	ACGCAC	667.53	764	1.145	0.135
TH	ACACAT	1192.94	1186	0.994	-0.006
TH	ACTCAC	1454.76	1384	0.951	-0.050
TH	ACCCAT	1473.60	1287	0.873	-0.135
TH	ACACAC	1645.05	1383	0.841	-0.174
TH	ACGCAT	484.07	302	0.624	-0.472
TI	ACCATC	2842.70	5915	2.081	0.733
TI	ACCATT	2247.97	2878	1.280	0.247
TI	ACAATA	836.96	980	1.171	0.158
TI	ACCATA	1033.87	1137	1.100	0.095
TI	ACAATT	1819.82	1579	0.868	-0.142
TI	ACTATA	740.14	642	0.867	-0.142
TI	ACTATT	1609.31	1337	0.831	-0.185
TI	ACGATA	339.62	190	0.559	-0.581
TI	ACGATT	738.45	389	0.527	-0.641
TI	ACGATC	933.81	463	0.496	-0.702
TI	ACTATC	2035.08	942	0.463	-0.770
TI	ACAATC	2301.27	1027	0.446	-0.807
TK	ACCAAG	3878.56	6678	1.722	0.543
TK	ACCAAA	2994.77	3789	1.265	0.235
TK	ACAAAA	2424.38	2546	1.050	0.049
TK	ACAAAG	3139.84	2507	0.798	-0.225
TK	ACTAAA	2143.95	1684	0.785	-0.241
TK	ACGAAG	1274.09	708	0.556	-0.588
TK	ACGAAA	983.77	511	0.519	-0.655
TK	ACTAAG	2776.65	1193	0.430	-0.845
TL	ACGCTG	1815.48	3357	1.849	0.615
TL	ACTTTA	765.72	1207	1.576	0.455
TL	ACTTTG	1286.34	1876	1.458	0.377
TL	ACATTA	865.87	1115	1.288	0.253
TL	ACCTTG	1796.82	2257	1.256	0.228
TL	ACTCTA	707.99	876	1.237	0.213
TL	ACGCTC	873.61	1057	1.210	0.191
TL	ACCCTC	2659.44	3133	1.178	0.164
TL	ACCCTG	5526.65	6354	1.150	0.140
TL	ACTCTT	1312.81	1469	1.119	0.112
TL	ACACTA	800.60	799	0.998	-0.002
TL	ACGCTA	324.87	307	0.945	-0.057
TL	ACCTTA	1069.59	957	0.895	-0.111
TL	ACACTT	1484.53	1316	0.886	-0.121
TL	ACGTTG	590.25	505	0.856	-0.156
TL	ACATTG	1454.60	1210	0.832	-0.184
TL	ACCCTT	1833.80	1515	0.826	-0.191
TL	ACCCTA	988.95	802	0.811	-0.210
TL	ACTCTG	3956.51	3120	0.789	-0.238
TL	ACGTTA	351.36	262	0.746	-0.293
TL	ACTCTC	1903.88	1391	0.731	-0.314
TL	ACGCTT	602.39	427	0.709	-0.344

TL	ACACTG	4474.03	3013	0.673	-0.395
TL	ACACTC	2152.92	1274	0.592	-0.525
TM	ACCATG	2733.42	4467	1.634	0.491
TM	ACAATG	2212.81	1641	0.742	-0.299
TM	ACGATG	897.92	655	0.729	-0.315
TM	ACTATG	1956.85	1038	0.530	-0.634
TN	ACCAAC	2378.62	4300	1.808	0.592
TN	ACAAAT	1748.34	2194	1.255	0.227
TN	ACCAAT	2159.68	2454	1.136	0.128
TN	ACAAAC	1925.59	1486	0.772	-0.259
TN	ACTAAT	1546.11	1077	0.697	-0.362
TN	ACGAAT	709.45	336	0.474	-0.747
TN	ACTAAC	1702.85	789	0.463	-0.769
TN	ACGAAC	781.37	316	0.404	-0.905
TP	ACGCCG	349.03	632	1.811	0.594
TP	ACGCCC	963.29	1491	1.548	0.437
TP	ACTCCA	1814.66	2359	1.300	0.262
TP	ACCCCG	1062.52	1331	1.253	0.225
TP	ACTCCT	1880.23	2186	1.163	0.151
TP	ACACCA	2052.02	2361	1.151	0.140
TP	ACCCCA	2534.80	2784	1.098	0.094
TP	ACACCT	2126.17	2104	0.990	-0.010
TP	ACCCCT	2626.39	2415	0.920	-0.084
TP	ACGCCA	832.67	748	0.898	-0.107
TP	ACCCCC	2932.43	2380	0.812	-0.209
TP	ACACCC	2373.91	1922	0.810	-0.211
TP	ACGCCT	862.76	697	0.808	-0.213
TP	ACTCCC	2099.31	1649	0.785	-0.241
TP	ACTCCG	760.66	538	0.707	-0.346
TP	ACACCG	860.15	534	0.621	-0.477
TQ	ACTCAA	1103.35	1368	1.240	0.215
TQ	ACCCAG	4303.71	5173	1.202	0.184
TQ	ACGCAG	1413.75	1518	1.074	0.071
TQ	ACACAA	1247.67	1328	1.064	0.062
TQ	ACTCAG	3081.01	2839	0.921	-0.082
TQ	ACCCAA	1541.21	1410	0.915	-0.089
TQ	ACACAG	3484.02	2765	0.794	-0.231
TQ	ACGCAA	506.28	280	0.553	-0.592
TR	ACCAGG	1331.08	2049	1.539	0.431
TR	ACGCGC	403.79	605	1.498	0.404
TR	ACGCGG	441.63	661	1.497	0.403
TR	ACTCGA	521.72	717	1.374	0.318
TR	ACAAGA	1097.61	1429	1.302	0.264
TR	ACCCGC	1229.22	1547	1.259	0.230
TR	ACCCGG	1344.40	1668	1.241	0.216
TR	ACTCGT	376.76	448	1.189	0.173
TR	ACCAGA	1355.85	1599	1.179	0.165
TR	ACCCGA	728.77	758	1.040	0.039

TR	ACCCGT	526.27	535	1.017	0.016
TR	ACAAGG	1077.56	1072	0.995	-0.005
TR	ACGAGG	437.25	433	0.990	-0.010
TR	ACTCGG	962.45	823	0.855	-0.157
TR	ACGCGT	172.88	141	0.816	-0.204
TR	ACACGT	426.04	329	0.772	-0.258
TR	ACGAGA	445.39	331	0.743	-0.297
TR	ACACGA	589.97	432	0.732	-0.312
TR	ACACGG	1088.34	756	0.695	-0.364
TR	ACTCGC	879.99	607	0.690	-0.371
TR	ACTAGA	970.65	624	0.643	-0.442
TR	ACGCGA	239.40	150	0.627	-0.468
TR	ACACGC	995.10	498	0.500	-0.692
TR	ACTAGG	952.91	383	0.402	-0.911
TS	ACCAGC	2807.29	4575	1.630	0.488
TS	ACCTCG	655.24	1060	1.618	0.481
TS	ACGTCT	215.24	348	1.617	0.480
TS	ACTTCA	1247.51	1844	1.478	0.391
TS	ACTTCT	1543.11	1974	1.279	0.246
TS	ACATCA	1410.69	1754	1.243	0.218
TS	ACCAGT	1771.14	2194	1.239	0.214
TS	ACCTCC	2477.85	3050	1.231	0.208
TS	ACCTCA	1742.59	1938	1.112	0.106
TS	ACATCT	1744.95	1911	1.095	0.091
TS	ACGTCC	813.96	840	1.032	0.031
TS	ACCTCT	2155.49	2072	0.961	-0.040
TS	ACAAGT	1433.80	1335	0.931	-0.071
TS	ACTTCC	1773.89	1524	0.859	-0.152
TS	ACGTCA	572.43	450	0.786	-0.241
TS	ACATCC	2005.92	1570	0.783	-0.245
TS	ACTTCG	469.09	353	0.753	-0.284
TS	ACGTCT	708.07	527	0.744	-0.295
TS	ACATCG	530.44	361	0.681	-0.385
TS	ACTAGT	1267.95	725	0.572	-0.559
TS	ACAAGC	2272.61	1275	0.561	-0.578
TS	ACGAGT	581.81	297	0.510	-0.672
TS	ACGAGC	922.18	469	0.509	-0.676
TS	ACTAGC	2009.73	687	0.342	-1.073
TT	ACCACG	875.88	1567	1.789	0.582
TT	ACCACC	2666.32	4767	1.788	0.581
TT	ACCACA	2158.49	2882	1.335	0.289
TT	ACCACT	1908.81	2309	1.210	0.190
TT	ACAACA	1747.38	1793	1.026	0.026
TT	ACAACT	1545.26	1567	1.014	0.014
TT	ACGACG	287.72	252	0.876	-0.133
TT	ACTACT	1366.51	1065	0.779	-0.249
TT	ACTACA	1545.26	1196	0.774	-0.256
TT	ACGACC	875.88	575	0.656	-0.421

TT	ACGACA	709.06	437	0.616	-0.484
TT	ACAACC	2158.49	1310	0.607	-0.499
TT	ACGACT	627.04	357	0.569	-0.563
TT	ACTACC	1908.81	992	0.520	-0.655
TT	ACAACG	709.06	365	0.515	-0.664
TT	ACTACG	627.04	283	0.451	-0.796
TV	ACTGTA	845.20	1425	1.686	0.522
TV	ACTGTT	1301.64	2058	1.581	0.458
TV	ACGGTG	1512.80	2306	1.524	0.422
TV	ACAGTA	955.76	1371	1.434	0.361
TV	ACTGTC	1666.51	2289	1.374	0.317
TV	ACAGTT	1471.90	2019	1.372	0.316
TV	ACTGTG	3296.87	4505	1.366	0.312
TV	ACGGTC	764.70	911	1.191	0.175
TV	ACAGTG	3728.11	4108	1.102	0.097
TV	ACAGTC	1884.50	1933	1.026	0.025
TV	ACGGTA	387.83	286	0.737	-0.305
TV	ACGGTT	597.27	415	0.695	-0.364
TV	ACCGTG	4605.23	2640	0.573	-0.556
TV	ACCGTC	2327.87	1285	0.552	-0.594
TV	ACCGTT	1818.19	496	0.273	-1.299
TV	ACCGTA	1180.62	298	0.252	-1.377
TW	ACGTGG	606.25	837	1.381	0.323
TW	ACCTGG	1845.52	2403	1.302	0.264
TW	ACATGG	1494.02	1089	0.729	-0.316
TW	ACTTGG	1321.21	938	0.710	-0.343
TY	ACCTAC	2130.11	3648	1.713	0.538
TY	ACCTAT	1730.88	1778	1.027	0.027
TY	ACTTAC	1524.94	1383	0.907	-0.098
TY	ACGTAC	699.73	621	0.887	-0.119
TY	ACATAT	1401.21	1136	0.811	-0.210
TY	ACTTAT	1239.13	907	0.732	-0.312
TY	ACGTAT	568.59	408	0.718	-0.332
TY	ACATAC	1724.41	1138	0.660	-0.416
VA	GTGGCC	6082.92	9316	1.532	0.426
VA	GTAGCA	897.78	1347	1.500	0.406
VA	GTTGCT	1579.41	2217	1.404	0.339
VA	GTAGCT	1025.57	1407	1.372	0.316
VA	GTGGCT	4000.44	5252	1.313	0.272
VA	GTGGCG	1644.71	2099	1.276	0.244
VA	GTTGCA	1382.62	1728	1.250	0.223
VA	GTGGCA	3501.98	3859	1.102	0.097
VA	GTAGCC	1559.44	1363	0.874	-0.135
VA	GTTGCC	2401.60	1808	0.753	-0.284
VA	GTAGCG	421.64	216	0.512	-0.669
VA	GTTGCG	649.35	234	0.360	-1.021
VA	GTCGCG	831.37	284	0.342	-1.074
VA	GTCGCC	3074.82	992	0.323	-1.131

VA	GTCGCT	2022.16	406	0.201	-1.606
VA	GTCGCA	1770.19	318	0.180	-1.717
VC	GTCTGC	1410.66	2160	1.531	0.426
VC	GTCTGT	1188.18	1572	1.323	0.280
VC	GTTTGT	928.03	942	1.015	0.015
VC	GTATGT	602.60	594	0.986	-0.014
VC	GTGTGC	2790.71	2583	0.926	-0.077
VC	GTGTGT	2350.57	1996	0.849	-0.164
VC	GTTTGC	1101.80	830	0.753	-0.283
VC	GTATGC	715.44	411	0.574	-0.554
VD	GTAGAT	1225.65	1924	1.570	0.451
VD	GTGGAC	5400.58	7734	1.432	0.359
VD	GTTGAT	1887.55	2389	1.266	0.236
VD	GTGGAT	4780.91	5727	1.198	0.181
VD	GTAGAC	1384.52	1346	0.972	-0.028
VD	GTTGAC	2132.21	1791	0.840	-0.174
VD	GTCGAC	2729.91	602	0.221	-1.512
VD	GTCGAT	2416.67	445	0.184	-1.692
VE	GTAGAA	1456.83	2855	1.960	0.673
VE	GTGGAG	7599.48	11579	1.524	0.421
VE	GTTGAA	2243.56	2905	1.295	0.258
VE	GTGGAA	5682.64	6229	1.096	0.092
VE	GTAGAG	1948.24	2002	1.028	0.027
VE	GTTGAG	3000.36	1987	0.662	-0.412
VE	GTCGAG	3841.42	721	0.188	-1.673
VE	GTCGAA	2872.48	367	0.128	-2.058
VF	GTCTTC	2309.08	4216	1.826	0.602
VF	GTATTT	1023.16	1512	1.478	0.391
VF	GTCTTT	2017.40	2238	1.109	0.104
VF	GTTTTT	1575.70	1706	1.083	0.079
VF	GTTTTC	1803.52	1604	0.889	-0.117
VF	GTGTTT	3991.02	3257	0.816	-0.203
VF	GTGTTC	4568.05	3205	0.702	-0.354
VF	GTATTC	1171.09	721	0.616	-0.485
VG	GTTGGT	779.74	1617	2.074	0.729
VG	GTTGGA	1204.37	2315	1.922	0.653
VG	GTGGGC	4136.07	5977	1.445	0.368
VG	GTAGGA	782.04	1089	1.393	0.331
VG	GTTGGG	1175.77	1510	1.284	0.250
VG	GTTGGC	1632.96	1794	1.099	0.094
VG	GTAGGT	506.31	554	1.094	0.090
VG	GTGGGG	2978.07	3255	1.093	0.089
VG	GTGGGT	1974.96	2009	1.017	0.017
VG	GTAGGG	763.47	683	0.895	-0.111
VG	GTGGGA	3050.51	2599	0.852	-0.160
VG	GTAGGC	1060.34	676	0.638	-0.450
VG	GTCGGG	1505.36	734	0.488	-0.718
VG	GTCGGC	2090.72	734	0.351	-1.047

VG	GTCGGT	998.31	292	0.292	-1.229
VG	GTCGGA	1541.98	343	0.222	-1.503
VH	GTTCAT	911.79	1418	1.555	0.442
VH	GTACAT	592.06	773	1.306	0.267
VH	GTCCAC	1609.82	2085	1.295	0.259
VH	GTCCAT	1167.39	1313	1.125	0.118
VH	GTTCAC	1257.35	1319	1.049	0.048
VH	GTGCAC	3184.70	2856	0.897	-0.109
VH	GTACAC	816.44	613	0.751	-0.287
VH	GTGCAT	2309.44	1472	0.637	-0.450
VI	GTCATC	2367.78	5207	2.199	0.788
VI	GTCATT	1872.41	2827	1.510	0.412
VI	GTAATA	436.74	614	1.406	0.341
VI	GTAATT	949.63	1074	1.131	0.123
VI	GTTATT	1462.46	1595	1.091	0.087
VI	GTCATA	861.15	904	1.050	0.049
VI	GTTATA	672.60	702	1.044	0.043
VI	GTGATT	3704.20	2742	0.740	-0.301
VI	GTGATC	4684.19	3353	0.716	-0.334
VI	GTGATA	1703.61	1117	0.656	-0.422
VI	GTTATC	1849.37	1053	0.569	-0.563
VI	GTAATC	1200.86	577	0.480	-0.733
VK	GTAAAA	1288.46	1945	1.510	0.412
VK	GTCAAG	3290.24	3982	1.210	0.191
VK	GTGAAG	6509.08	7513	1.154	0.143
VK	GTAAAG	1668.70	1704	1.021	0.021
VK	GTCAAA	2540.51	2376	0.935	-0.067
VK	GTTAAA	1984.27	1777	0.896	-0.110
VK	GTGAAA	5025.89	4409	0.877	-0.131
VK	GTTAAG	2569.85	1171	0.456	-0.786
VL	GTTTTA	668.83	1311	1.960	0.673
VL	GTTCTT	1146.70	1859	1.621	0.483
VL	GTTTTG	1123.58	1737	1.546	0.436
VL	GTATTA	434.30	646	1.487	0.397
VL	GTCCCTC	2129.16	3019	1.418	0.349
VL	GTTCTA	618.41	832	1.345	0.297
VL	GTCCCTG	4424.65	5574	1.260	0.231
VL	GTCCCTT	1468.14	1722	1.173	0.159
VL	GTGCTG	8753.31	10107	1.155	0.144
VL	GTCTTG	1438.54	1628	1.132	0.124
VL	GTACTA	401.55	447	1.113	0.107
VL	GTCCCTA	791.76	874	1.104	0.099
VL	GTCTTA	856.32	863	1.008	0.008
VL	GTATTG	729.58	711	0.975	-0.026
VL	GTACTT	744.59	693	0.931	-0.072
VL	GTTCTC	1662.99	1501	0.903	-0.102
VL	GTGCTC	4212.12	3765	0.894	-0.112
VL	GTGCTA	1566.34	1286	0.821	-0.197

