

Interpretation of mutations (FluSurver)

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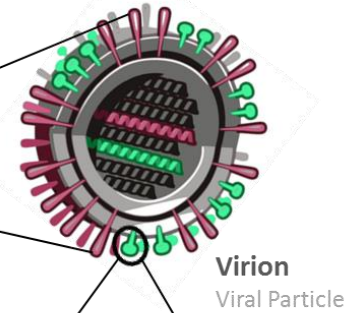
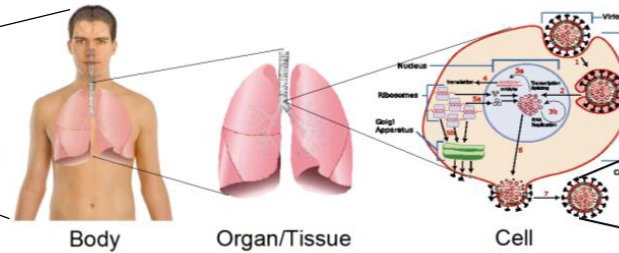
DTG
GISAID

Outline

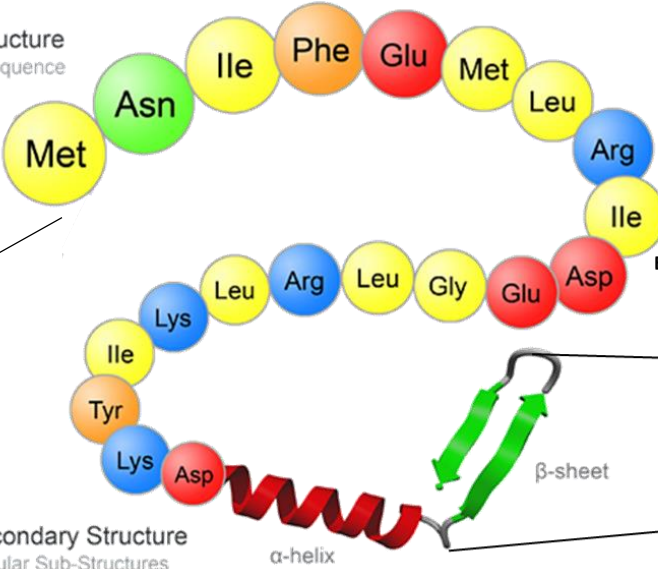
- I. Intro
- II. Tutorial for using FluSurver in EpiFlu
- III. Quick Reference for Browsing FluSurver Results
- IV. Example Findings with FluSurver
- V. Full Reference for Browsing FluSurver Results

From the **sequence** and **structure** we can partially deduce important **properties** of the virus

- Infect different hosts
- Spread more easily
- More or less severe
- Antigenic drift, drug resistance



Primary Structure
Amino Acid Sequence

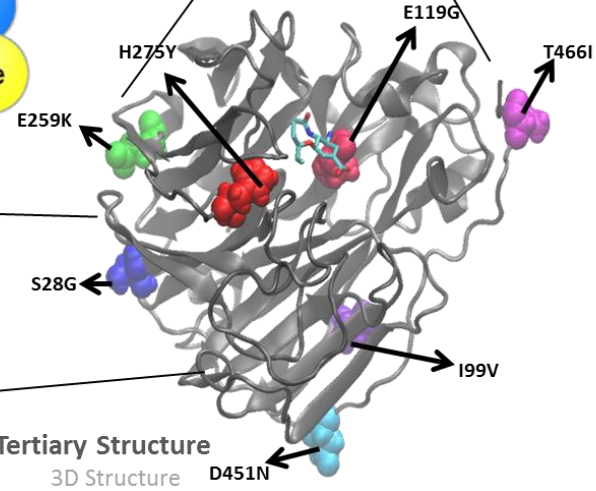
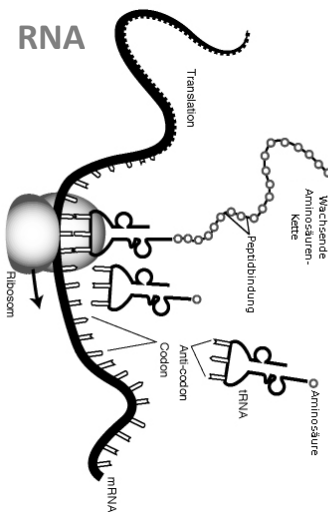


Secondary Structure
Regular Sub-Structures

α -helix

Protein Tertiary Structure
3D Structure

D451N

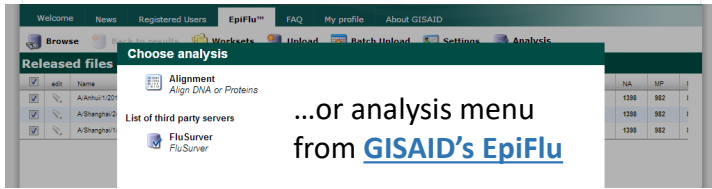


Simply paste/upload your sequence(s):

Paste your protein or nucleotide FASTA sequence(s) into the text area below. (Sample FASTA sequences: 2009 H1N1 NA and HA)

```
>HA_H1N1_Human_2009_Norway3206-3_gi269978854|gb|ACZ56080.1|hemagglutinin|Influenza A virus (A/Norway/3206-3/2009(H1N1))
MKAKLVLYLTFATANADTLGIGVHANNSTDTDTVLEKRVIVYTHSLLLEDKHKNGKCLKLRGVAPLHLGKONIAIGWLNQPECELSLTAASSWVIVE
TSSSDNGSTVRFVDFVDEEELVSRVSTFDFRPFKTSVSRHPLVLAACVSAQVAKSFKVWLVKLVKQVQKSKVYINDGKVELVWGS
IHHFSTSDAIVRFRVDFVDEEELVSRVSTFDFRPFKTSVSRHPLVLAACVSAQVAKSFKVWLVKLVKQVQKSKVYINDGKVELVWGS
EGSGVYAADLKTQNA
IDETIKVNSTENIITQVFAVSEKFRICARREKRVKDDGFLDWTYTRAEVLLLEERTLDVHDSNRVLYEKVRSQDNNNAKEINGNCFEYFH
KDDNTOMESVKNQITVDPKYSEAKUNREEDGKLESTRYQILVYQVSTVASSLVVYKLGAGFVWCSNGSLQDRCV
```

<http://flusurver.bii.a-star.edu.sg>



...or analysis menu from [GISAID's EpiFlu](http://www.gisaid.org)