VL	GTTCTG	3455.90	2350	0.680	-0.386
VL	GTGTTG	2845.87	1910	0.671	-0.399
VL	GTGCTT	2904.43	1933	0.666	-0.407
VL	GTGTTA	1694.06	965	0.570	-0.563
VL	GTACTC	1079.84	541	0.501	-0.691
VL	GTACTG	2244.04	1121	0.500	-0.694
VM	GTCATG	2149.52	3308	1.539	0.431
VM	GTGATG	4252.41	3872	0.911	-0.094
VM	GTAATG	1090.17	935	0.858	-0.154
VM	GTTATG	1678.90	1056	0.629	-0.464
VN	GTCAAC	2052.00	3311	1.614	0.478
VN	GTAAAT	944.92	1518	1.606	0.474
VN	GTCAAT	1863.13	2155	1.157	0.146
VN	GTTAAT	1455.20	1325	0.911	-0.094
VN	GTGAAC	4059.49	3551	0.875	-0.134
VN	GTGAAT	3685.83	3110	0.844	-0.170
VN	GTAAAC	1040.71	854	0.821	-0.198
VN	GTTAAC	1602.73	880	0.549	-0.600
VP	GTTCCCT	1434.04	2257	1.574	0.454
VP	GTTCCA	1384.03	1911	1.381	0.323
VP	GTGCCC	4055.45	4998	1.232	0.209
VP	GTACCT	931.17	1048	1.125	0.118
VP	GTCCCC	2049.96	2260	1.102	0.098
VP	GTCCCT	1836.02	2014	1.097	0.093
VP	GTACCA	898.70	963	1.072	0.069
VP	GTCCCG	742.77	786	1.058	0.057
VP	GTTCCC	1601.13	1506	0.941	-0.061
VP	GTCCCA	1772.00	1596	0.901	-0.105
VP	GTGCCT	3632.21	3062	0.843	-0.171
VP	GTGCCG	1469.43	1228	0.836	-0.179
VP	GTACCC	1039.67	809	0.778	-0.251
VP	GTGCCA	3505.55	2431	0.693	-0.366
VP	GTTCCG	580.15	279	0.481	-0.732
VP	GTACCG	376.71	161	0.427	-0.850
VQ	GTACAA	633.37	1049	1.656	0.505
VQ	GTTCAA	975.42	1485	1.522	0.420
VQ	GTCCAG	3487.32	3907	1.120	0.114
VQ	GTACAG	1768.65	1752	0.991	-0.009
VQ	GTTCAG	2723.79	2689	0.987	-0.013
VQ	GTGCAG	6898.98	6734	0.976	-0.024
VQ	GTCCAA	1248.85	1067	0.854	-0.157
VQ	GTGCAA	2470.60	1524	0.617	-0.483
VR	GTTCGA	463.33	867	1.871	0.627
VR	GTTCGT	334.59	580	1.733	0.550
VR	GTCCGA	593.21	805	1.357	0.305
VR	GTCCGC	1000.57	1332	1.331	0.286
VR	GTGCGC	1979.43	2543	1.285	0.251
VR	GTCCGT	428.38	549	1.282	0.248

VR	GTCCGG	1094.32	1346	1.230	0.207
VR	GTACGA	300.86	361	1.200	0.182
VR	GTAAGA	559.73	660	1.179	0.165
VR	GTGCGG	2164.91	2552	1.179	0.164
VR	GTCAGA	1103.65	1291	1.170	0.157
VR	GTACGT	217.26	253	1.165	0.152
VR	GTCAGG	1083.48	1238	1.143	0.133
VR	GTGAGG	2143.46	1986	0.927	-0.076
VR	GTGCGT	847.46	761	0.898	-0.108
VR	GTAAGG	549.51	444	0.808	-0.213
VR	GTTCGG	854.73	650	0.760	-0.274
VR	GTGCGA	1173.55	826	0.704	-0.351
VR	GTTCGC	781.50	545	0.697	-0.360
VR	GTGAGA	2183.35	1511	0.692	-0.368
VR	GTACGG	555.00	377	0.679	-0.387
VR	GTTAGA	862.01	556	0.645	-0.438
VR	GTACGC	507.46	286	0.564	-0.573
VR	GTTAGG	846.26	309	0.365	-1.007
VS	GTTTCT	1206.81	2161	1.791	0.583
VS	GTCTCC	1776.18	2936	1.653	0.503
VS	GTCAGC	2012.32	3223	1.602	0.471
VS	GTTTCA	975.63	1465	1.502	0.407
VS	GTCAGT	1269.59	1841	1.450	0.372
VS	GTATCT	783.62	1093	1.395	0.333
VS	GTATCA	633.51	806	1.272	0.241
VS	GTCTCT	1545.10	1847	1.195	0.178
VS	GTTTCC	1387.29	1604	1.156	0.145
VS	GTCTCG	469.69	542	1.154	0.143
VS	GTCTCA	1249.12	1333	1.067	0.065
VS	GTGTCC	3513.81	3722	1.059	0.058
VS	GTGTCT	929.19	860	0.926	-0.077
VS	GTGTCT	3056.67	2784	0.911	-0.093
VS	GTATCC	900.82	763	0.847	-0.166
VS	GTAAGT	643.89	499	0.775	-0.255
VS	GTGAGC	3980.98	2901	0.729	-0.316
VS	GTGTCA	2471.14	1710	0.692	-0.368
VS	GTTAGT	991.62	640	0.645	-0.438
VS	GTATCG	238.21	138	0.579	-0.546
VS	GTTTCG	366.85	202	0.551	-0.597
VS	GTGAGT	2511.63	1371	0.546	-0.605
VS	GTAAGC	1020.58	514	0.504	-0.686
VS	GTTAGC	1571.73	551	0.351	-1.048
VT	GTCACC	2294.69	4477	1.951	0.668
VT	GTCACT	1642.76	2452	1.493	0.401
VT	GTCACG	753.80	997	1.323	0.280
VT	GTAACCT	833.15	1046	1.255	0.228
VT	GTCACA	1857.64	2207	1.188	0.172
VT	GTAACA	942.13	1096	1.163	0.151

VT	GTTACT	1283.09	1208	0.941	-0.060
VT	GTGACC	4539.59	4223	0.930	-0.072
VT	GTGACG	1491.24	1318	0.884	-0.123
VT	GTGACT	3249.88	2758	0.849	-0.164
VT	GTGACA	3674.98	2947	0.802	-0.221
VT	GTTACA	1450.92	1111	0.766	-0.267
VT	GTAACC	1163.79	758	0.651	-0.429
VT	GTTACC	1792.28	969	0.541	-0.615
VT	GTAACG	382.30	191	0.500	-0.694
VT	GTTACG	588.76	183	0.311	-1.169
VV	GTTGTA	655.54	1109	1.692	0.526
VV	GTTGTT	1009.55	1701	1.685	0.522
VV	GTAGTA	425.66	698	1.640	0.495
VV	GTGGTG	6476.64	9025	1.393	0.332
VV	GTGGTC	3273.84	4256	1.300	0.262
VV	GTAGTT	655.54	800	1.220	0.199
VV	GTTGTC	1292.55	1561	1.208	0.189
VV	GTGGTA	1660.38	1777	1.070	0.068
VV	GTGGTT	2557.05	2613	1.022	0.022
VV	GTTGTG	2557.05	2261	0.884	-0.123
VV	GTAGTG	1660.38	1161	0.699	-0.358
VV	GTAGTC	839.30	553	0.659	-0.417
VV	GTCGTC	1654.87	858	0.518	-0.657
VV	GTCGTG	3273.84	1250	0.382	-0.963
VV	GTCGTA	839.30	213	0.254	-1.371
VV	GTCGTT	1292.55	288	0.223	-1.501
VW	GTCTGG	1316.29	1763	1.339	0.292
VW	GTGTGG	2604.03	2451	0.941	-0.061
VW	GTATGG	667.58	578	0.866	-0.144
VW	GTTTGG	1028.10	824	0.801	-0.221
VY	GTCTAC	1602.79	2490	1.554	0.441
VY	GTTTAT	1017.23	1438	1.414	0.346
VY	GTATAT	660.53	875	1.325	0.281
VY	GTCTAT	1302.39	1544	1.186	0.170
VY	GTGTAC	3170.80	2654	0.837	-0.178
VY	GTTTAC	1251.87	1008	0.805	-0.217
VY	GTATAC	812.88	582	0.716	-0.334
VY	GTGTAT	2576.51	1804	0.700	-0.356
WA	TGGGCA	1469.77	1535	1.044	0.043
WA	TGGGCG	690.28	695	1.007	0.007
WA	TGGGCT	1678.97	1664	0.991	-0.009
WA	TGGGCC	2552.98	2498	0.978	-0.022
WC	TGGTGC	1057.38	1066	1.008	0.008
WC	TGGTGT	890.62	882	0.990	-0.010
WD	TGGGAC	2699.37	2807	1.040	0.039
WD	TGGGAT	2389.63	2282	0.955	-0.046
WE	TGGGAG	3580.00	3650	1.020	0.019
WE	TGGGAA	2677.00	2607	0.974	-0.026

WF	TGGTTT	1639.95	1735	1.058	0.056
WF	TGGTTC	1877.05	1782	0.949	-0.052
WG	TGGGGT	955.95	1064	1.113	0.107
WG	TGGGGC	2002.00	2179	1.088	0.085
WG	TGGGGA	1476.56	1454	0.985	-0.015
WG	TGGGGG	1441.49	1179	0.818	-0.201
WH	TGGCAT	971.42	1000	1.029	0.029
WH	TGGCAC	1339.58	1311	0.979	-0.022
WI	TGGATT	1537.91	1627	1.058	0.056
WI	TGGATA	707.30	714	1.009	0.009
WI	TGGATC	1944.78	1849	0.951	-0.051
WK	TGGAAG	3491.83	3645	1.044	0.043
WK	TGGAAA	2696.17	2543	0.943	-0.058
WL	TGGCTA	683.88	798	1.167	0.154
WL	TGGCTG	3821.78	4228	1.106	0.101
WL	TGGCTT	1268.11	1334	1.052	0.051
WL	TGGCTC	1839.05	1879	1.022	0.021
WL	TGGTTG	1242.54	855	0.688	-0.374
WL	TGGTTA	739.64	501	0.677	-0.390
WM	TGGATG	2335.00	2335	1.000	0.000
WN	TGGAAT	1978.70	2005	1.013	0.013
WN	TGGAAC	2179.30	2153	0.988	-0.012
WP	TGGCCC	1302.21	1381	1.061	0.059
WP	TGGCCG	471.84	486	1.030	0.030
WP	TGGCCA	1125.64	1123	0.998	-0.002
WP	TGGCCT	1166.31	1076	0.923	-0.081
WQ	TGGCAG	2983.56	2997	1.005	0.004
WQ	TGGCAA	1068.44	1055	0.987	-0.013
WR	TGGAGG	1198.99	1665	1.389	0.328
WR	TGGAGA	1221.30	1472	1.205	0.187
WR	TGGCGG	1210.98	979	0.808	-0.213
WR	TGGCGC	1107.23	895	0.808	-0.213
WR	TGGCGT	474.05	377	0.795	-0.229
WR	TGGCGA	656.45	481	0.733	-0.311
WS	TGGAGT	1031.75	1239	1.201	0.183
WS	TGGAGC	1635.35	1956	1.196	0.179
WS	TGGTCA	1015.12	898	0.885	-0.123
WS	TGGTCC	1443.44	1271	0.881	-0.127
WS	TGGTCT	1255.65	1076	0.857	-0.154
WS	TGGTCG	381.70	323	0.846	-0.167
WT	TGGACG	598.07	674	1.127	0.120
WT	TGGACA	1473.88	1559	1.058	0.056
WT	TGGACT	1303.39	1240	0.951	-0.050
WT	TGGACC	1820.65	1723	0.946	-0.055
WV	TGGGTC	1318.64	1378	1.045	0.044
WV	TGGGTG	2608.66	2633	1.009	0.009
WV	TGGGTA	668.77	665	0.994	-0.006
WV	TGGGTT	1029.93	950	0.922	-0.081

WW	TGGTGG	1559.00	1559	1.000	0.000
WY	TGGTAC	1444.91	1520	1.052	0.051
WY	TGGTAT	1174.09	1099	0.936	-0.066
YA	TATGCA	1120.39	2249	2.007	0.697
YA	TATGCT	1279.86	2296	1.794	0.584
YA	TATGCC	1946.11	2862	1.471	0.386
YA	TACGCG	647.56	622	0.961	-0.040
YA	TATGCG	526.19	482	0.916	-0.088
YA	TACGCC	2395.00	1402	0.585	-0.535
YA	TACGCA	1378.81	512	0.371	-0.991
YA	TACGCT	1575.07	444	0.282	-1.266
YC	TACTGC	1588.07	2411	1.518	0.418
YC	TACTGT	1337.61	1587	1.186	0.171
YC	TATTGT	1086.90	659	0.606	-0.500
YC	TATTGC	1290.42	646	0.501	-0.692
YD	TATGAT	2091.17	3707	1.773	0.572
YD	TATGAC	2362.22	3731	1.579	0.457
YD	TACGAC	2907.08	1653	0.569	-0.565
YD	TACGAT	2573.52	843	0.328	-1.116
YE	TATGAA	2515.85	5225	2.077	0.731
YE	TATGAG	3364.48	4722	1.403	0.339
YE	TACGAG	4140.53	2309	0.558	-0.584
YE	TACGAA	3096.14	861	0.278	-1.280
YF	TACTTC	2766.63	3380	1.222	0.200
YF	TATTTT	1964.12	2124	1.081	0.078
YF	TACTTT	2417.16	2201	0.911	-0.094
YF	TATTTT	2248.09	1691	0.752	-0.285
YG	TATGGA	1472.35	2874	1.952	0.669
YG	TATGGT	953.23	1665	1.747	0.558
YG	TATGGG	1437.38	2129	1.481	0.393
YG	TATGGC	1996.30	2749	1.377	0.320
YG	TACGGG	1768.93	1088	0.615	-0.486
YG	TACGGC	2456.76	1484	0.604	-0.504
YG	TACGGT	1173.10	448	0.382	-0.963
YG	TACGGA	1811.96	633	0.349	-1.052
YH	TACCAC	1862.81	2378	1.277	0.244
YH	TACCAT	1350.85	1420	1.051	0.050
YH	TATCAT	1097.67	1021	0.930	-0.072
YH	TATCAC	1513.67	1006	0.665	-0.409
YI	TACATC	2684.66	3935	1.466	0.382
YI	TACATT	2122.99	2162	1.018	0.018
YI	TATATT	1725.09	1554	0.901	-0.104
YI	TACATA	976.39	846	0.866	-0.143
YI	TATATA	793.39	648	0.817	-0.202
YI	TATATC	2181.48	1339	0.614	-0.488
YK	TACAAG	3508.58	4372	1.246	0.220
YK	TACAAA	2709.10	2847	1.051	0.050
YK	TATAAA	2201.34	2262	1.028	0.027

YK	TATAAG	2850.98	1789	0.628	-0.466
YL	TACCTG	4522.42	6324	1.398	0.335
YL	TATTTA	711.20	966	1.358	0.306
YL	TACCTC	2176.20	2598	1.194	0.177
YL	TACTTG	1470.33	1701	1.157	0.146
YL	TATTTG	1194.75	1358	1.137	0.128
YL	TACCTA	809.25	876	1.082	0.079
YL	TACCTT	1500.58	1449	0.966	-0.035
YL	TATCTT	1219.33	1166	0.956	-0.045
YL	TACTTA	875.24	763	0.872	-0.137
YL	TATCTA	657.58	541	0.823	-0.195
YL	TATCTC	1768.32	1087	0.615	-0.487
YL	TATCTG	3674.80	1751	0.476	-0.741
YM	TACATG	2325.97	3055	1.313	0.273
YM	TATATG	1890.03	1161	0.614	-0.487
YN	TACAAC	2442.24	3341	1.368	0.313
YN	TACAAT	2217.44	2200	0.992	-0.008
YN	TATAAT	1801.83	1629	0.904	-0.101
YN	TATAAC	1984.50	1276	0.643	-0.442
YP	TACCCG	668.65	1004	1.502	0.406
YP	TACCCA	1595.15	1925	1.207	0.188
YP	TATCCA	1296.18	1438	1.109	0.104
YP	TACCCC	1845.38	1961	1.063	0.061
YP	TATCCT	1343.02	1379	1.027	0.026
YP	TACCCT	1652.79	1558	0.943	-0.059
YP	TATCCC	1499.51	937	0.625	-0.470
YP	TATCCG	543.32	242	0.445	-0.809
YQ	TACCAG	3987.12	5013	1.257	0.229
YQ	TATCAA	1160.22	1179	1.016	0.016
YQ	TACCAA	1427.83	1397	0.978	-0.022
YQ	TATCAG	3239.83	2226	0.687	-0.375
YR	TACCGC	1307.70	2153	1.646	0.499
YR	TACCGA	775.30	990	1.277	0.244
YR	TACAGA	1442.41	1834	1.271	0.240
YR	TACCGG	1430.23	1796	1.256	0.228
YR	TACAGG	1416.06	1671	1.180	0.166
YR	TACCGT	559.87	642	1.147	0.137
YR	TATCGA	629.99	570	0.905	-0.100
YR	TATCGT	454.94	383	0.842	-0.172
YR	TATAGA	1172.07	827	0.706	-0.349
YR	TATCGG	1162.17	629	0.541	-0.614
YR	TATAGG	1150.66	560	0.487	-0.720
YR	TATCGC	1062.60	509	0.479	-0.736
YS	TACAGC	2204.13	3590	1.629	0.488
YS	TACTCG	514.46	783	1.522	0.420
YS	TACAGT	1390.60	1887	1.357	0.305
YS	TATTCA	1111.75	1210	1.088	0.085
YS	TACTCC	1945.47	2088	1.073	0.071

YS	TATTCT	1375.18	1466	1.066	0.064
YS	TACTCA	1368.18	1188	0.868	-0.141
YS	TATTCC	1580.84	1306	0.826	-0.191
YS	TACTCT	1692.37	1173	0.693	-0.367
YS	TATAGT	1129.96	728	0.644	-0.440
YS	TATTCG	418.04	229	0.548	-0.602
YS	TATAGC	1791.02	874	0.488	-0.717
YT	TACACG	697.26	1311	1.880	0.631
YT	TACACC	2122.58	2696	1.270	0.239
YT	TACACA	1718.31	2158	1.256	0.228
YT	TCACT	1519.54	1409	0.927	-0.076
YT	TATACT	1234.74	1049	0.850	-0.163
YT	TATACA	1396.25	1049	0.751	-0.286
YT	TATACC	1724.75	1063	0.616	-0.484
YT	TATACG	566.57	245	0.432	-0.838
YV	TATGTT	986.79	1723	1.746	0.557
YV	TATGTA	640.76	1113	1.737	0.552
YV	TATGTC	1263.40	1862	1.474	0.388
YV	TATGTG	2499.39	3382	1.353	0.302
YV	TACGTG	3075.90	2279	0.741	-0.300
YV	TACGTC	1554.82	991	0.637	-0.450
YV	TACGTA	788.55	284	0.360	-1.021
YV	TACGTT	1214.40	390	0.321	-1.136
YW	TACTGG	1609.87	2212	1.374	0.318
YW	TATTGG	1308.13	706	0.540	-0.617
YY	TACTAC	2256.03	2854	1.265	0.235
YY	TATTAT	1489.60	1459	0.979	-0.021
YY	TACTAT	1833.19	1760	0.960	-0.041
YY	TATTAC	1833.19	1339	0.730	-0.314

We Claim:

1. An attenuated influenza virus in which expression of hemagglutinin (HA) and neuraminidase (NA) is reduced compared to a parent virus, wherein the reduction in expression is the result of recoding the HA protein-encoding sequence and recoding the NA protein-encoding sequence, and expression of other influenza proteins are not substantially reduced.

2. The attenuated influenza virus of claim 1, wherein one or both of the HA protein-encoding sequence and the NA protein-encoding sequence are recoded by lowering the codon pair bias of the protein-encoding sequence.

3. The method of claim 2, wherein reducing the codon-pair bias comprises identifying a codon pair in the parent protein-encoding sequence having a codon-pair score that can be reduced, and reducing the codon-pair bias by substituting the codon pair with a codon pair that has a lower codon-pair score.

4. The method of claim 2, wherein reducing the codon-pair bias comprises rearranging the codons of a parent protein-encoding sequence.

5. The attenuated influenza virus of claim 1, wherein each of the recoded HA protein-encoding sequence and the recoded NA protein-encoding sequence have a codon pair bias less than -0.1, or less than -0.2, or less than -0.3, or less than -0.4.

6. The attenuated influenza virus of claim 1, wherein one or both of the HA protein-encoding sequence and the NA protein-encoding sequence are recoded by replacing one or more codons with synonymous codons that are less frequent in the viral host.

7. An influenza vaccine composition for inducing a protective immune response in a subject, which comprises the attenuated virus of claim 1.

8. A method of eliciting a protective immune response in a subject comprising administering to the subject a prophylactically or therapeutically effective dose of a vaccine composition comprising the attenuated virus of claim 1.

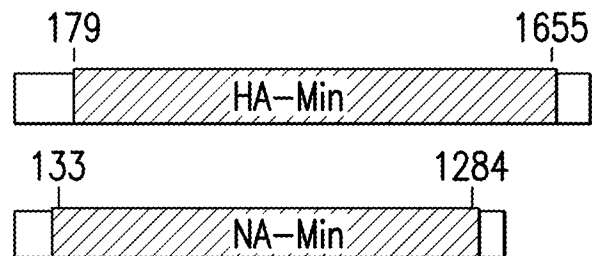
9. The method of claim 8, further comprising administering to the subject at least one adjuvant.

10. The method of claim 8, wherein the immune response is cross-protective against a heterologous influenza virus.

11. A method of making an attenuated influenza virus genome comprising:

- a) obtaining the nucleotide sequence encoding the hemagglutinin protein of an influenza virus and the nucleotide sequence encoding the neuraminidase protein of an influenza virus;
- b) recoding the hemagglutinin-encoding nucleotide sequence to reduce protein expression and recoding the neuraminidase-encoding nucleotide sequence to reduce protein expression, and
- c) substituting a nucleic acid having the recoded hemagglutinin-encoding nucleotide sequence and a nucleic acid having the recoded neuraminidase-encoding nucleotide sequence into a parent influenza virus genome to make an attenuated influenza virus genome; whereby expression of the recoded hemagglutinin-encoding nucleotide sequence and expression of the recoded neuraminidase-encoding nucleotide sequence is reduced compared to the parent virus; wherein expression of other influenza proteins are not substantially reduced.

1/29



Virus	Mutations/Length (nt)
HA ^{Min}	353/1775
NA ^{Min}	265/1413
(NA+HA) ^{Min}	618/3188