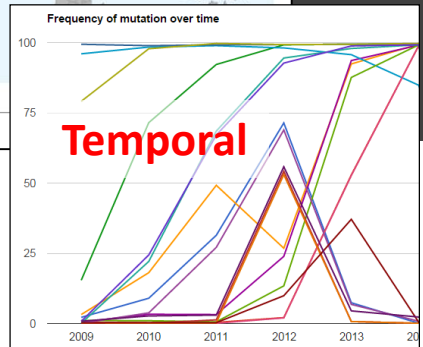
Get list of identified mutations

Result for comparison with reference selection: HA_H1N1_Human_2009_California07 [Back to Reference Selection](#)

Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
HA_H1N1_Human_2009_Norway3206-3_gi269978854 gb ACZ56080.1	HA A/California/07/2009(H1N1) find closest related sequences	99.117	<u>100.000</u>	5	P100S , P154S , S220T , D239G , I338V show in structure

Get exhaustive annotation for each mutation

The FluSurver in a nutshell



Key to alternative position numbering:

- FluSurver numbering (absolute as in 2009 H1N1 pandemic)
- Classical H3N2 strain numbering
- Classical H1N1 strain numbering

Chosen reference: HA_H1N1_Human_2009_Norway3206-3_gi269978854|gb|ACZ56080.1|

Position in reference: HA D239G

AA in reference: D

AA in query: **Alternative numberings**

Mutation HA D239G already occurred 194 times (1.37% of all samples with HA sequence) in 28 countries. The first strain with this mutation, collected in April 2009, was A/Texas/11/2009(H1N1). The mutation most recently occurred in strain A/New York/06/2014(H1N1), collected in April 2014. ([see map](#))

[See detailed global statistics for this position](#)

A mutation at the position equivalent to HA 239 has been reported in the literature to be related to [host specificity shift](#).

A combination of mutations including the position equivalent to HA 239 has been reported in the literature to be related to [host specificity shift](#).

As seen in resolved structures of proteins from related strains, the HA position equivalent to your mutation is involved in:

- [host cell receptor binding](#)
- [viral oligomerization interfaces](#)
- [binding small ligands](#)
- [antibody recognition sites](#)

[See all interactions for this position](#)

[PubMed search for this mutation \(including alternative numbering\)](#)

Reference: HA_H1N1_Human_2009_California07 (Structure Model Details)

Patient/Sample: HA_H1N1_Human_2009_Norway3206-3_gi269978854|gb|ACZ56080.1|

Mutation(s): I338V, S220T, P100S, P154S, D239G

Wildtype residue only displayed if position is part of available structure.

Hover with mouse over residue to see its position number. Right-click for more options.

Structure models

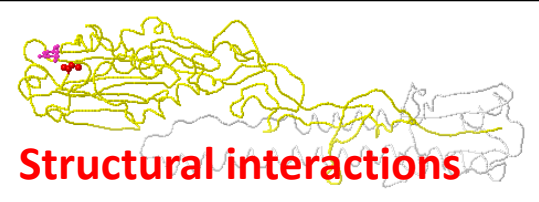
Known effect(s) of mutations at position equivalent to your mutation:

Protein: HA
Influenza type: Avian, Human H1N1 (2009)

Mutation (as in paper): D222G or D225G
neutral AA: D
neg. eff. AA: G
Effect: host specificity shift

Comment:
HA D239G is also referred to in the literature as D222G or D225G using alternative (e.g. seasonal H1/H3) numberings. It has been found to alter host cell receptor specificity from human alpha-2,6 to also include avian-like alpha-2,3 galactosyl residues in the respiratory tract. While this mutation has been found in higher proportions in severe cases, it is IMPORTANT to note that it also can occur as a minor proportion in mild cases, its effect would only be relevant for surveillance if the mutation is also found in the original clinical sample.

[Literature reference](#)
(Mutation D222G or D225G in the paper is at an equivalent position of the mutation in your query)



Effect with Literature links

Section II

TUTORIAL FOR USING FLUSURVER IN EPIFLU

First steps: find, select and add isolates to analyze from the EpiFlu™ database

The screenshot shows the GISAID EpiFlu™ interface. At the top, there is a navigation bar with links for Welcome, News, Registered Users, EpiFlu™, FAQ, My profile, and About GISAID. Below this is a secondary navigation bar with icons for Browse, Back to results, Worksets, Upload, Batch Upload, Settings, and Analysis. The main content area is titled "Released files" and contains a table with columns for Name, Isolate ID, Subtype, Host, Collection date, Passage, PB2, PB1, PA, HA, NP, NA, and MP. Three rows are visible, each with a checked checkbox in the first column. Below the table, there are navigation controls including "Total: 3 isolates" and a search box. At the bottom right, there are buttons for "Go back", "Help", "Copy to...", "Add to analysis", and "Download". A red arrow points to the "Add to analysis" button.

<input checked="" type="checkbox"/>	edit	Name	Isolate ID	Subtype	Host	Collection date	Passage	PB2	PB1	PA	HA	NP	NA	MP
<input checked="" type="checkbox"/>		A/Anhui/1/2013	EPI_ISL_138739	H7N9	Human	2013	E1	2280	2274	2151	1683	1497	1398	982
<input checked="" type="checkbox"/>		A/Shanghai/2/2013	EPI_ISL_138738	H7N9	Human	2013	E1	2280	2274	2151	1683	1497	1398	982
<input checked="" type="checkbox"/>		A/Shanghai/1/2013	EPI_ISL_138737	H7N9	Human	2013	E1	2280	2274	2151	1683	1497	1398	982

After selecting strains on the left, click add to analysis

1

The screenshot shows the "Choose analysis" dialog box. It has a title bar "Choose analysis" and a list of options. The first option is "Alignment" with the subtext "Align DNA or Proteins". Below this is a section titled "List of third party servers" which includes "FluSurver" with the subtext "FluSurver". A red arrow points to the "FluSurver" option. The background shows the same table of released files as the previous screenshot.

Choose analysis

- Alignment**
Align DNA or Proteins
- List of third party servers**
 - FluSurver**
FluSurver

2

Select "FluSurver"

Next steps: Select proteins to analyze [1], e.g. HA, then click on continue [2], wait for submission form to load and then click “Analyze with FluSurver” [3].

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FluSurver

Filter Align DNA (NC) Align Proteins (AA)

all NP P3 HA M1 M2 BM2 CM2 M NA NB NS1 NEP NS2 PA PB1-F2 PB1 HE PB2

<input type="checkbox"/>	Sequence name	EPI/WSS-Nr	Isolate name	NCBI-Id	Length
<input checked="" type="checkbox"/>	A/Anhui/1/2013 (HA)	EPI439507	A/Anhui/1/2013		1883 (compl)
<input checked="" type="checkbox"/>	A/Shanghai/1/2013 (HA)	EPI439488	A/Shanghai/1/2013		1883 (compl)
<input checked="" type="checkbox"/>	A/Shanghai/2/2013 (HA)	EPI439502	A/Shanghai/2/2013		1883 (compl)

Go back

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Important usage notes:
The main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidate mutations for further research and should ideally be combined with experimental testing and verification of any predicted phenotypes. Importantly, any direct diagnostic use, assumed severity or recommendation on patient treatment should not be based solely on these computational predictions. Our curated reference sequences used for annotation transfer of equivalent mutations are mainly comprised of strains that recently infected humans. Therefore, the **usage scenario that will give the most fruitful and reliable results are current surveillance sequences with very close relation to used vaccine strains, including some candidates for avian flu and novel reassortant swine flu H3N2v.**

Please take a look at the [Frequently Asked Questions](#) and [Tutorial](#) if you are new to FluSurver.

Loaded protein sequences of your selected isolates for FluSurver analysis:

```
>HA_A/Shanghai/2/2013_138738
MNTQILVFALIAIIPFNADKICLGHAVSNGTKVNTLTERGEVVEVNATETVERTNIPRCSKGRKRTVDLGGCGLLGTITGPPQCDQFLEFSADLIIERREGSDVCYFGKRVNE
EALRQILRESGGIDKEAMGFTYSIGIRTINGATSACRRSGSSFYAEMKWLSSNTDAAFFQMTKSYKNTKRSFALIVGIIHHSVSTAEQTKLYGSGNKLVTVGSNNYQQSFVPSF
GARFQVNLGSGRIDFHWMLNPNNDIVTFSGNFIAPDRASFLRQKSMGIQSGVQVDANCEGDCYHSGGTIIISNLPFQNIIDSRVAVKCPRIYVQKRSLLLATGMKNVPEIFPKGR
GLFGAIAAGFIENGWGLIDGWYFRHQNAQEGTAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEFNEVEKQIGNVINWTRDSITEVWSYNAELLVAMENQHTIDLADS
EMDKLYERVKRQLRENAEEDGTGCFEIFHRKDDDCMASIRNNTYDHSKYREEMQNRQIQIDPVLKSSGVKDVILWFSFGASCIFLLAIVMGLVFCVKNGNMNRCTICI
>HA_A/Anhui/1/2013_138739
MNTQILVFALIAIIPFNADKICLGHAVSNGTKVNTLTERGEVVEVNATETVERTNIPRCSKGRKRTVDLGGCGLLGTITGPPQCDQFLEFSADLIIERREGSDVCYFGKRVNE
EALRQILRESGGIDKEAMGFTYSIGIRTINGATSACRRSGSSFYAEMKWLSSNTDAAFFQMTKSYKNTKRSFALIVGIIHHSVSTAEQTKLYGSGNKLVTVGSNNYQQSFVPSF
GARFQVNLGSGRIDFHWMLNPNNDIVTFSGNFIAPDRASFLRQKSMGIQSGVQVDANCEGDCYHSGGTIIISNLPFQNIIDSRVAVKCPRIYVQKRSLLLATGMKNVPEIFPKGR
```


Please select the reference strain(s) to compare to:
Automatic detection of closest reference (larger selection of strains, not always full genomes, NOT SUITED to judge reassortment) ▼

Analyze with FluSurver

FluSurver

Note: unless one wants to compare to a specific selected reference strain, the drop-down option can be left at default which is an automatic detection of the closest reference.

Warning:
In the current EpiFlu version, there can be a server time-out if too many sequences are selected, <20 sequences for analysis should work fine.


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The main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidate mutations for further research and should ideally be combined with experimental testing and verification of any predicted phenotypes. Importantly, any direct diagnostic use, assumed severity or recommendation on patient treatment should not be based solely on these computational predictions. Our curated reference sequences used for annotation transfer of equivalent mutations are mainly comprised of strains that recently infected humans. Therefore, the usage scenario that will give the most fruitful and reliable results are current surveillance sequences with very close relation to used vaccine strains, including some candidates for avian flu and novel reassortant swine flu H3N2v. Please take a look at the [Frequently Asked Questions](#) and [Tutorial](#) if you are new to FluSurver. There is also a [special note for using FluSurver results in publications](#).

Result for comparison with reference selection: H7N7_Human_2003_Netherlands219 [Back to Reference Selection](#)

Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
HA_A/Anhui/1/2013_138739	HA A/Netherlands/219/2003(H7N7) find closest related sequences	96.071	98.418	22	V18I , S20I , V63I , T137A , T150A , D190S , I195V , G202V , T205A , I218V , Q242L , I252M , E286G , N314D , E328R , R347G , T419N , R423K , M436I , N464D , I515M , A550V show in structure
HA_A/Shanghai/1/2013_138737	HA A/Netherlands/219/2003(H7N7) find closest related sequences	96.071	98.418	22	V18I , S20I , V63I , T137A , T150A , A153S , D190N , I195V , T205A , I218V , P237T , I252M , E286G , N292D , H299Y , N314D , E328R , R347G , R423K , M436I , N464D , I515M show in structure
HA_A/Shanghai/2/2013_138738	HA A/Netherlands/219/2003(H7N7) find closest related sequences	96.071	98.418	22	V18I , S20I , V63I , T137A , T150A , D190S , I195V , G202V , T205A , I218V , Q242L , I252M , E286G , N314D , E328R , R347G , T419N , R423K , M436I , N464D , I515M , A550V show in structure

[Right-click here to save/download mutation report table for archiving or import to Excel](#)

[Back to Reference Selection](#)

For each of the query sequences, there are six columns of information generated in the result summary page. From here, users may proceed to look at the query sequence's alignment to the reference strain, get more information on each mutation, generate a structural view of all the mutations in the query sequence ("show in structure") or view a summary of the mutations in a table to download (at end of results).