FIG. 1A

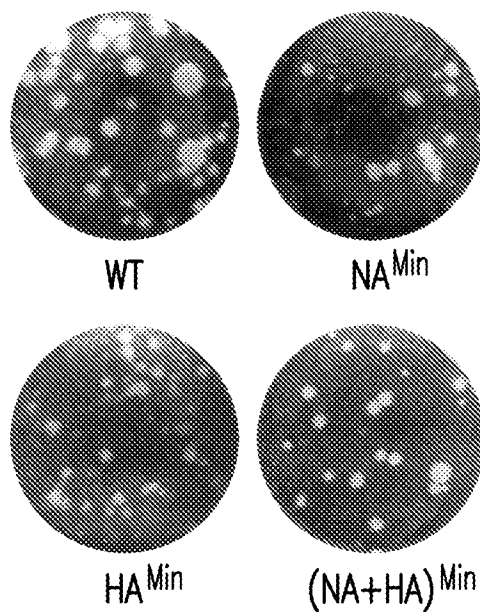


FIG. 1B

2/29

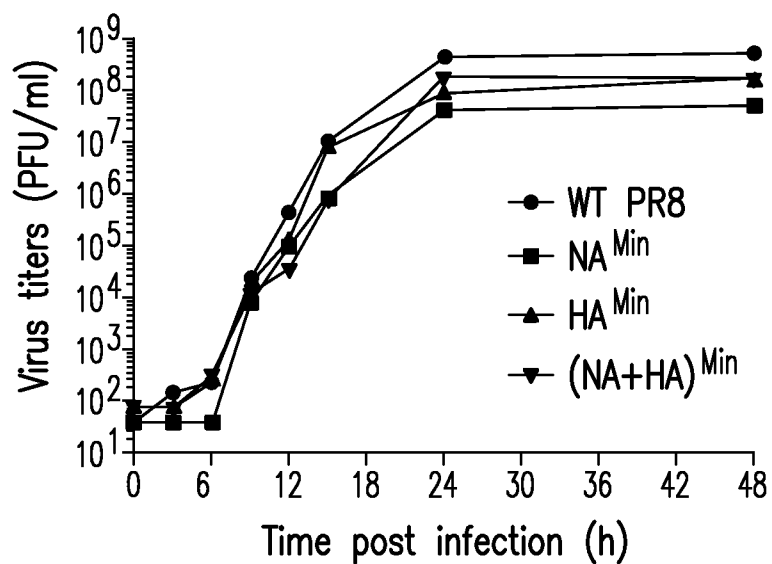


FIG. 1C

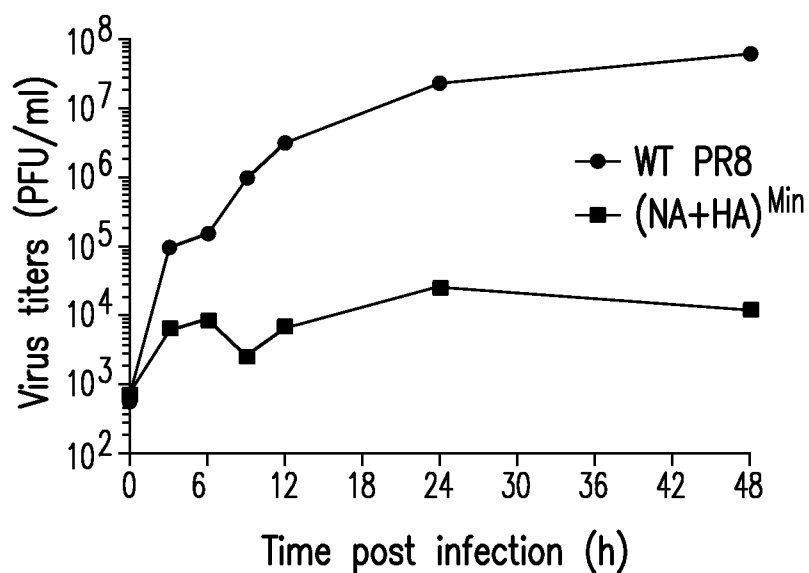


FIG. 1D

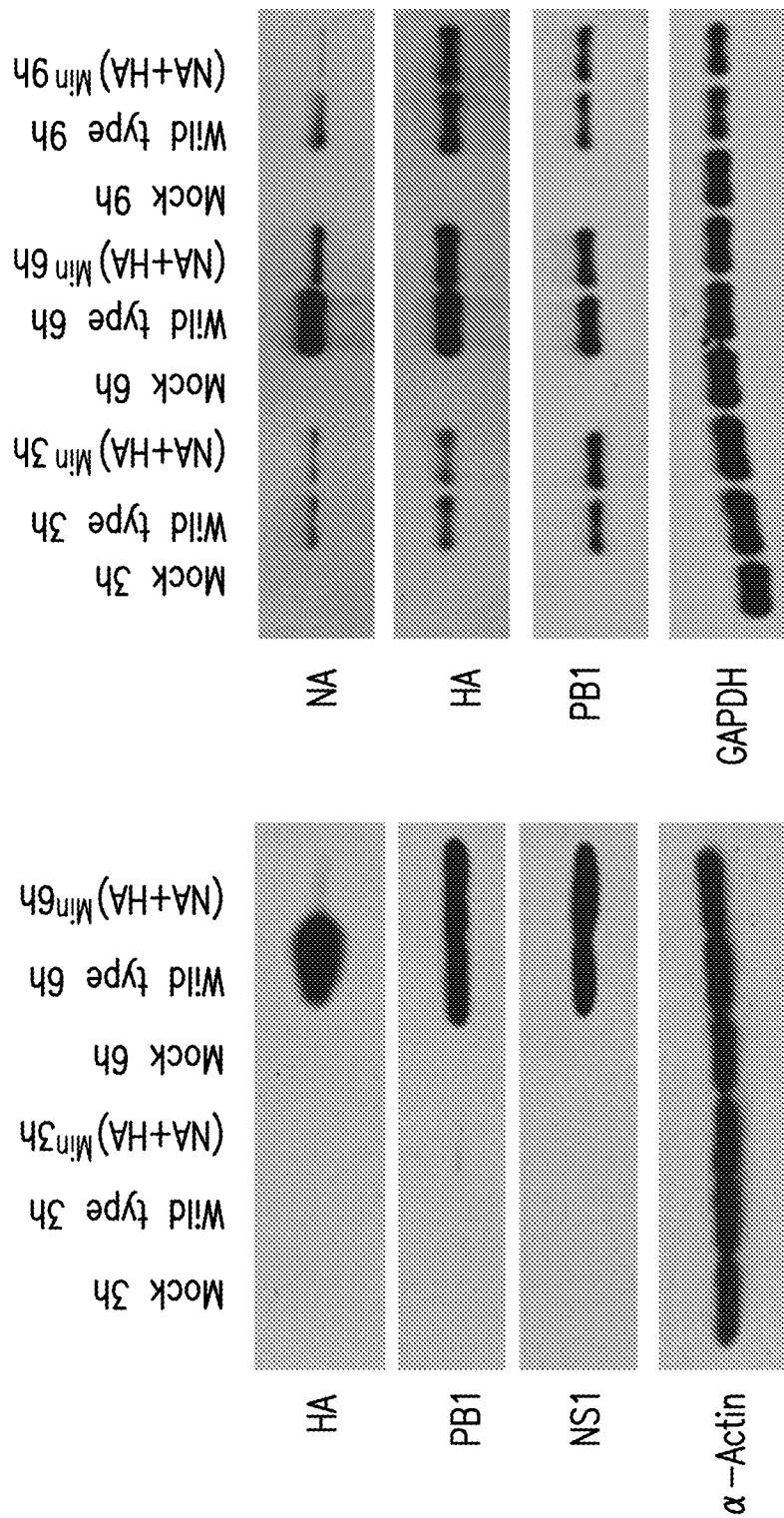


FIG. 2B

FIG. 2A

4/29

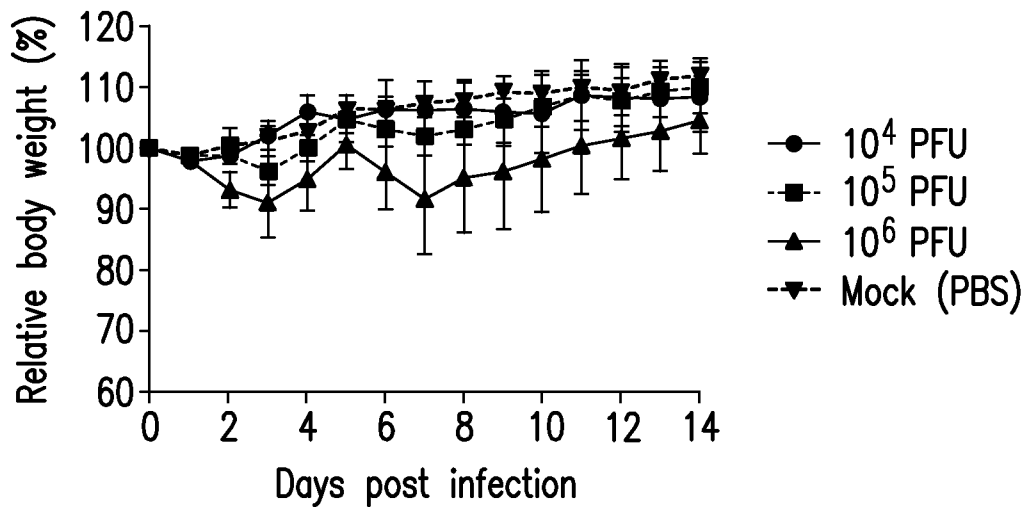


FIG. 3A

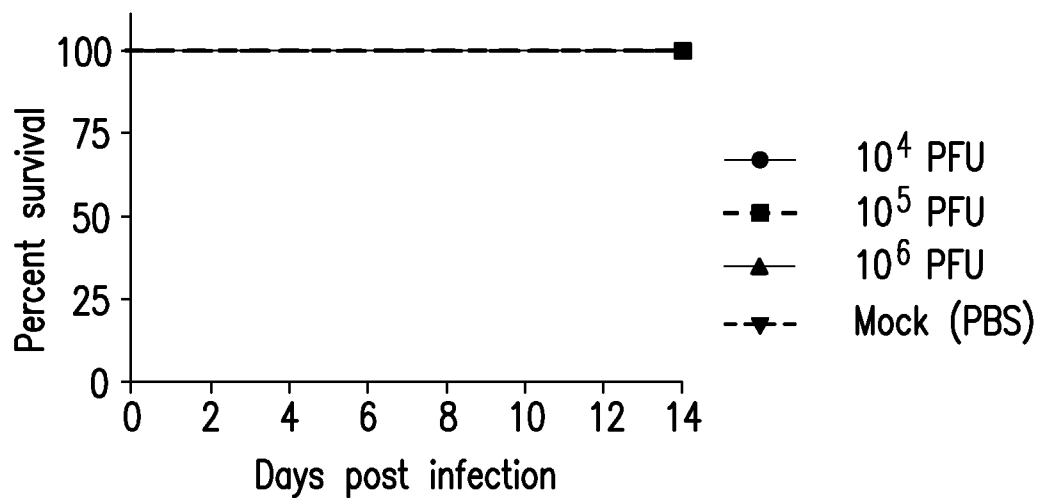


FIG. 3B

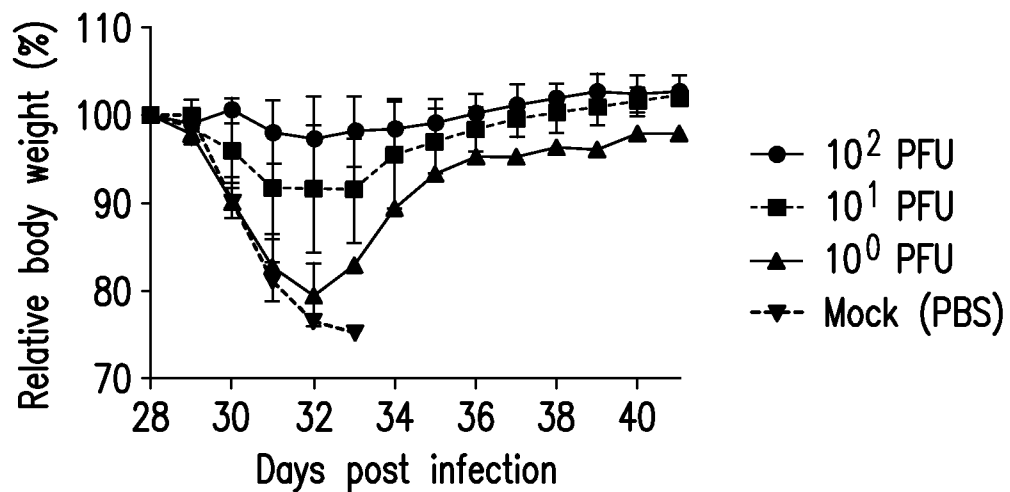


FIG. 3C

5/29

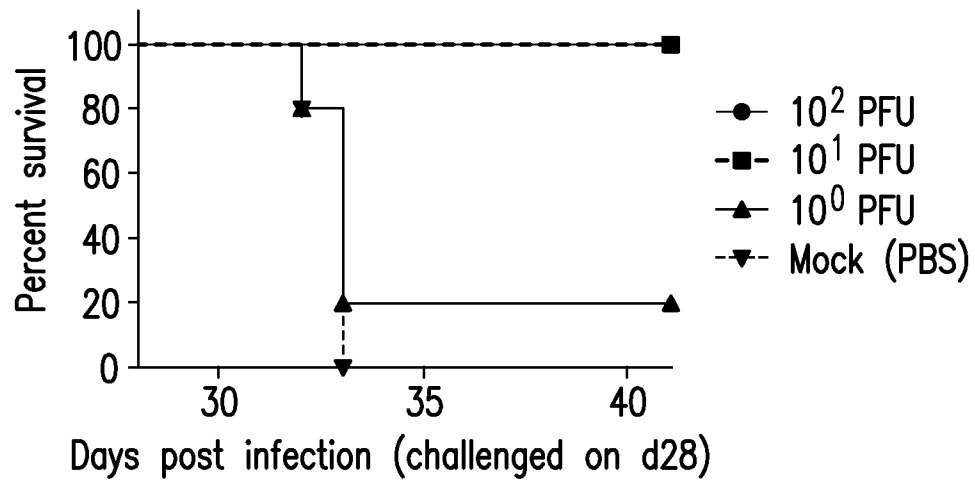


FIG. 3D

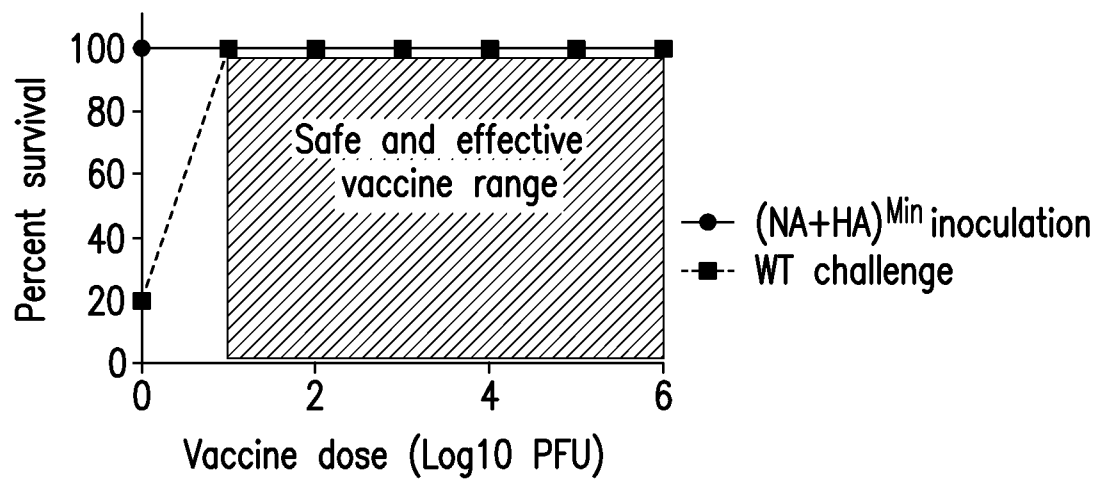


FIG. 3E

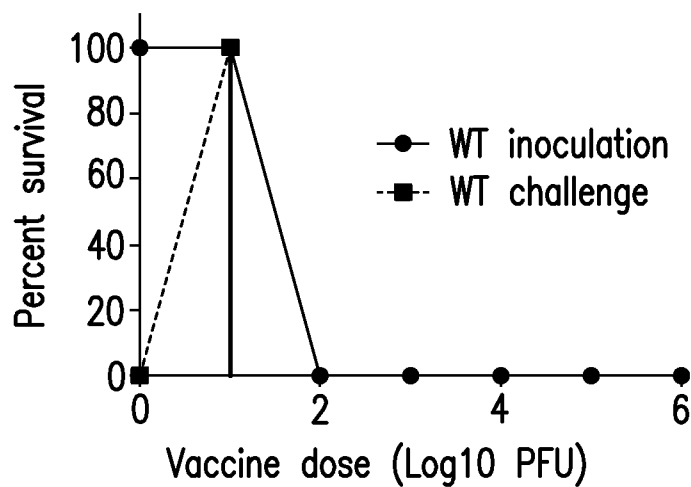


FIG. 3F

6/29

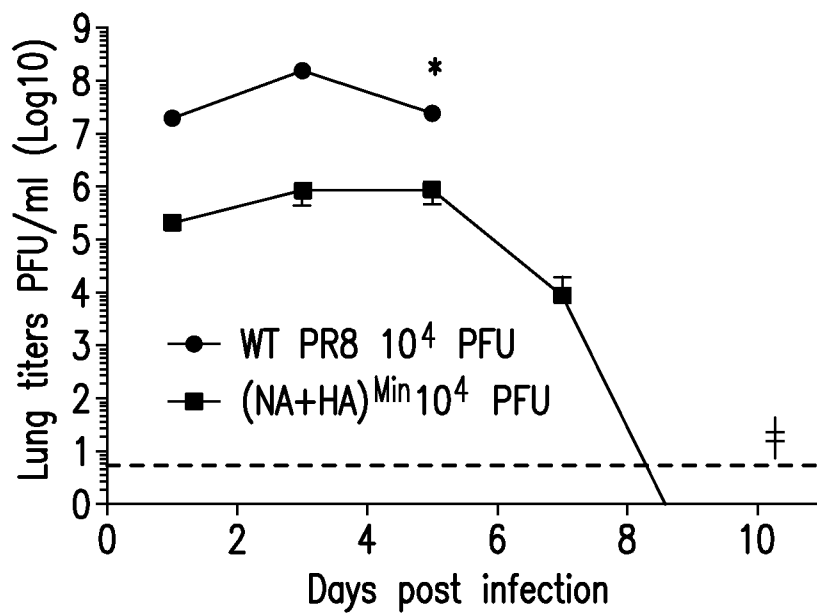