More details on browsing the results further can be found online at:
<http://flusurver.bii.a-star.edu.sg/help/tutorialpage.html#part2>

Section III

QUICK REFERENCE FOR BROWSING FLUSURVER RESULTS

Mutation identification in sequence and 3D structure

The main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidate mutations for further research and should ideally be combined with experimental testing and verification of any predicted phenotypes. Importantly, any direct diagnostic use, assumed severity or recommendation on patient treatment should not be based solely on these computational predictions. Our curated reference sequences used for annotation transfer of equivalent mutations are mainly comprised of strains that recently infected humans. Therefore, the usage scenario that will give the most fruitful and reliable results are current surveillance sequences with very close relation to used vaccine strains, including some candidates for avian flu and novel reassortant swine flu H3N2v. Please take a look at the [Frequently Asked Questions](#) and [Tutorial](#) if you are new to FluSurver. There is also a [special note for using FluSurver results in publications](#).



Result for comparison with reference selection: auto [Back to Reference Selection](#)

Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
A/Maryland/06/2016 EPI_ISL_221290 2016-05-17 A/H1N1	NA A/California/07/2009(H1N1) find closest related sequences	96.375	100.000	17	V13I I34V L40I N44S T48A V53I N200S V241I N248D V264I N270K H275Y I314M I321V N369K N386K K432E show in structure NA drug sensitivity positions: 33, 0, 1 Reduced sensitivity or resistance!
A/New York/36/2016 EPI_ISL_221634 2016-05-20 A/H1N1	NA A/California/07/2009(H1N1) find closest related sequences	96.802	100.000	15	V13I I34V L40I N44S N200S V241I N248D V264I N270K H275Y I314M I321V N369K N386K K432E show in structure NA drug sensitivity positions: 33, 0, 1 Reduced sensitivity or resistance!
A/Pennsylvania/25/2016 EPI_ISL_221283 2016-05-17 A/H1N1	NA A/California/07/2009(H1N1) find closest related sequences	96.802	100.000	15	V13I I34V L40I N44S N200S V241I N248D V264I N270K H275Y I314M I321V N369K N386K K432E show in structure NA drug sensitivity positions: 33, 0, 1 Reduced sensitivity or resistance!
A/Washington/31/2016 EPI_ISL_221289 2016-05-17 A/H1N1	NA A/California/07/2009(H1N1) find closest related sequences	96.588	100.000	16	V13I I34V L40I N44S N200S V241I N248D V264I N270K P272L H275Y I314M I321V N369K N386K K432E show in structure NA drug sensitivity positions: 33, 0, 1 Reduced sensitivity or resistance!
A/Wyoming/16/2016 EPI_ISL_221287 2016-05-17 A/H1N1	NA A/California/07/2009(H1N1) find closest related sequences	96.802	100.000	15	V13I I34V L40I N44S N200S V241I N248D V264I N270K H275Y I314M I321V N369K N386K K432E show in structure NA drug sensitivity positions: 33, 0, 1 Reduced sensitivity or resistance!

[Right-click here to save/download mutation report table for archiving or import to Excel](#)

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https://gisaid2.ble.de/GISAID/flusurverout/tmp/tmp_NA_H1N1_Human_2009

Reference: NA_H1N1_Human_2009_California07 ([Structure/Model Details](#))
 Patient/Sample: A/Maryland/06/2016 | EPI_ISL_221290 | 2016-05-17 | A/H1N1 |
 Mutation(s): [V13I](#) [V53I](#) [L40I](#) [I34V](#) [V241I](#) [I314M](#) [N270K](#) [V264I](#) [T48A](#) [K432E](#) [I321V](#) [N369K](#) [N248D](#) [N200S](#) [N386K](#) [N44S](#) [H275Y](#)
 Wildtype residue only displayed if position is part of available structure.
 Hover with mouse over residue to see its position number. Right-click for more options.

FluSurver-JSmol

[Spin ON](#) [Spin OFF](#) [Save IMAGE](#)

[See interactions of position NA 270 in related structures.](#)

Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
A/Maryland/06/2016 EPI_ISL_221290 2016-05-17 A/H1N1	NA A/California/07/2009(H1N1) find closest related sequences	96.375	100.000	17	V13I I34V L40I N44S T48A V53I N200S V241I N248D V264I N270K H275Y I314M I321V N369K N386K K432E show in structure NA drug sensitivity positions: 33, 0, 1 Reduced sensitivity or resistance!

Detailed mutation information

The main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidate mutations for further research and should ideally be combined with experimental testing and verification of any predicted phenotypes. Importantly, any direct diagnostic use, assumed severity or recommendation on patient treatment should not be based solely on these computational predictions. Our curated reference sequences used for annotation transfer of equivalent mutations are mainly comprised of strains that recently infected humans. Therefore, the usage scenario that will give the most fruitful and reliable results are current surveillance sequences with very close relation to used vaccine strains, including some candidates for avian flu and novel reassortant swine flu H3N2v. Please take a look at the [Frequently Asked Questions](#) and [Tutorial](#) if you are new to FluSurver. There is also a [special note for using FluSurver results in publications](#).



Result for comparison with reference selection: auto [Back to Reference Selection](#)

Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
A/Maryland/06/2016 EPI_ISL_221290 2016-05-17 A/H1N1	NA A/California/07/2009(H1N1) find closest related sequences	96.375	100.000	17	V13I , I34V , L40I , N44S , T48A , V53I , N200S , V241I , N248D , V264I , N270K , H275Y , I314M , I321V , N369K , N386K , K432E show in structure NA drug sensitivity positions: 33, 0, 1 Reduced sensitivity or resistance!
A/New York/36/2016 EPI_ISL_221634 2016-05-20 A/H1N1	NA A/California/07/2009(H1N1) find closest related sequences	96.802	100.000	15	V13I , I34V , L40I , N44S , N200S , V241I , N248D , V264I , N270K , H275Y , I314M , I321V , N369K , N386K , K432E show in structure NA drug sensitivity positions: 33, 0, 1 Reduced sensitivity or resistance!
A/Pennsylvania/25/2016 EPI_ISL_221283 2016-05-17 A/H1N1	NA A/California/07/2009(H1N1) find closest related sequences	96.802	100.000	15	V13I , I34V , L40I , N44S , N200S , V241I , N248D , V264I , N270K , H275Y , I314M , I321V , N369K , N386K , K432E show in structure NA drug sensitivity positions: 33, 0, 1 Reduced sensitivity or resistance!
A/Washington/31/2016 EPI_ISL_221289 2016-05-17 A/H1N1	NA A/California/07/2009(H1N1) find closest related sequences	96.588	100.000	16	V13I , I34V , L40I , N44S , N200S , V241I , N248D , V264I , N270K , P272L , H275Y , I314M , I321V , N369K , N386K , K432E show in structure NA drug sensitivity positions: 33, 0, 1 Reduced sensitivity or resistance!
A/Wyoming/16/2016 EPI_ISL_221287 2016-05-17 A/H1N1	NA A/California/07/2009(H1N1) find closest related sequences	96.802	100.000	15	V13I , I34V , L40I , N44S , N200S , V241I , N248D , V264I , N270K , H275Y , I314M , I321V , N369K , N386K , K432E show in structure NA drug sensitivity positions: 33, 0, 1 Reduced sensitivity or resistance!

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NA H275Y

Key to alternative position numbering:

275	FluSurver numbering
274	(absolute as in 2009 H1N1 pandemic)
275	Classical H3N2 strain numbering
	Classical H1N1 strain numbering

Chosen reference: NA_H1N1_Human_2009_California07

Position in reference: 275

AA in reference: H

AA in query: Y

Mutation NA H275Y already occurred 577 times (3.29% of all samples with NA sequence) in 31 countries. The first strain with this mutation, collected in May 2009, was A/Mexico city/CIA10/2009. The mutation most recently occurred in strain A/Murcia/2010/2016_NA, collected in April 2016. ([see map](#))

[See detailed global statistics for this position](#)

A mutation at the position equivalent to NA 275 has been reported in the literature to be related to [mild drug resistance](#) and [strong drug resistance](#).

A combination of mutations including the position equivalent to NA 275 has been reported in the literature to be related to [strong drug resistance](#).

As seen in resolved structures of proteins from related strains, the NA position equivalent to your mutation is involved in:
 - [drug binding](#)

[See all interactions for this position](#)

Based on FoldX structural stability calculations H275Y is predicted to be **strongly destabilizing** which could represent a fitness disadvantage (ddG = 4.55 kcal/mol)

[PubMed search for this mutation \(including alternative numbering\)](#)

Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
A/Maryland/06/2016 EPI_ISL_221290 2016-05-17 A/H1N1	NA A/California/07/2009(H1N1) find closest related sequences	96.375	100.000	17	V13I , I34V , L40I , N44S , T48A , V53I , N200S , V241I , N248D , V264I , N270K , H275Y , I314M , I321V , N369K , N386K , K432E show in structure NA drug sensitivity positions: 33, 0, 1 Reduced sensitivity or resistance!

Alternative numbering information

FluSurfer

Query: NA H275Y

Key to alternative position numbering:

275	(absolute as in 2009 H1N1 pandemic)
274	Classical H3N2 strain numbering
275	Classical H1N1 strain numbering

Chosen reference: NA_H1N1_Human_2009_California07

Position in reference: 275

AA in reference: H

AA in query: Y

Mutation NA H275Y already occurred 577 times (3.29% of all samples with NA sequence) in 31 countries. The first strain with this mutation, collected in May 2009, was A/Mexico city/CIA10/2009. The mutation most recently occurred in strain A/Murcia/2010/2016_NA, collected in April 2016. ([see map](#))

[See detailed global statistics for this position](#)

A mutation at the position equivalent to NA 275 has been reported in the literature to be related to [mild drug resistance](#) and [strong drug resistance](#).

A combination of mutations including the position equivalent to NA 275 has been reported in the literature to be related to [strong drug resistance](#).

As seen in resolved structures of proteins from related strains, the NA position equivalent to your mutation is involved in: [drug binding](#)

[See all interactions for this position](#)

Based on FoldX structural stability calculations H275Y is predicted to be **strongly destabilizing** which could represent a fitness disadvantage (ddG = 4.55 kcal/mol)

[PubMed search for this mutation \(including alternative numbering\)](#)

NA H275Y

Key to alternative position numbering:

275	FluSurfer numbering (absolute as in 2009 H1N1 pandemic)
274	Classical H3N2 strain numbering
275	Classical H1N1 strain numbering

Chosen reference: NA_H1N1_Human_2009_California07

Position in reference: 275

AA in reference: H

AA in query: Y

Mutation NA H275Y already occurred 577 times (3.29% of all samples with NA sequence) in 31 countries. The first strain with this mutation, collected in May 2009, was A/Mexico city/CIA10/2009. The mutation most recently occurred in strain A/Murcia/2010/2016_NA, collected in April 2016. ([see map](#))

[See detailed global statistics for this position](#)

A mutation at the position equivalent to NA 275 has been reported in the literature to be related to [mild drug resistance](#) and [strong drug resistance](#).

A combination of mutations including the position equivalent to NA 275 has been reported in the literature to be related to [strong drug resistance](#).

As seen in resolved structures of proteins from related strains, the NA position equivalent to your mutation is involved in: [drug binding](#)

[See all interactions for this position](#)

Based on FoldX structural stability calculations H275Y is predicted to be **strongly destabilizing** which could represent a fitness disadvantage (ddG = 4.55 kcal/mol)

[PubMed search for this mutation \(including alternative numbering\)](#)

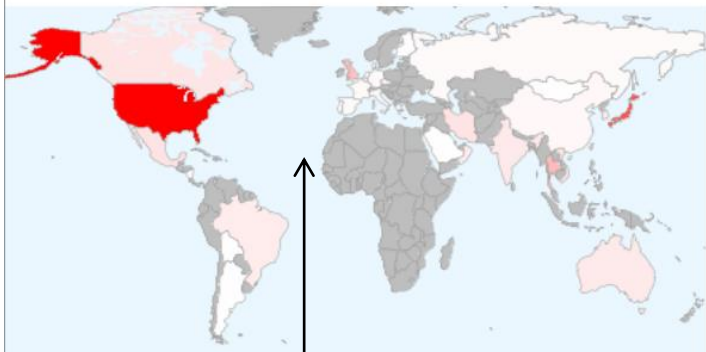
Geospatial and temporal occurrence



The city with **red** label indicates first appearance of the mutation. City with **yellow** label indicate later appearance of the mutation. The city with the most recent appearance of the mutation has the **green** label. Number in the label indicates frequency of occurrence of the mutation in that city. A dot in the label indicates that there are 10 or more occurrences in that city.

As there are too many cities with viral isolates carrying this mutation, cities with number of occurrences below 7 are not labeled in the map above.