FIG. 4A

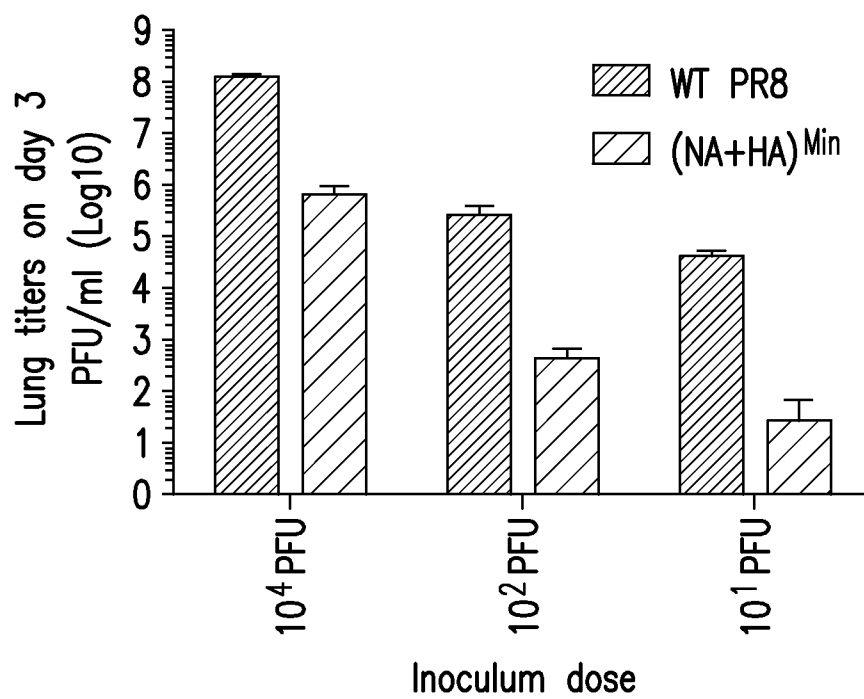


FIG. 4B

7/29

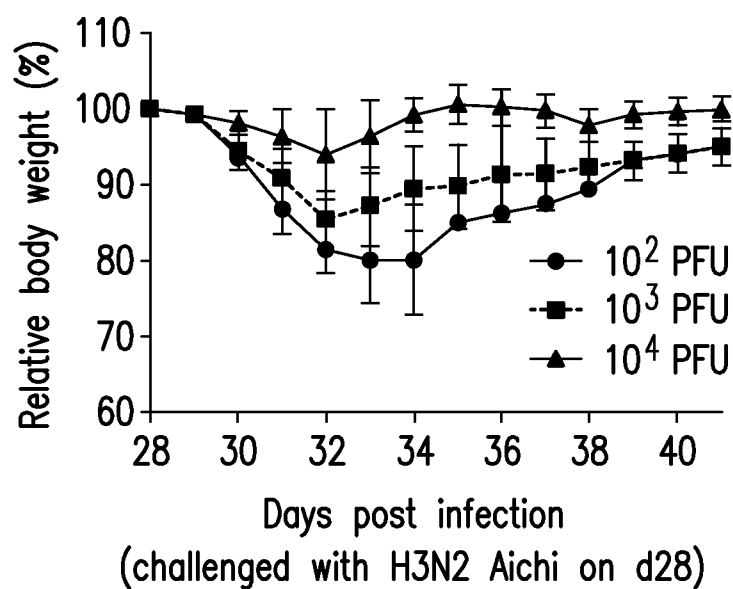


FIG. 5A

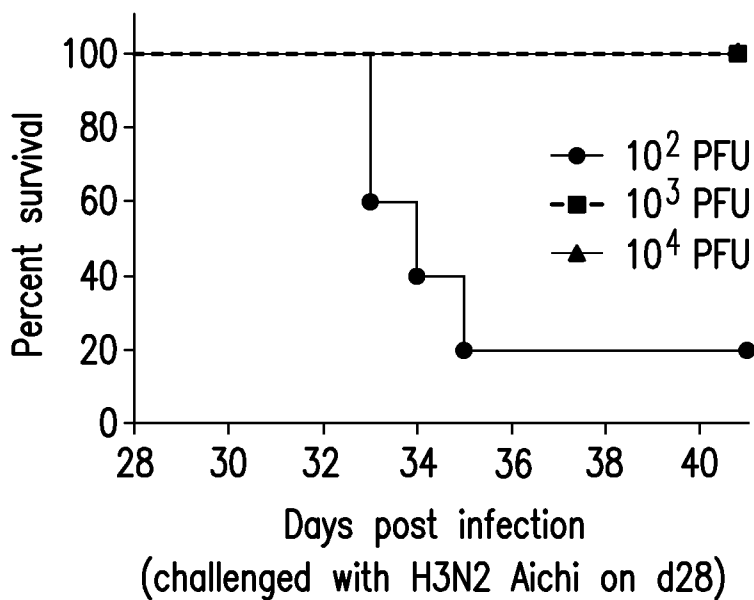


FIG. 5B

8/29

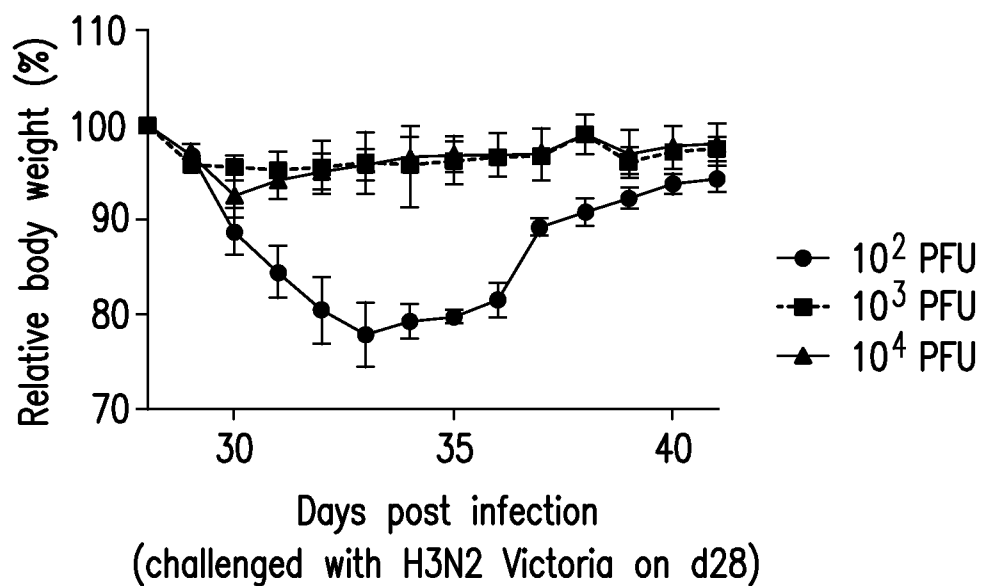


FIG. 5C

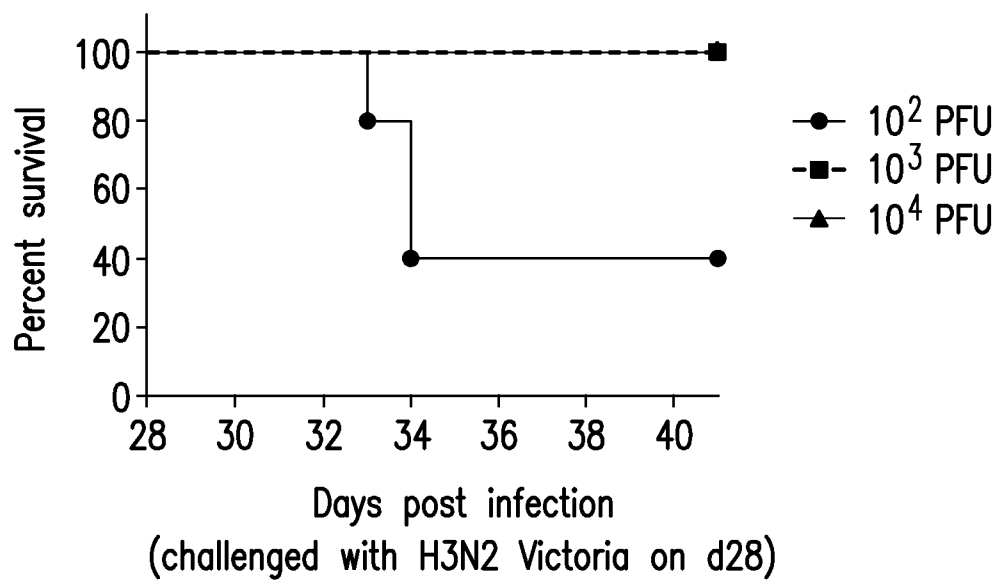


FIG. 5D

9/29

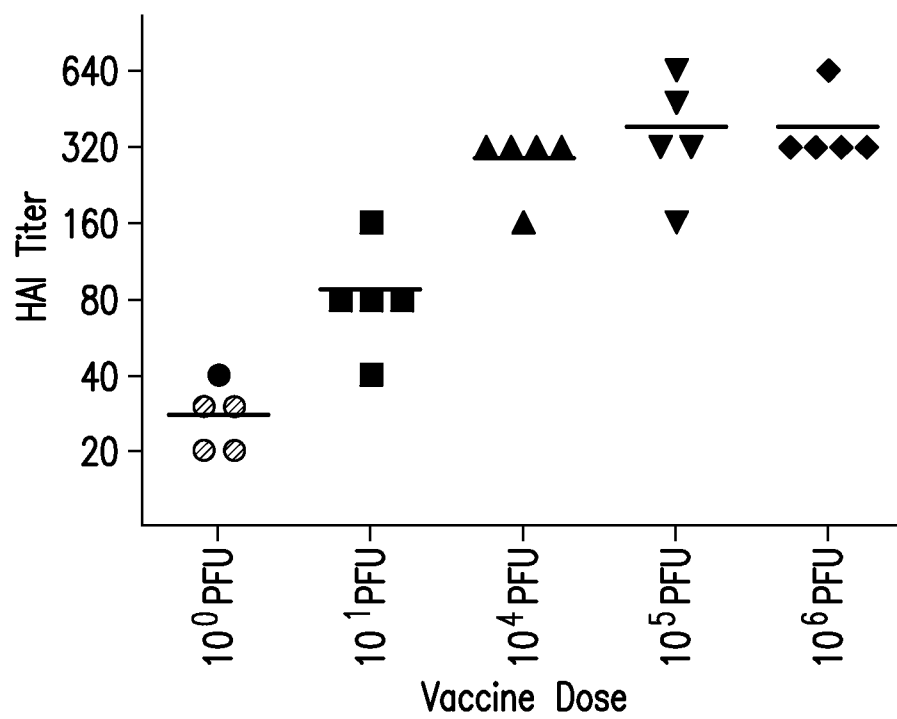


FIG. 6

10/29

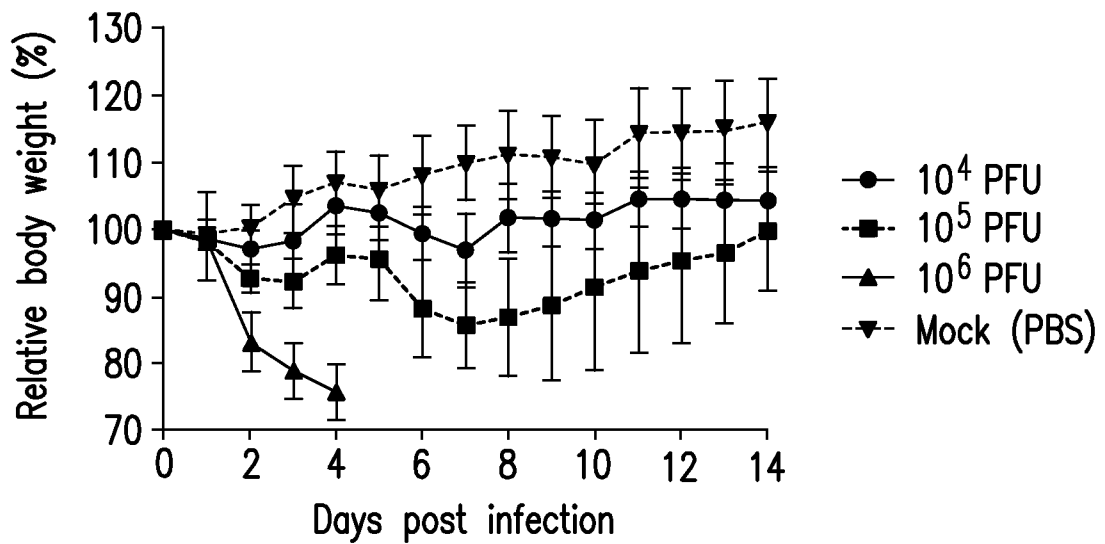


FIG. 7A

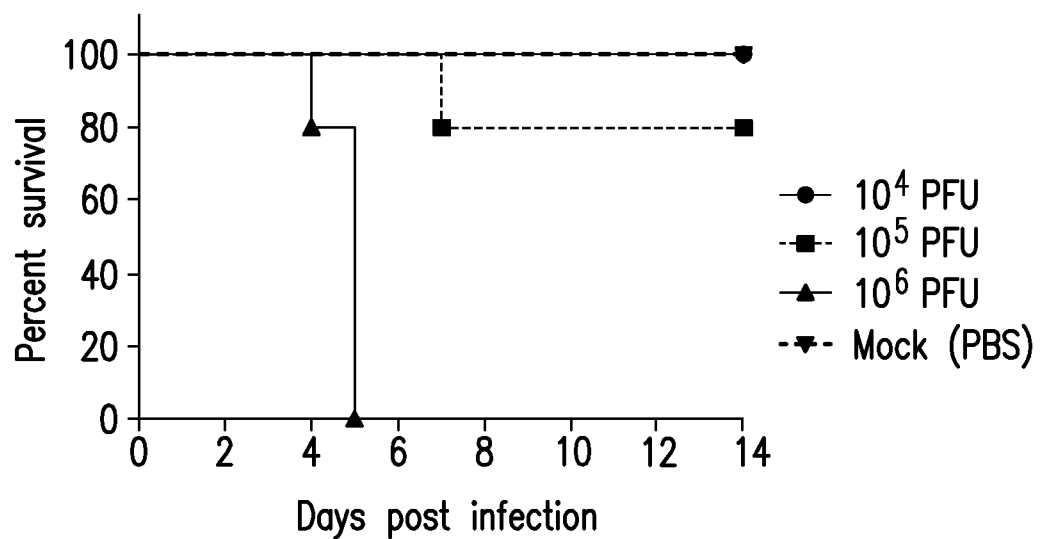


FIG. 7B

11/29

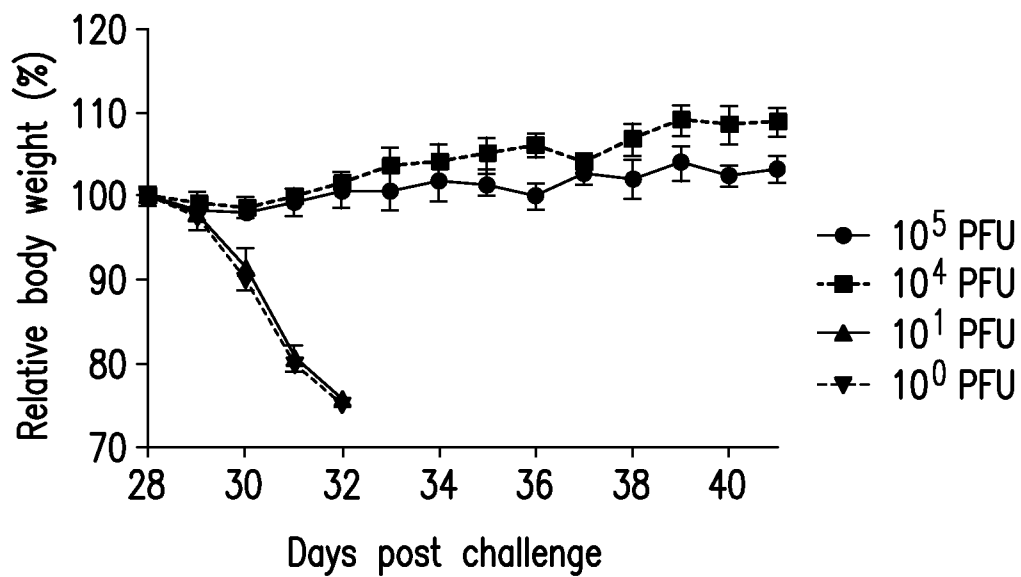


FIG. 7C

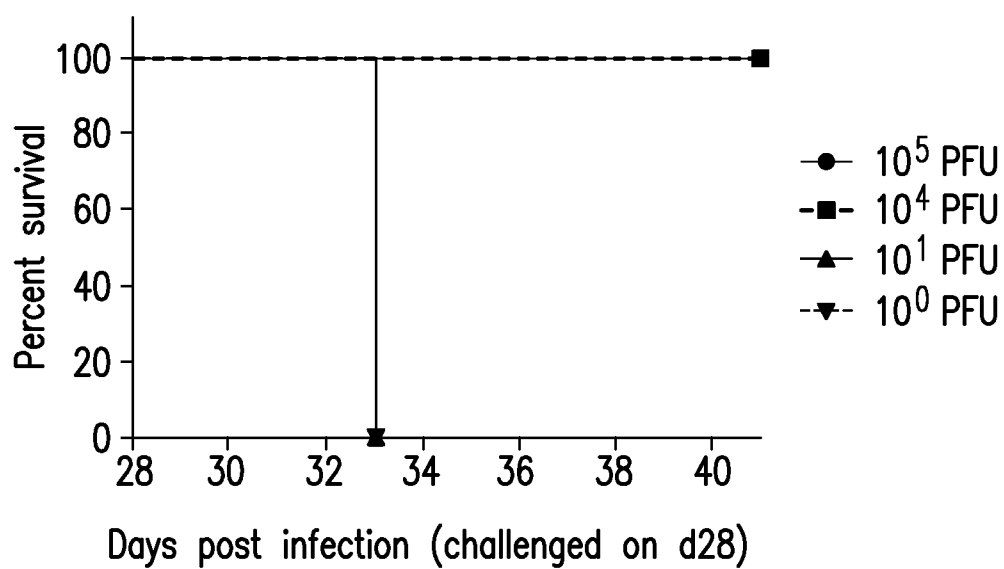


FIG. 7D

12/29

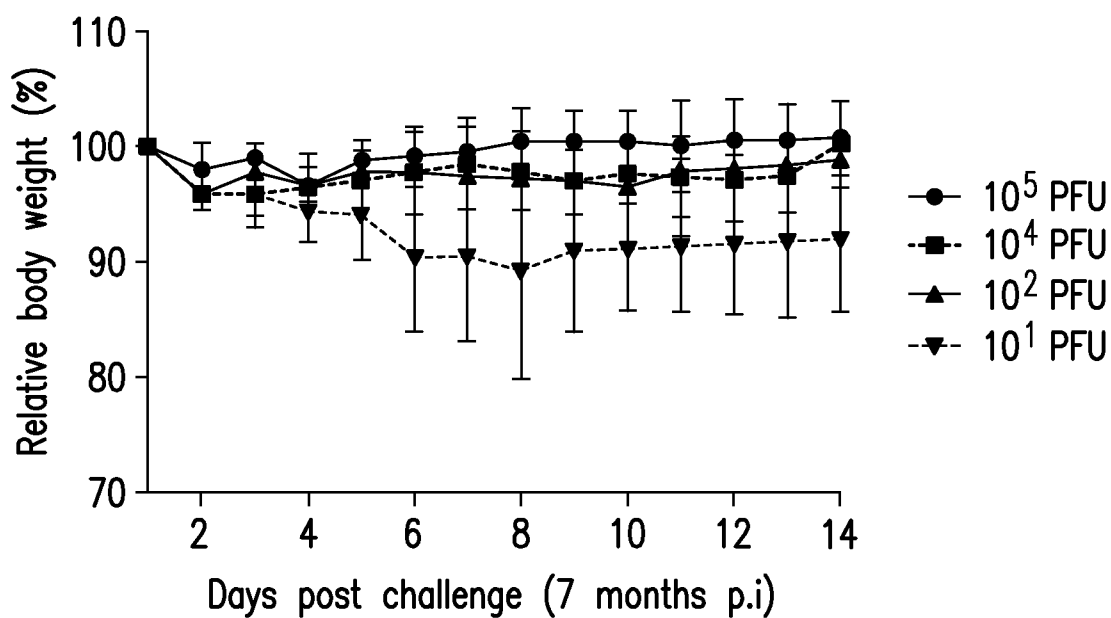