Map of countries with the NA H275Y mutation



Number of occurrences

Mutation statistics for NA at position 275

AA	# Occ.	%	Geo Distribution	Co-occurrences
X	57	0.32		
Y	577	3.29	(geo)	(co-occur)
-	17	0.10		
H	16891	96.28	reference aa	reference aa
R	1	0.01		(co-occur)
ALL	17543	100.00		

Sequences were compared to reference strain A/California/07/2009 [ACQ63272](#). Last updated on Jun 25th 2016 by Raphael Tze Chuen Lee

Above are the occurrences of all amino acid residues at position 275 in NA. For statistics of all position in NA in this subtype click here: [H1N1 NA mutations table](#)

NA H275Y

Key to alternative position numbering:

275	FluSurver numbering (absolute as in 2009 H1N1 pandemic)
274	Classical H3N2 strain numbering
275	Classical H1N1 strain numbering
Chosen reference:	NA_H1N1_Human_2009_California07
Position in reference:	275
AA in reference:	H
AA in query:	Y

Mutation NA H275Y already occurred 577 times (3.29% of all samples with NA sequence) in 31 countries. The first strain with this mutation, collected in May 2009, was A/Mexico city/CIA10/2009. The mutation most recently occurred in strain A/Murcia/2010/2016_NA, collected in April 2016. ([see map](#))

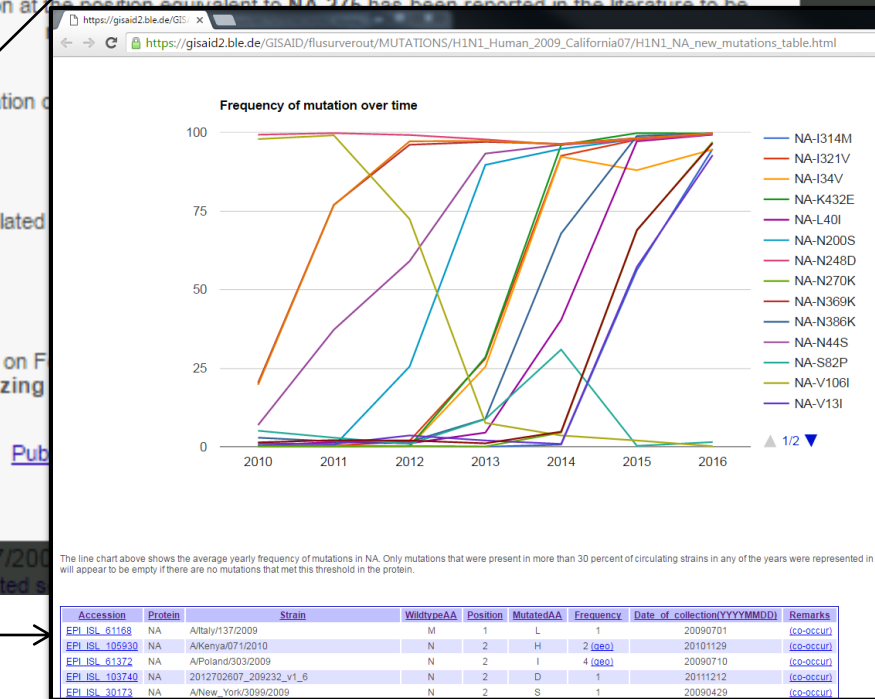
[See detailed global statistics for this position](#)

A mutation at this position equivalent to NA 275 has been reported in the literature to be

A combination of

related

Based on F destabilizing



The line chart above shows the average yearly frequency of mutations in NA. Only mutations that were present in more than 30 percent of circulating strains in any of the years were represented in the chart. The chart will appear to be empty if there are no mutations that met this threshold in the protein.

Accession	Protein	Strain	WildtypeAA	Position	MutatedAA	Frequency	Date of collection(YYYYMMDD)	Remarks
EPI_ISL_61168	NA	A/Italy/137/2009	M	1	L	1	20090701	(co-occur)
EPI_ISL_106930	NA	A/Kenya/071/2010	N	2	H	2 (geo)	20101129	(co-occur)
EPI_ISL_61372	NA	A/Poland/903/2009	N	2	I	4 (geo)	20090710	(co-occur)
EPI_ISL_103740	NA	2012702607_209232_v1_6	N	2	D	1	20111212	(co-occur)
EPI_ISL_30173	NA	A/New_York/3099/2009	N	2	S	1	20090429	(co-occur)

New: Direct link to phylogenetic context of mutation in NEXTFLU

FluSurver

Key to alternative position numbering:
 FluSurver numbering (absolute as in 2009 H1N1 pandemic)
 Classical H3N2 strain numbering
 Classical H1N1 strain numbering

Chosen reference: HA_H3N2_Human_2016_Singapore/NFIMH-16-0019_cell

Position in reference: 158
 AA in reference: G
 AA in query: R

Mutation HA G158R already occurred 1708 times (44.78% of all samples with HA sequence) in 15 countries. The first strain with this mutation, collected in June 2016, was A/Cameroon/16V-4959/2016. The mutation most recently occurred in strain A/swine/Oklahoma/A01678529/2017, collected in December 2017. ([see map](#))
[See detailed global statistics for this position](#)

A mutation at the position equivalent to HA 158 has been reported in the literature to be related to [antigenic drift / escape mutant](#).

A combination of mutations including the position equivalent to HA 158 has been reported in the literature to be related to [antigenic drift / escape mutant](#).

As seen in resolved structures of proteins from related strains, the HA position equivalent to your mutation is involved in:
 - [viral oligomerization interfaces](#)
 - [binding small ligand\(s\)](#)
 - [antibody recognition sites](#)

[See all interactions for this position](#)

[PubMed search for this mutation \(including alternative numbering\)](#)

NEW: [Phylogenetic context for this mutation at NEXTFLU](#)

nextflu

By Trevor Bedford & Richard Neher

About Methods

Dataset

flu
 h3n2
 ha
 3y

Date Range

2011-05-25 2018-02-02

Color By

genotype
 HA1
 142

Tree Options

Layout

RECTANGULAR
 RADIAL
 UNROOTED
 CLOCK

Branch Length

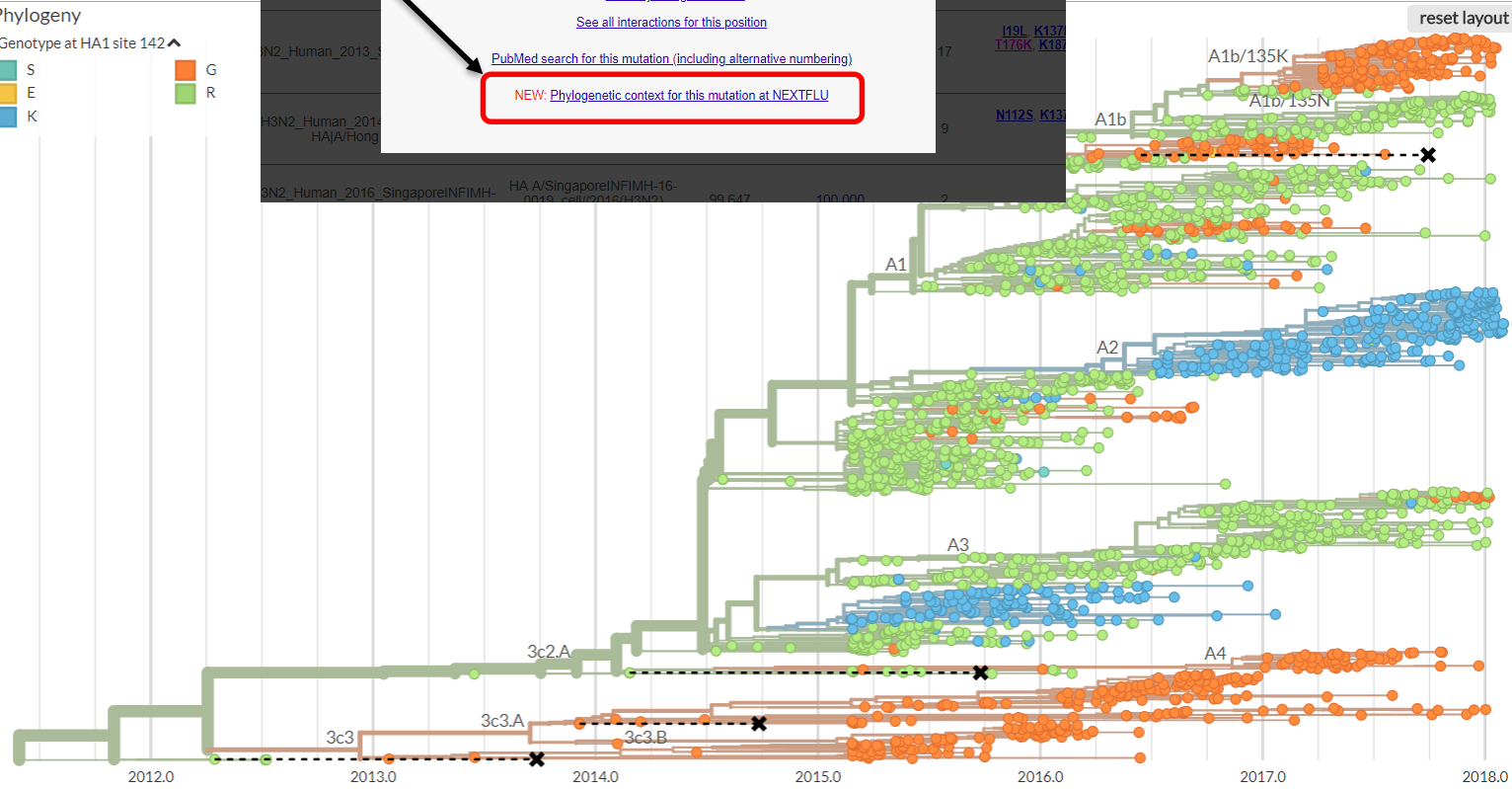
Real-time tracking

Showing 2095 of 2095 genomes, from

Phylogeny

Genotype at HA1 site 142

S E K G R



reset layout

Phenotype information

Protein: NA

Influenza type: Human H1N1 (2006)

Mutation (as in paper): H274Y

neutral AA: H

neg. eff. AA: Y

Effect: **strong drug resistance**
(drug name in comments)

Comment:

Tamiflu but not Relenza resistance (Table 3).

Literature reference

(Mutation H274Y in the paper is at an equivalent position of the mutation in your query)

NA H275Y

Key to alternative position numbering:

	FluSurver numbering (absolute as in 2009 H1N1 pandemic)
275	Classical H3N2 strain numbering
274	Classical H1N1 strain numbering
275	
Chosen reference:	NA_H1N1_Human_2009_California07
Position in reference:	275
AA in reference:	H
AA in query:	Y

Mutation NA H275Y already occurred 577 times (3.29% of all samples with NA sequence) in 31 countries. The first strain with this mutation, collected in May 2009, was A/Mexico city/CIA10/2009. The mutation most recently occurred in strain A/Murcia/2010/2016_NA, collected in April 2016. ([see map](#))

[See detailed global statistics for this position](#)

A mutation at the position equivalent to NA 275 has been reported in the literature to be related to [mild drug resistance](#) and [strong drug resistance](#).

A combination of mutations including the position equivalent to NA 275 has been reported in the literature to be related to [strong drug resistance](#).

As seen in resolved structures of proteins from related strains, the NA position equivalent to your mutation is involved in:
- [drug binding](#)

[See all interactions for this position](#)

Based on FoldX structural stability calculations H275Y is predicted to be **strongly destabilizing** which could represent a fitness disadvantage (ddG = 4.55 kcal/mol)

[PubMed search for this mutation \(including alternative numbering\)](#)

PubMed influenza AND (neuraminidase OR NA) AND (H275Y OR H274Y)

Create RSS Create alert Advanced

Format: Summary Sort by: Most Recent

Send to

Search results

Items: 1 to 20 of 323

<< First < Prev Page 1 of 17 Next > Last >>

[Competitive Fitness of Influenza B Viruses Possessing E119A and H274Y Neuraminidase Inhibitor](#)

1. [Resistance-Associated Substitutions in Ferrets](#)

Pascua PN, Marathe BM, Burnham AJ, Vogel P, Webby RJ, Webster RG, Govorkova EA

PLoS One. 2016 Jul 28;11(7):e0159847. doi: 10.1371/journal.pone.0159847. eCollection 2016.

PMID: 27466813 [Free Article](#)

[Similar articles](#)

[Influenza A\(H1N1\)pdm09 virus exhibiting enhanced cross-resistance to oseltamivir and peramivir due to a dual H275Y/G147R substitution, Japan, March 2016](#)

2. Takashita E, Fujisaki S, Shirakura M, Nakamura K, Kishida N, Kuwahara T, Shimazu Y, Shimomura T, Watanabe S, Odagiri T; [Influenza Virus Surveillance Group of Japan](#).