FIG. 8A

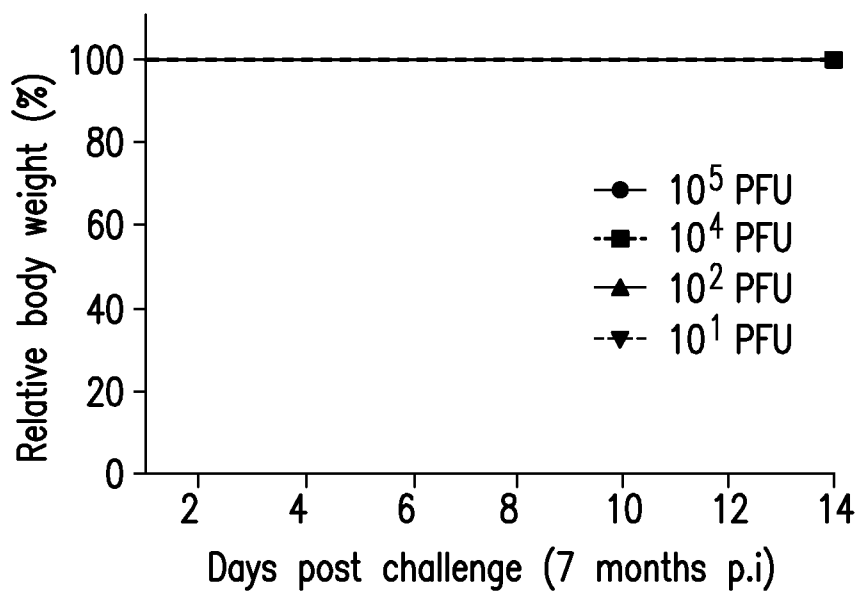


FIG. 8B

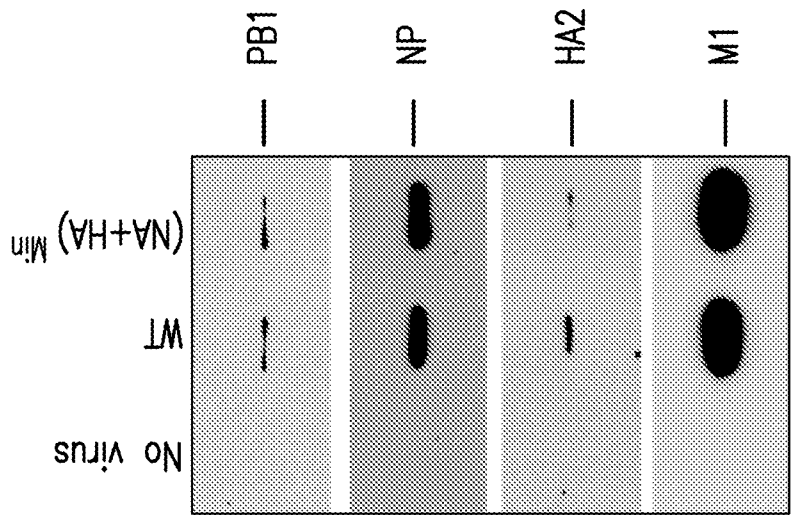


FIG. 9D

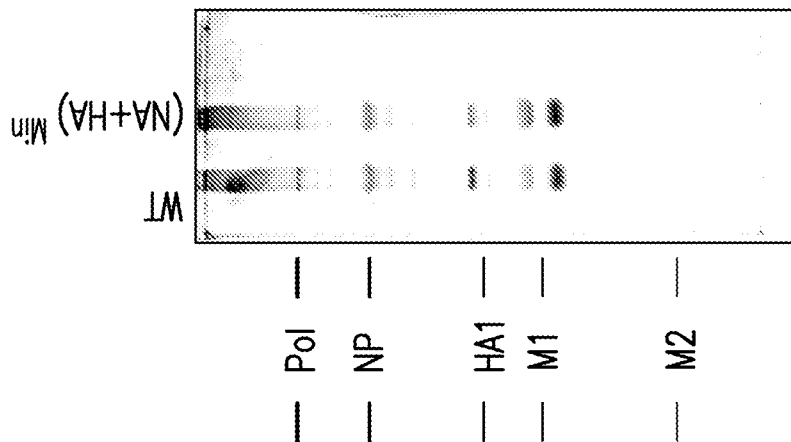


FIG. 9C

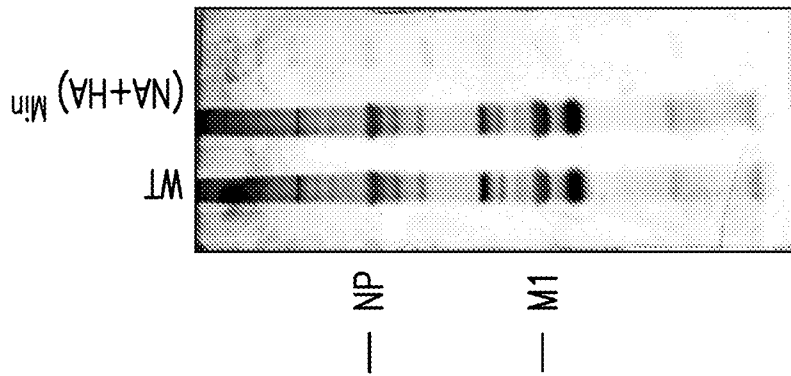


FIG. 9B

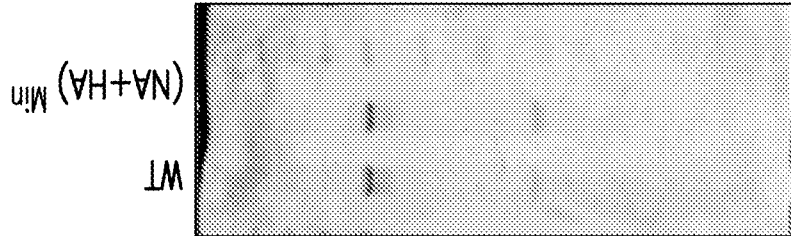


FIG. 9A

14/29

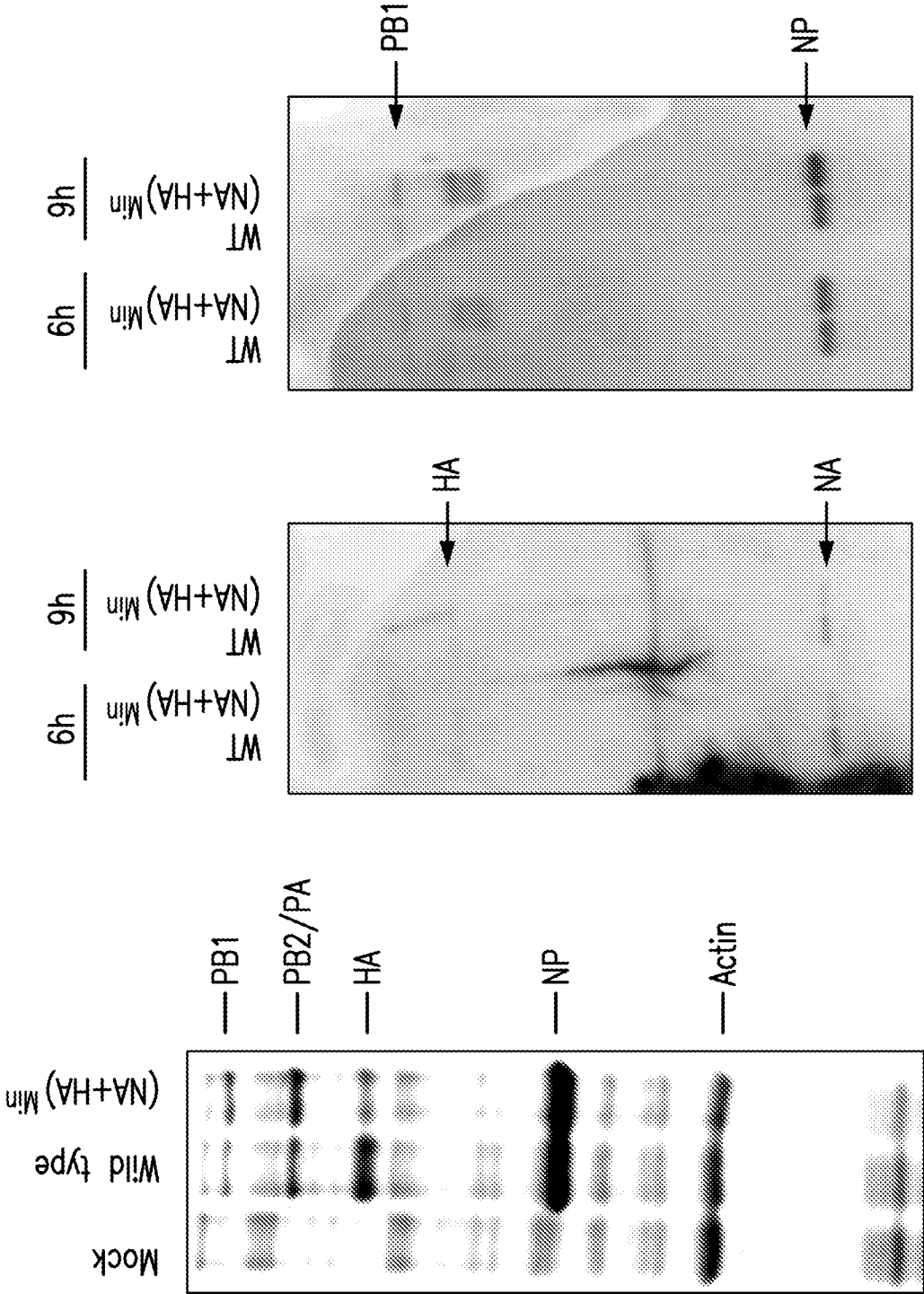


FIG. 10B

FIG. 10A

15/29

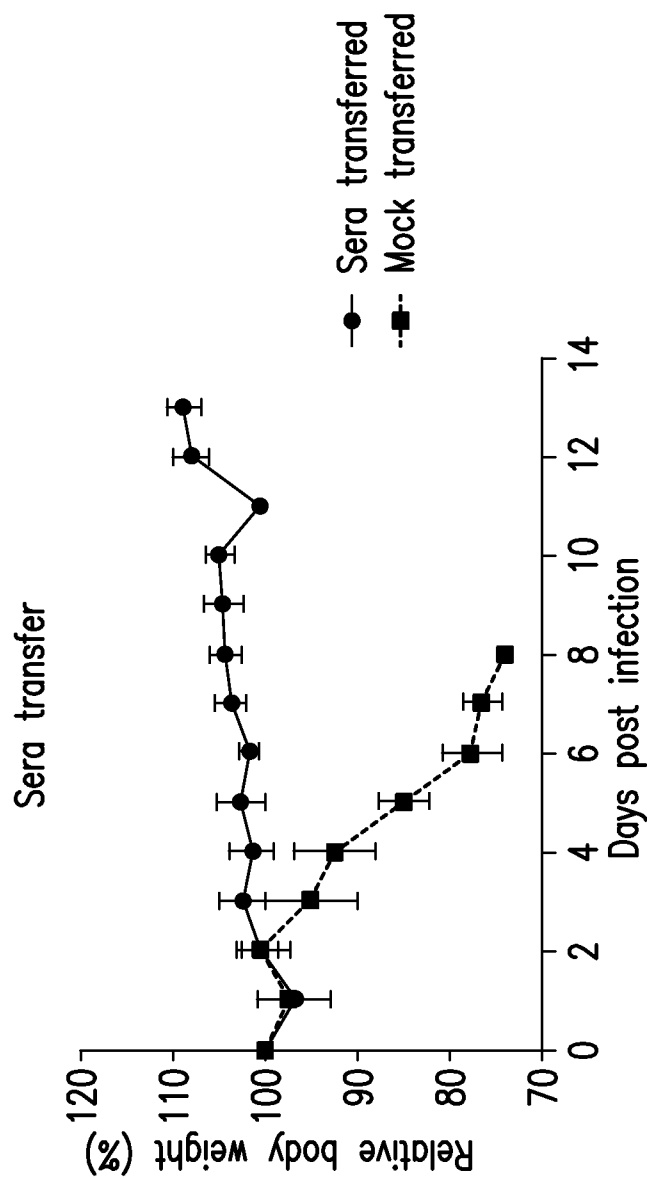


FIG. 11

16/29

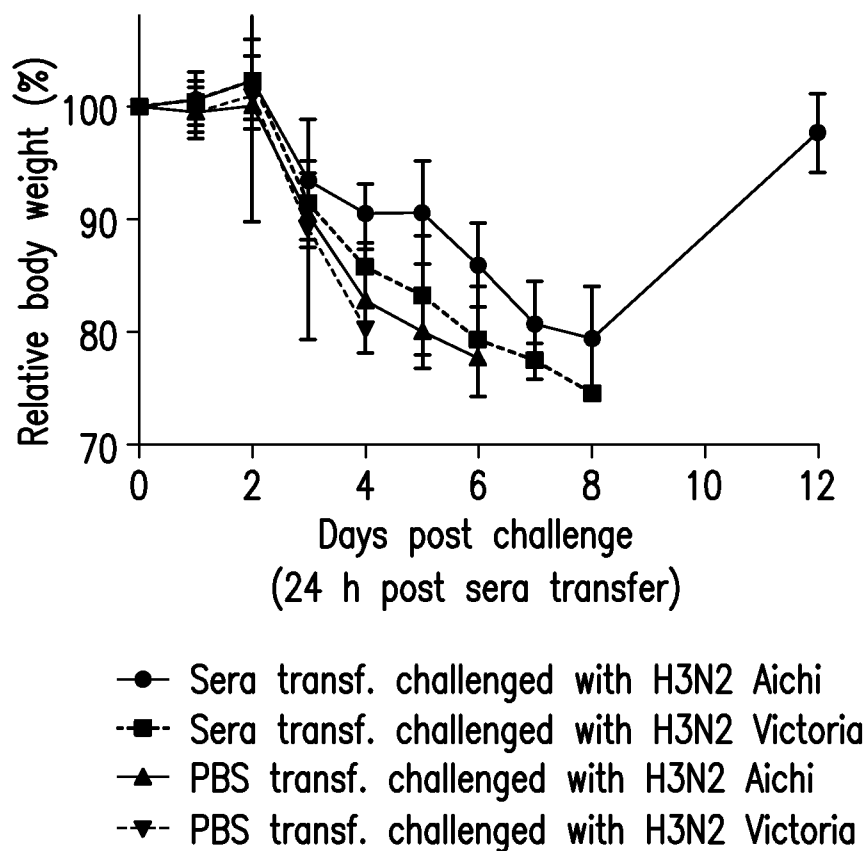


FIG. 12A

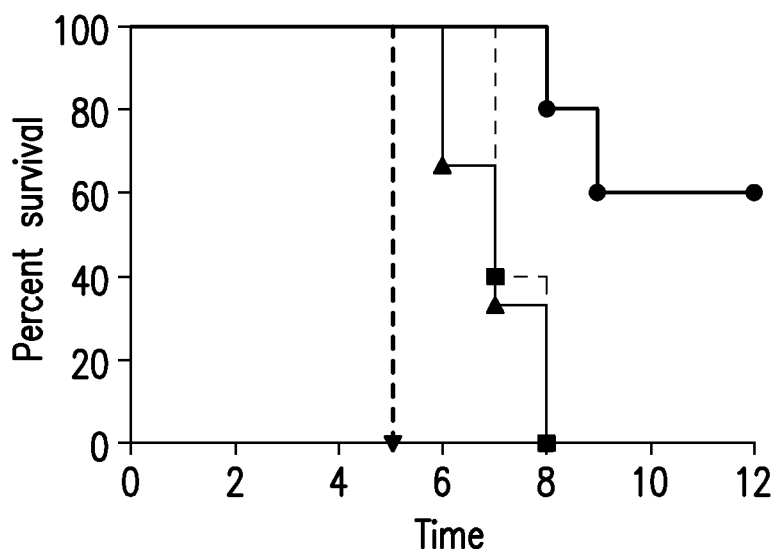
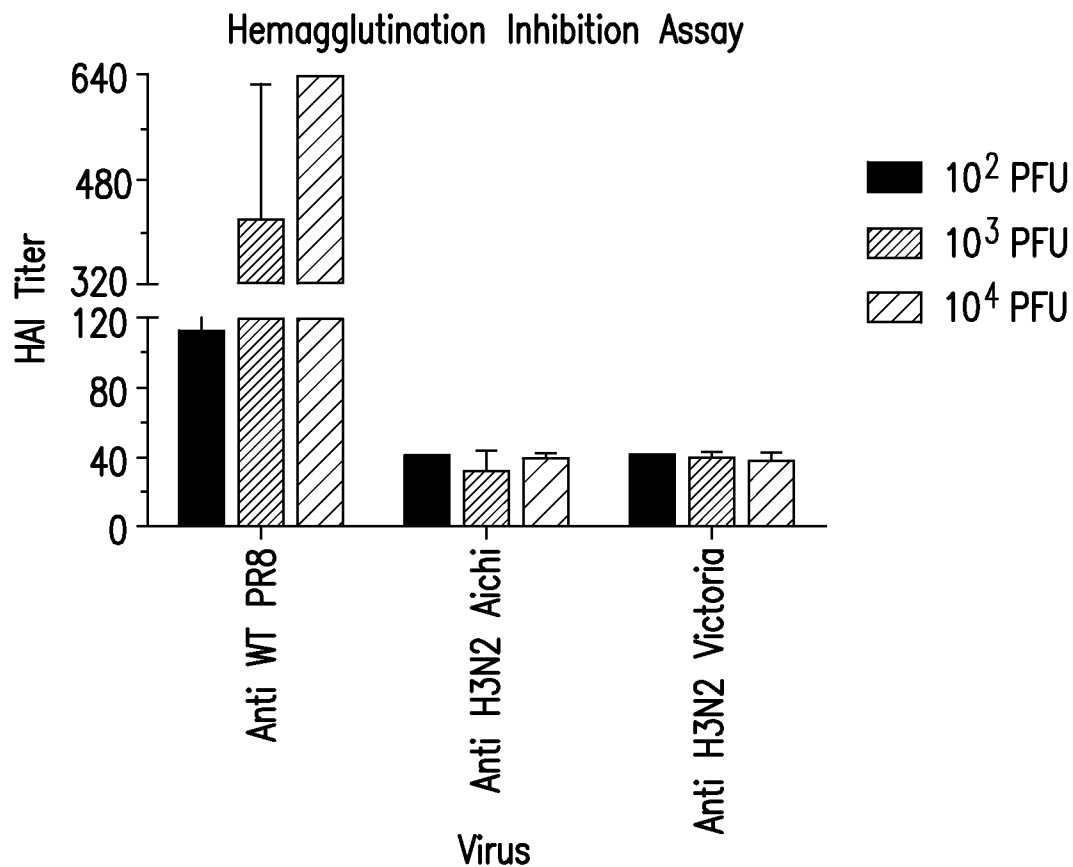
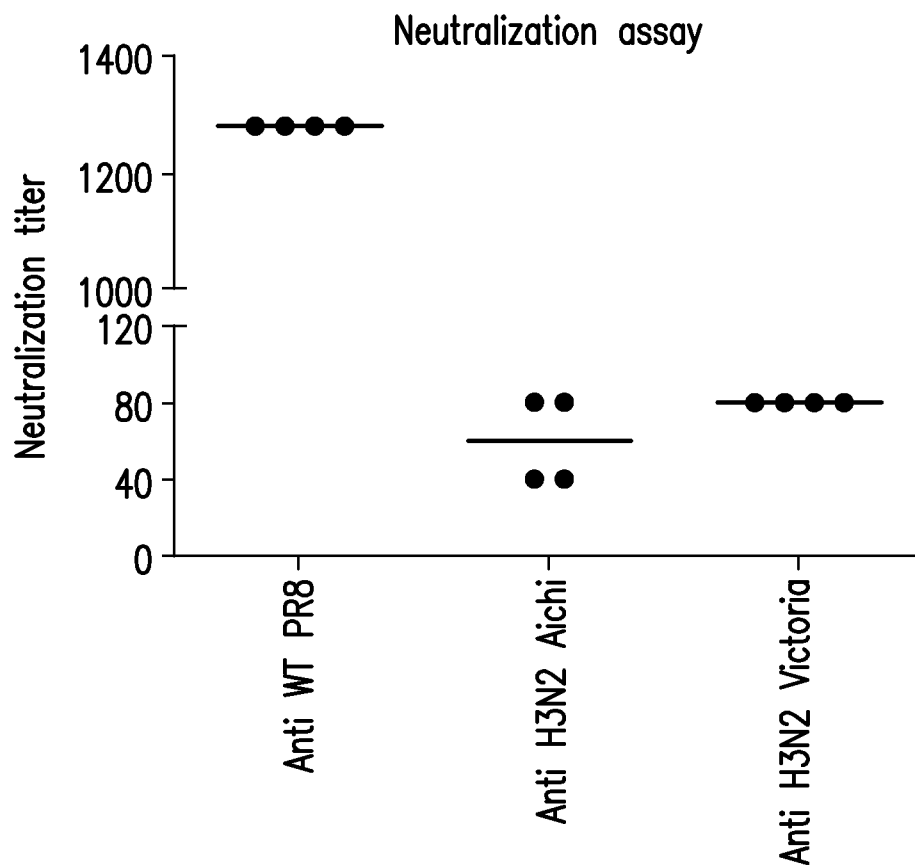


FIG. 12B

17/29

**FIG. 13A****FIG. 13B**

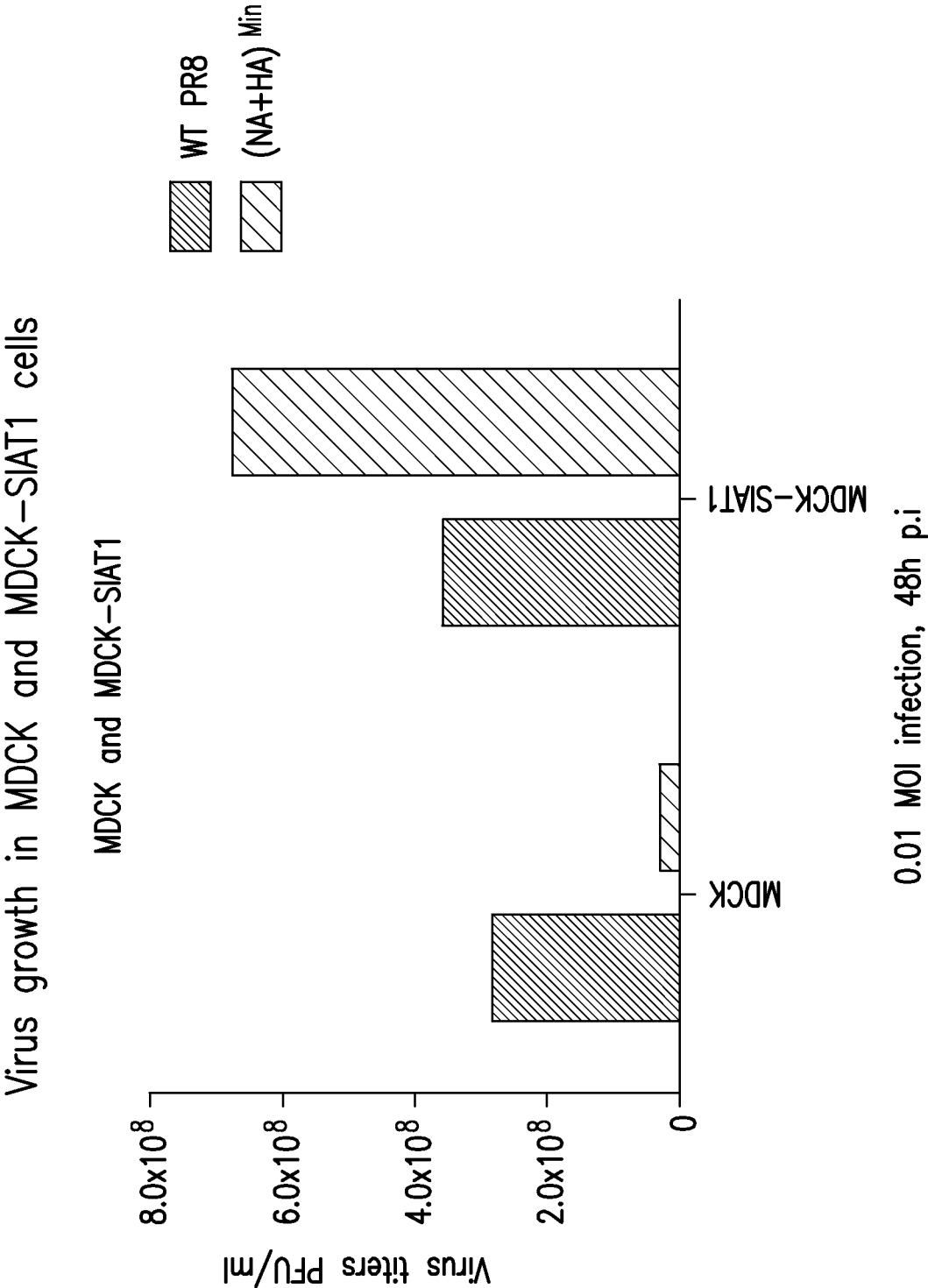


FIG. 14

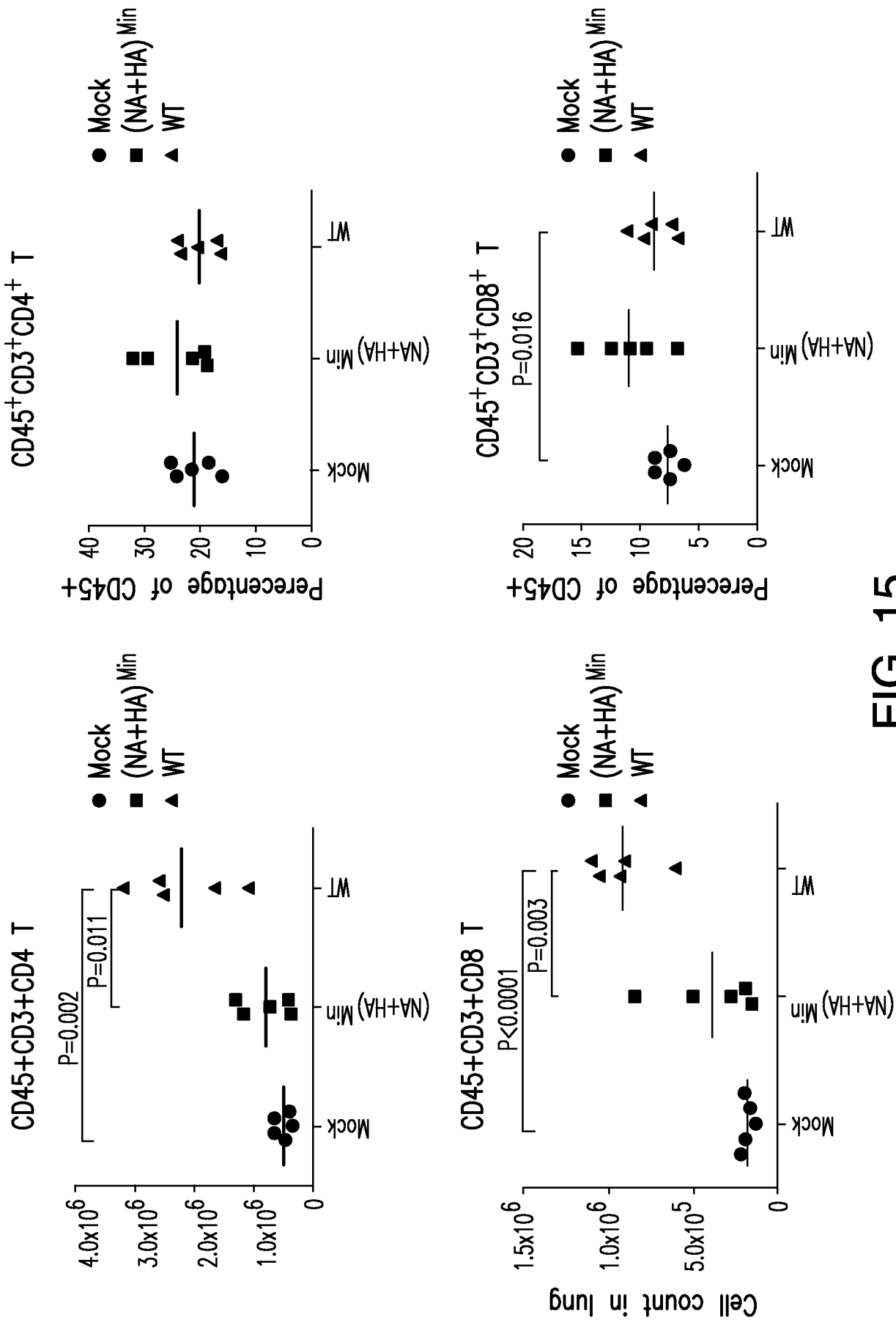


FIG. 15

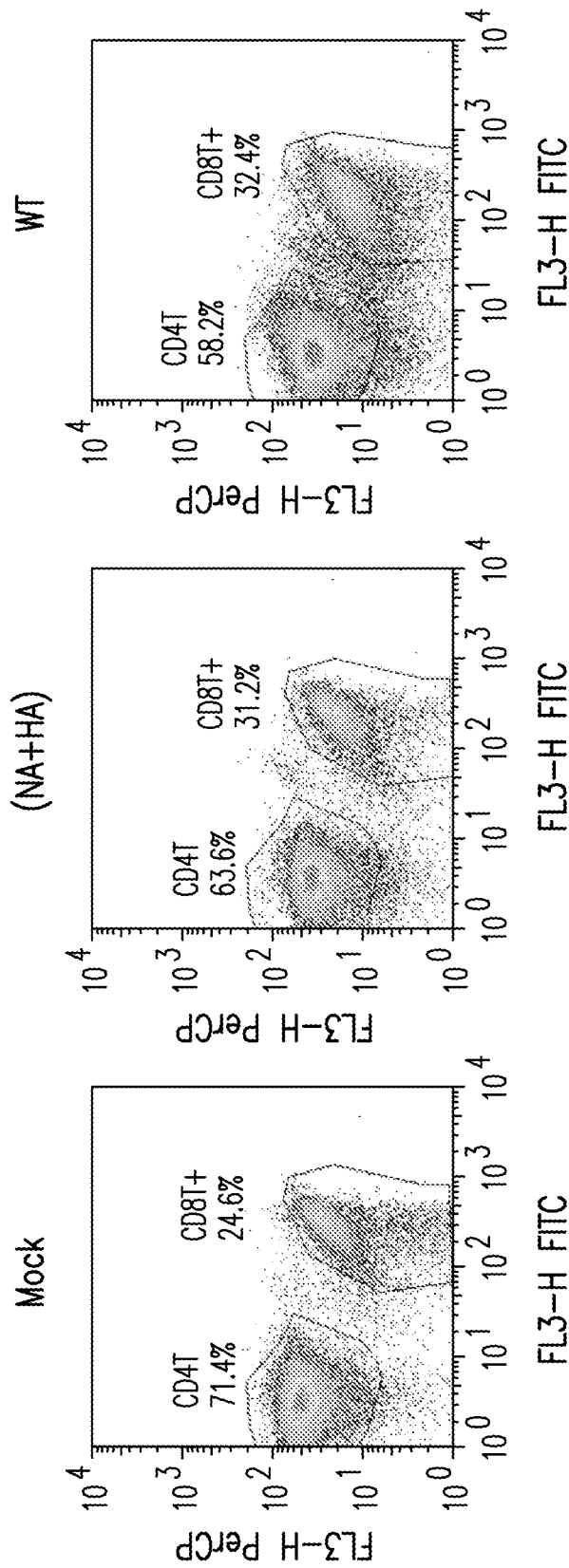


FIG. 15 CONTINUED

21/29

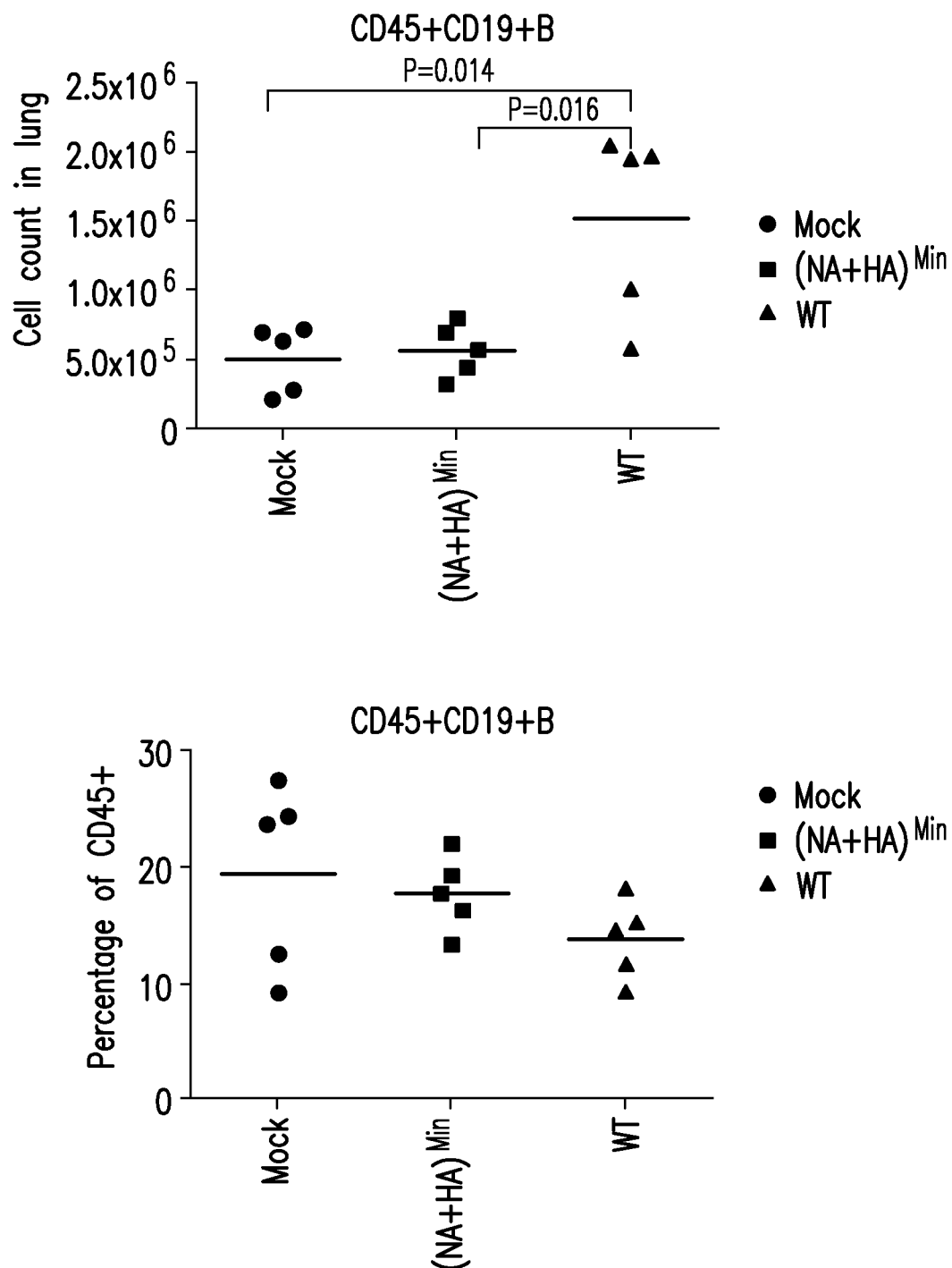


FIG. 16

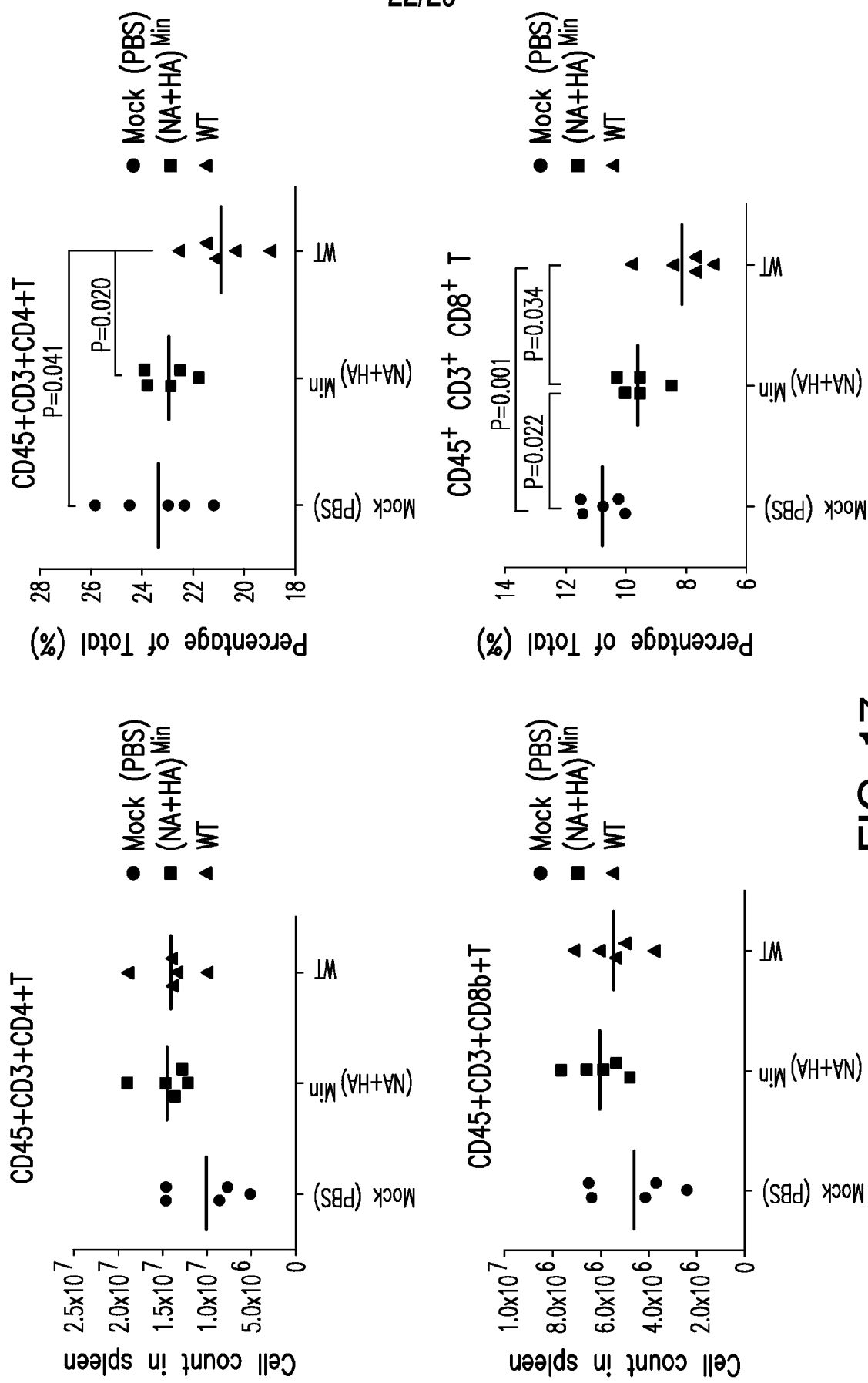


FIG. 17

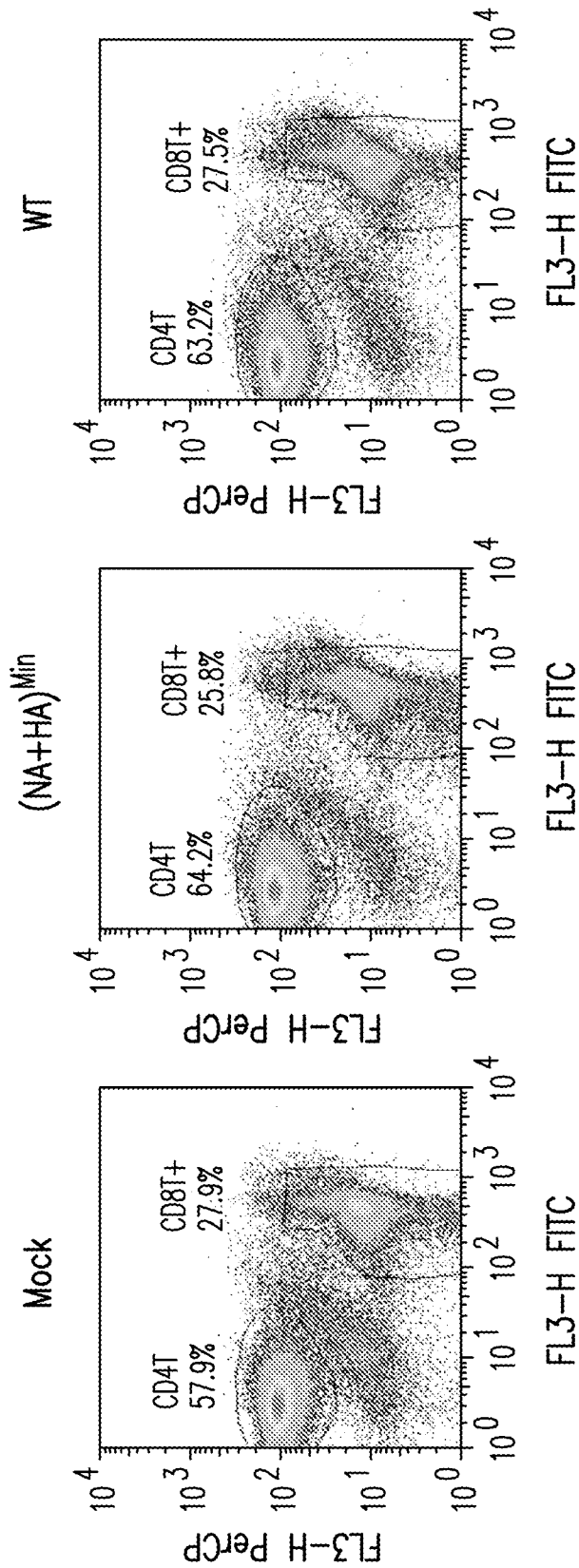


FIG. 17 CONTINUED

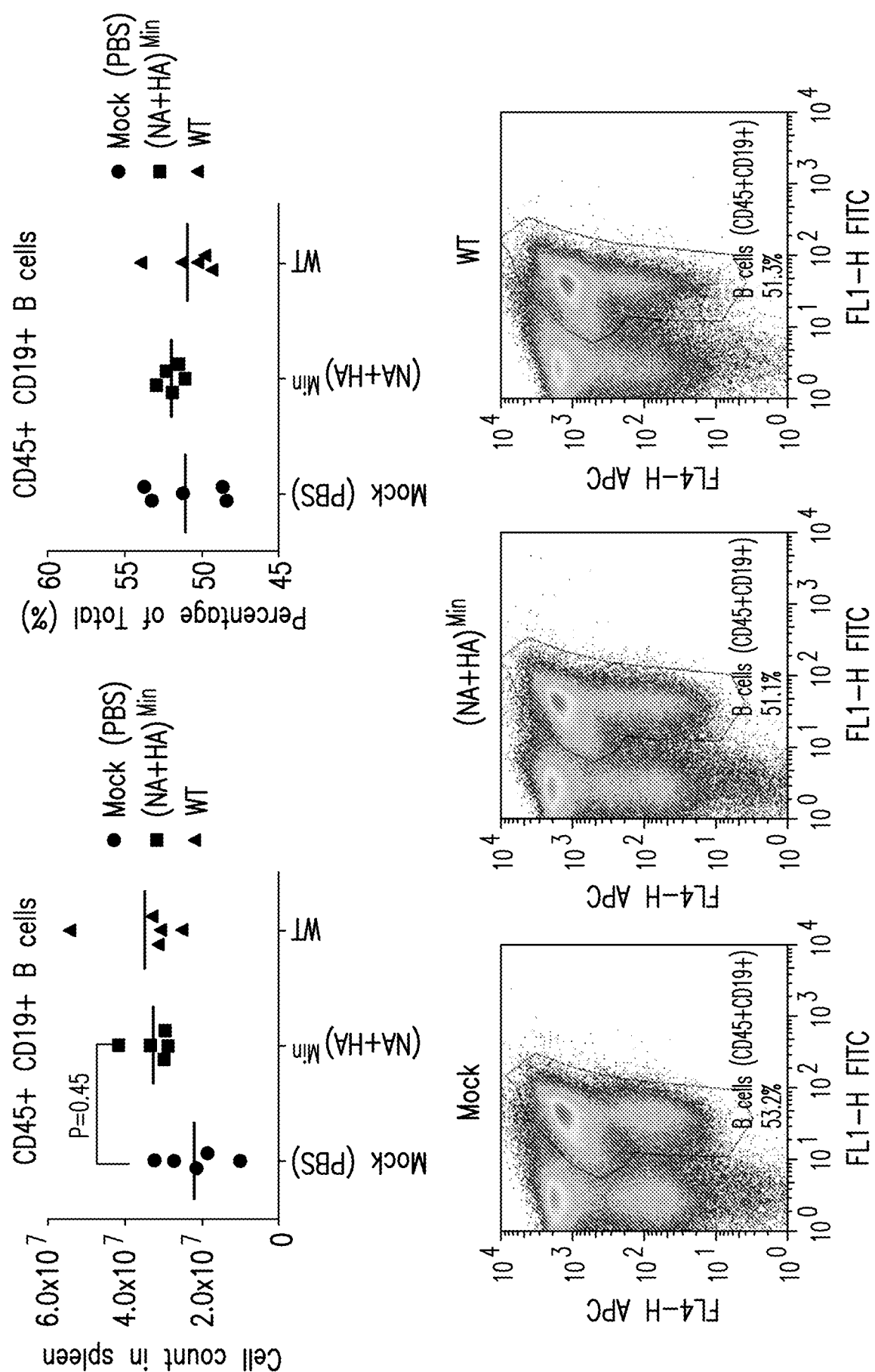


FIG. 18

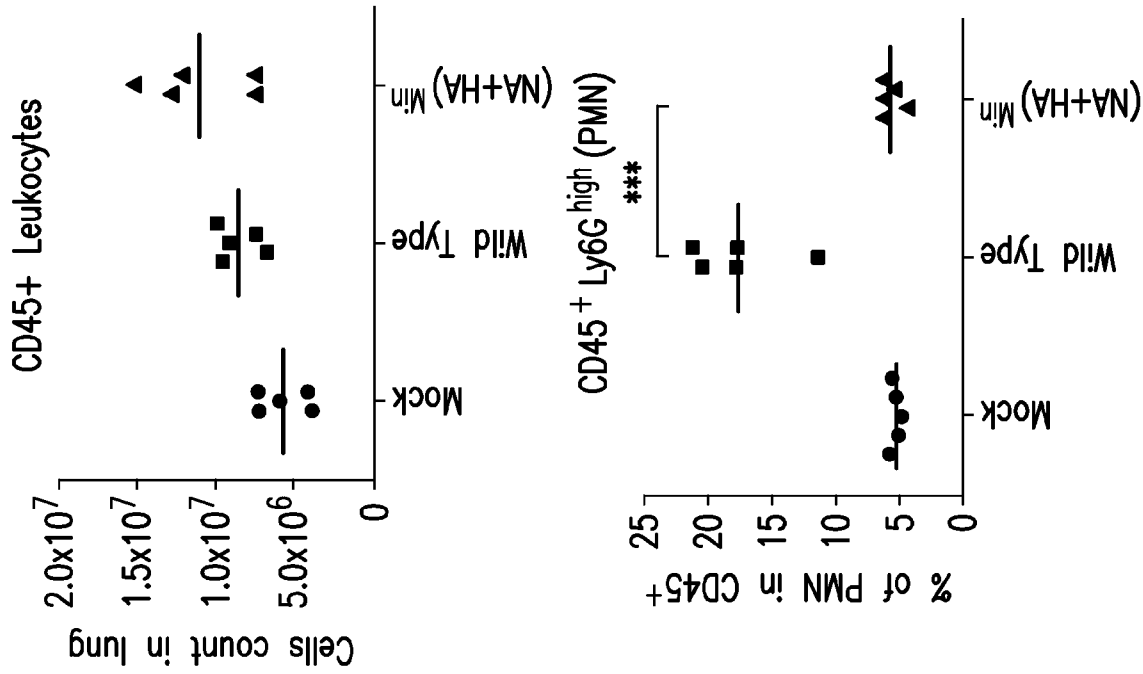


FIG. 19A

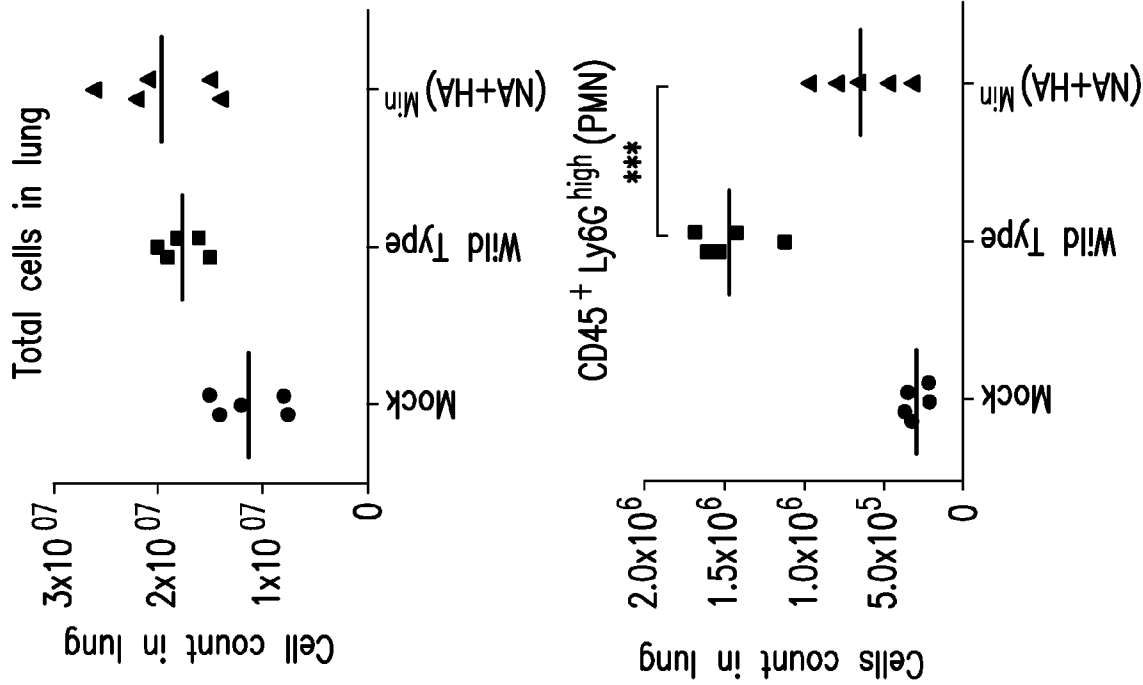


FIG. 19B

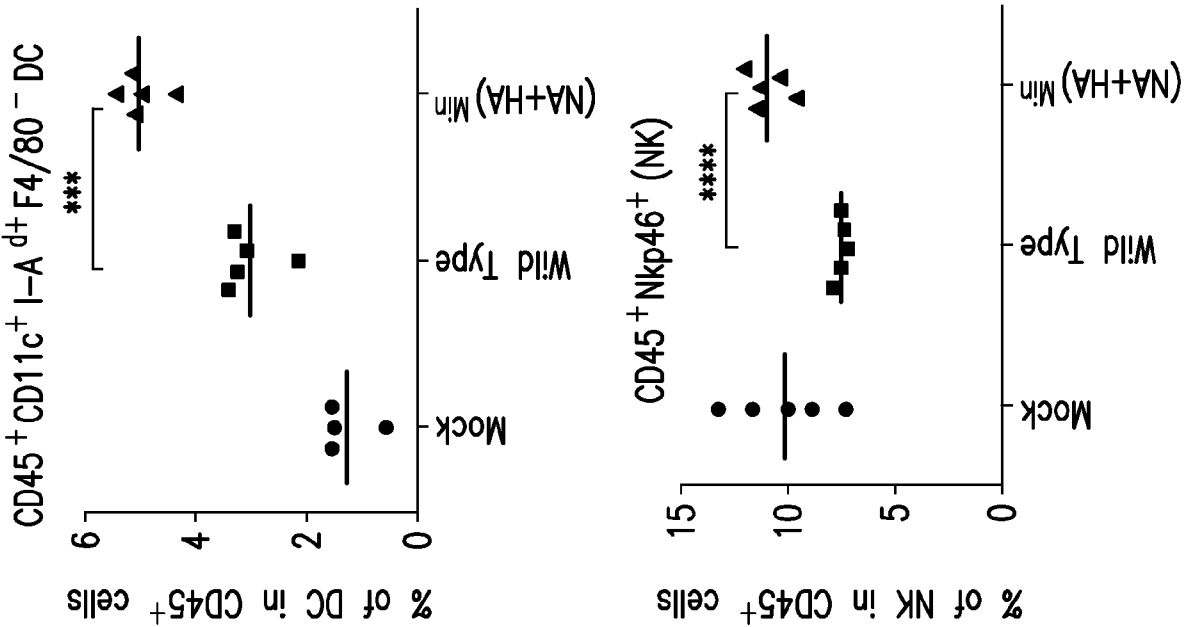


FIG. 19C

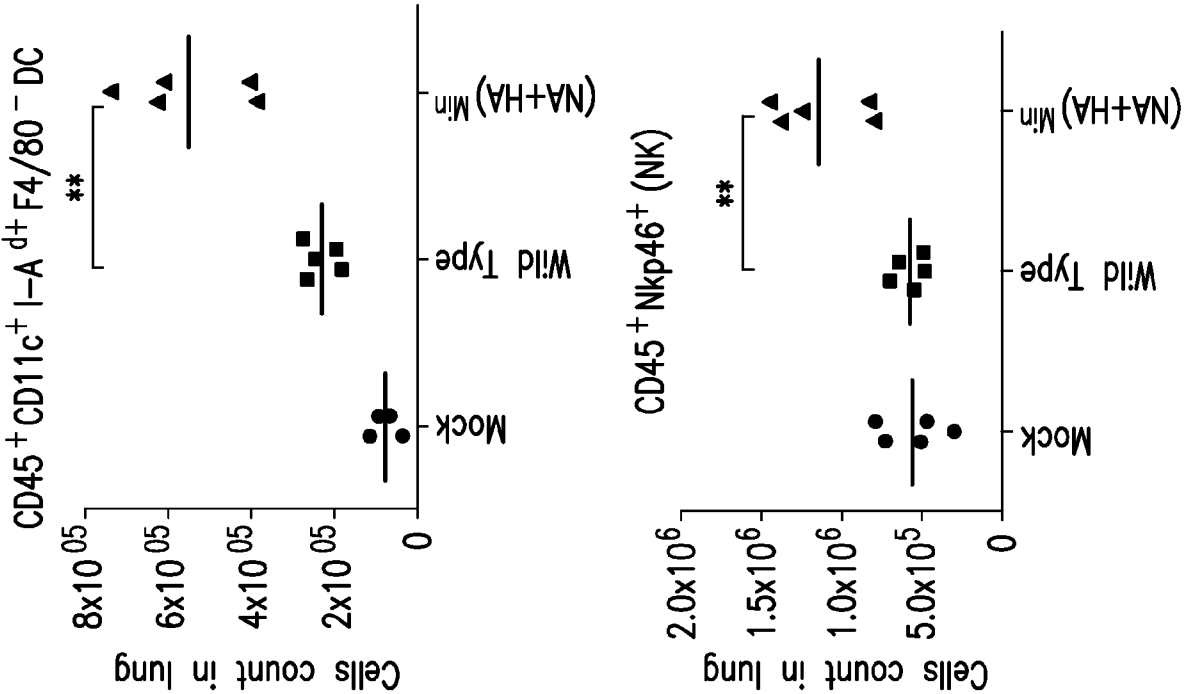


FIG. 19D

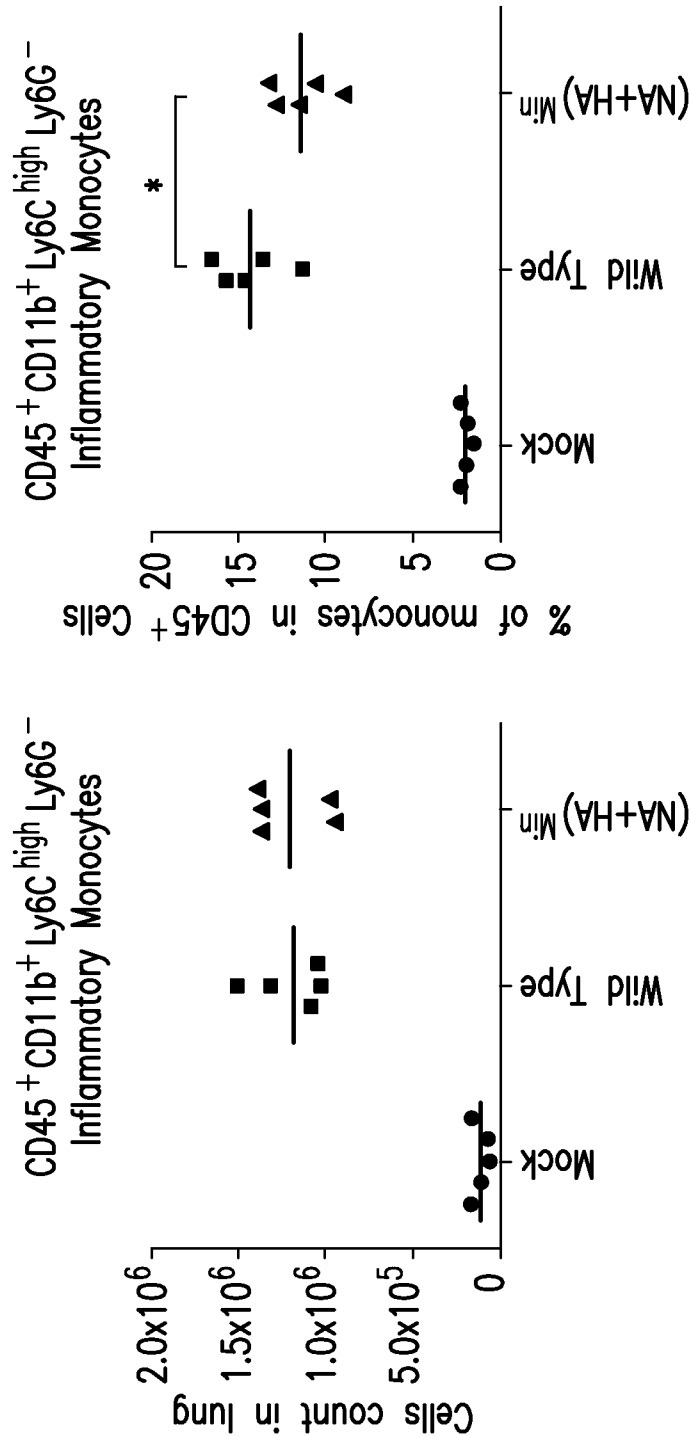


FIG. 19E

28/29

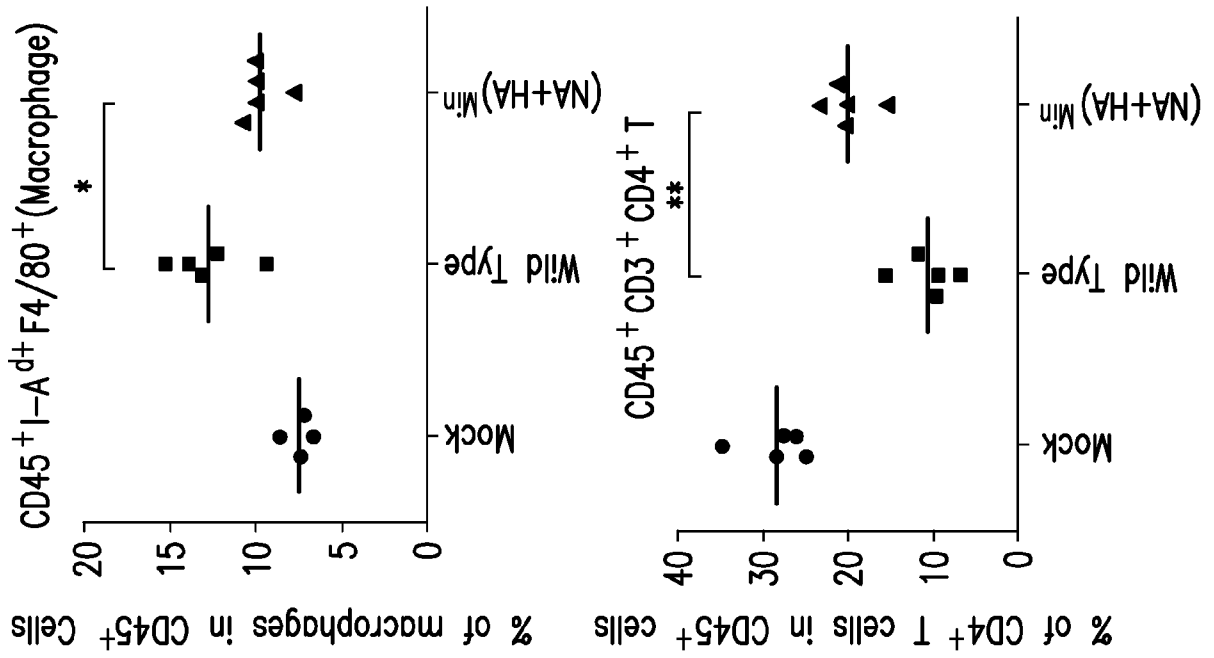


FIG. 19F

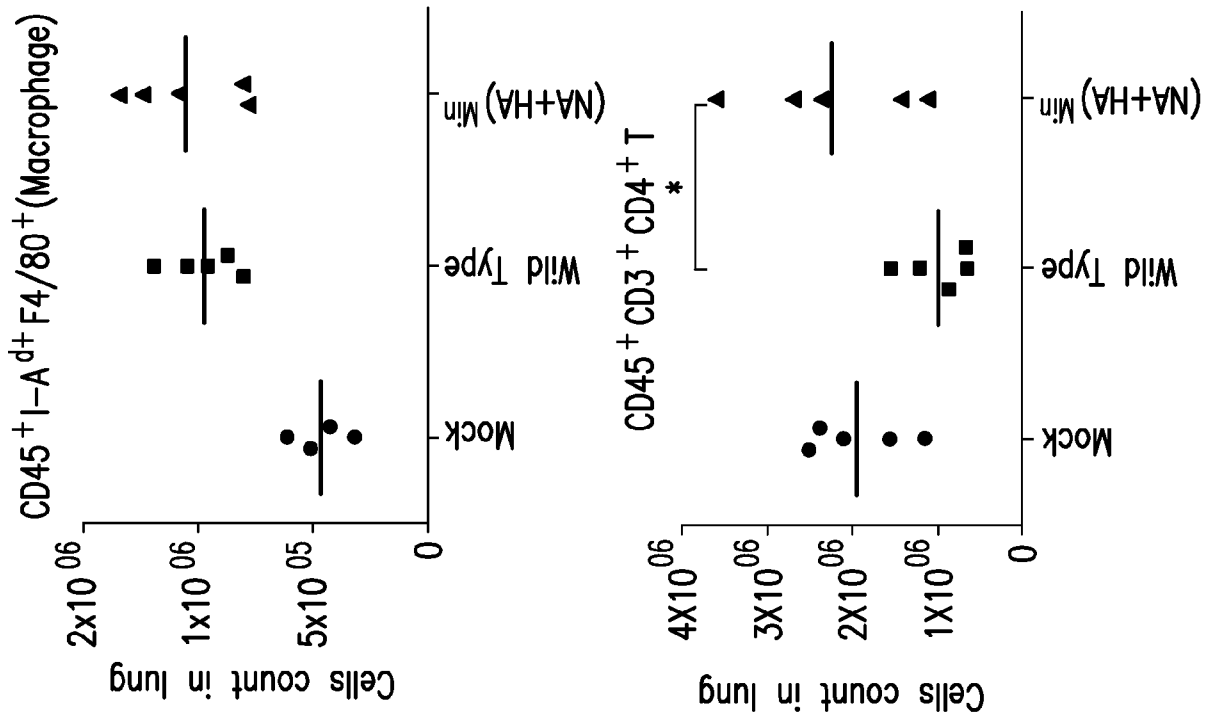


FIG. 19G

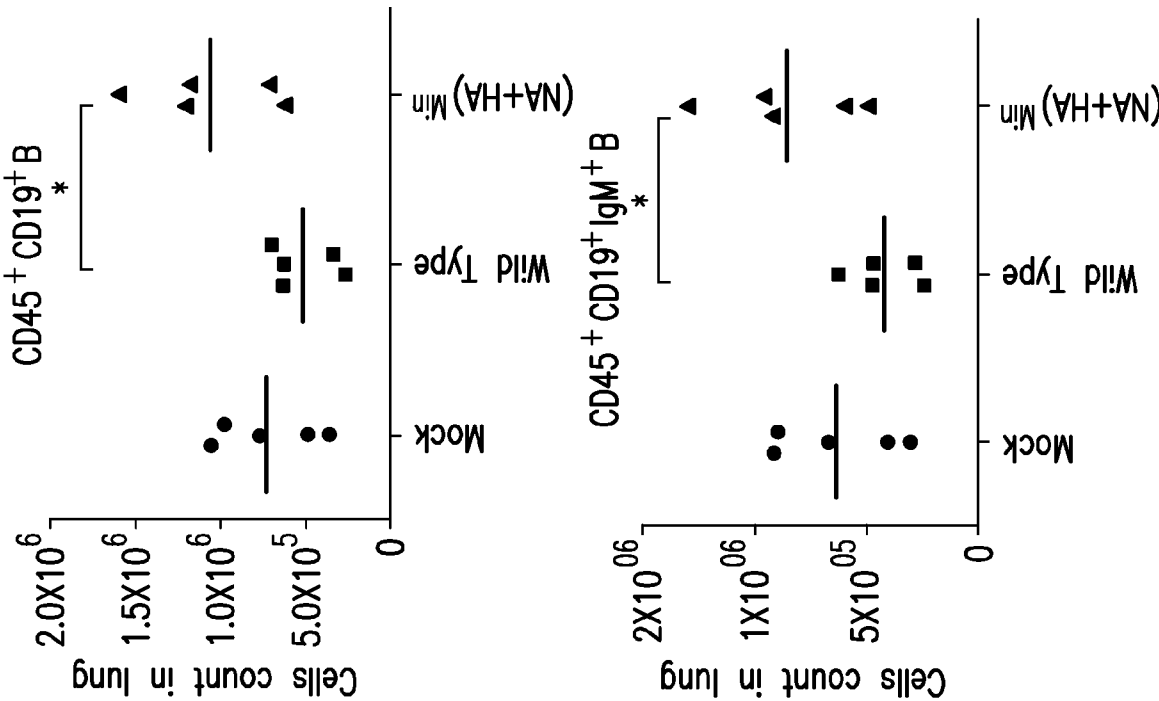
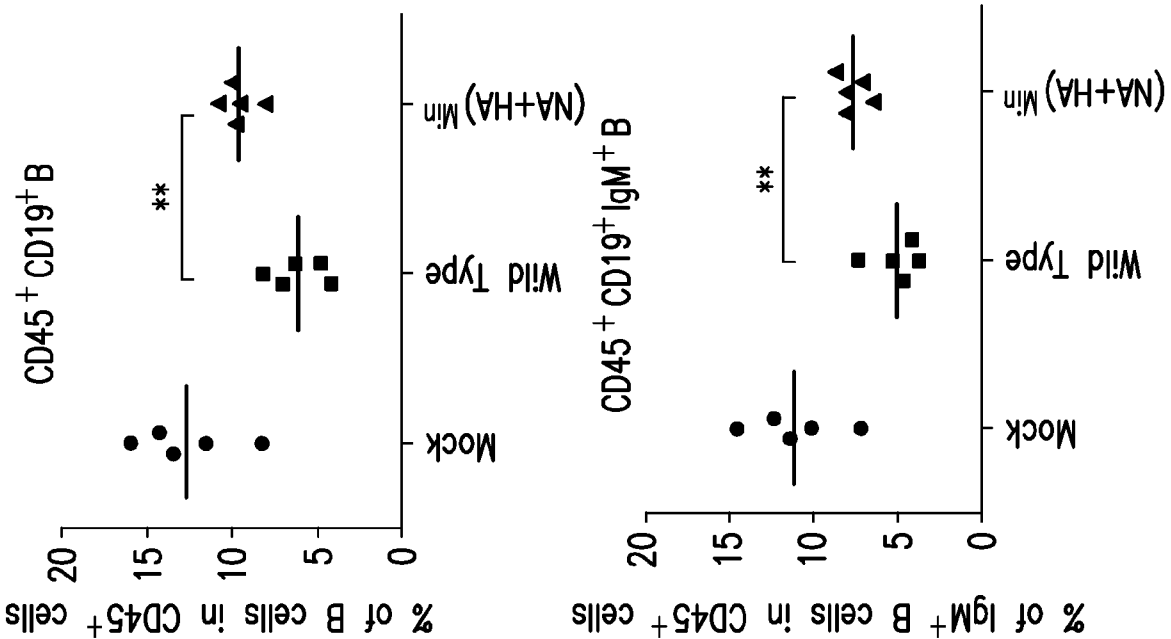


FIG. 19H

FIG. 19I

INTERNATIONAL SEARCH REPORT

PCT/US2014/030027 08-08-2014

International application No.

PCT/US 14/30027

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61P 31/16, C12N 7/04 (2014.01)

USPC - 424/206.1, 435/236

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61P 31/16, C12N 7/04 (2014.01)

USPC - 424/206.1, 435/236

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC - 424/205.1

(keyword limited; terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, PubWEST (USPT, PGPB, EPAB, JPAB), Google Scholar

Search terms: influenza, attenuated, vaccine, hemagglutinin, neuraminidase, codon, codon pair, codon pair bias, codon pair score, expression, reduced, lower, cross-protect

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2012/0269849 A1 (WIMMER et al.) 25 October 2012 (25.10.2012) para [0011], [0013], [0017], [0020], [0027], [0032], [0038]-[0054], [0057]-[0058], [0072], [0075], [0083]-[0084], [0093], [0100], claims 20-21	1-9, 11 ----- 10
Y	TAMURA et al., Mechanisms of broad cross-protection provided by influenza virus infection and their application to vaccines. Jpn J Infect Dis. August 2005, Vol 58, No 4, pp 195-207. Especially abstract	10
X, P	YANG et al., Deliberate reduction of hemagglutinin and neuraminidase expression of influenza virus leads to an ultraproductive live vaccine in mice. Proc Natl Acad Sci U S A. 04 June 2013, Vol 110, No 23, pp 9481-6. Entire document	1-11

☐

Further documents are listed in the continuation of Box C.

☐

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation, or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

11 July 2014 (11.07.2014)

Date of mailing of the international search report

08 AUG 2014

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774