Euro Surveill. 2016 Jun 16;21(24). doi: 10.2807/1560-7917.ES.2016.21.24.30258.

PMID: 27336226

[Similar articles](#)

california/07/2009(H1N1)

96.802

100,000

15

find closest related sequences

Literature-curated genotype to phenotype effect annotations

Effect Type	# Annotations
host specificity shift	136
virulence	106
antigenic drift / escape mutant	84
strong drug sensitivity change	40
mild drug sensitivity change	30
other	23
total (2019)	419

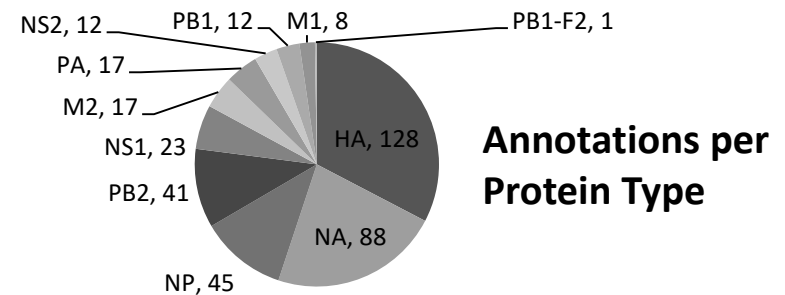
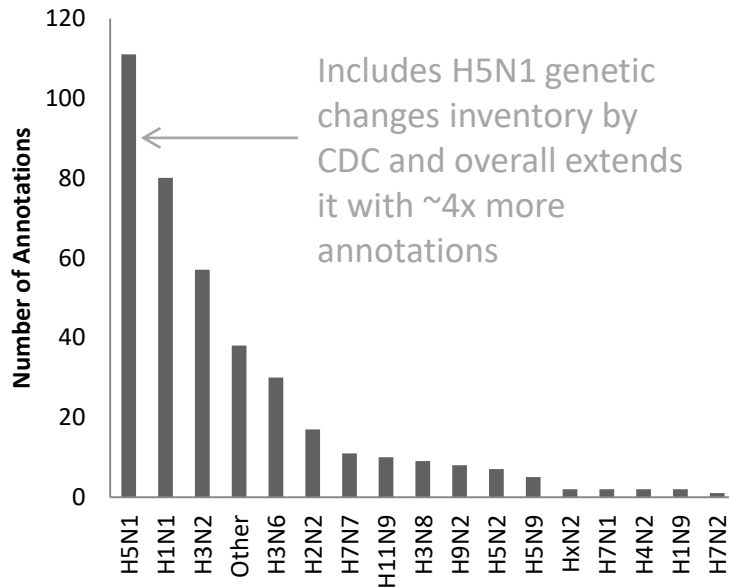
Example:

Known effect(s) of mutations at position equivalent to your mutation:

Protein: HA
 Influenza type: Avian, Human H1N1 (2009)
 Mutation (as in paper): D222G or D225G
 neutral AA: D
 neg. eff. AA: **G**
 Effect: host specificity shift

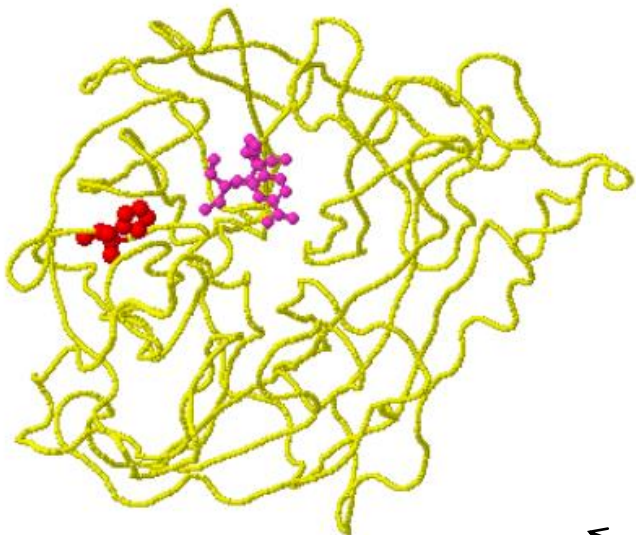
Comment:
 HA D239G is also referred to in the literature as D222G or D225G using alternative (e.g. seasonal H1/H3) numberings. It has been found to alter host cell receptor specificity from human alpha-2,6 to also include avian-like alpha-2,3 sialic acid which is more common in ciliated human cells of the lower respiratory tract. While this mutation has been found in higher proportions in severe cases, it is **IMPORTANT** to note that it also can occur as egg or cell culture adaptation. Therefore, its effect would only be relevant for surveillance if the mutation is also found in the original clinical sample.
[Literature reference](#)
 (Mutation D222G or D225G in the paper is at an equivalent position of the mutation in your query)

Annotations per Subtype



Structural interaction and stability information

NA_275_1B9V_A_273 - Google Chrome
https://gisaid2.ble.de/GISAID/flusurverout/INTERACTIONS/NA/273



Spin ON Spin OFF Save IMAGE

Description:
The mutation position (red atoms) corresponds to position 273 on viral A (yellow backbone) and is within 5 Å from drug RA2 (pink atoms).

NA H275Y

Key to alternative position numbering:

	FluSurver numbering (absolute as in 2009 H1N1 pandemic)
275	Classical H3N2 strain numbering
274	Classical H1N1 strain numbering
275	

Chosen reference: NA_H1N1_Human_2009_California07
Position in reference: 275
AA in reference: H
AA in query: Y

Mutation NA H275Y already occurred 577 times (3.29% of all samples with NA sequence) in 31 countries. The first strain with this mutation, collected in May 2009, was A/Mexico city/CIA10/2009. The mutation most recently occurred in strain A/Murcia/2010/2016_NA, collected in April 2016. ([see map](#))
[See detailed global statistics for this position](#)

A mutation at the position equivalent to NA 275 has been reported in the literature to be related to [mild drug resistance](#) and [strong drug resistance](#).

A combination of mutations including the position equivalent to NA 275 has been reported in the literature to be related to [strong drug resistance](#).

As seen in resolved structures of proteins from related strains, the NA position equivalent to your mutation is involved in:
- [drug binding](#)

[See all interactions for this position](#)

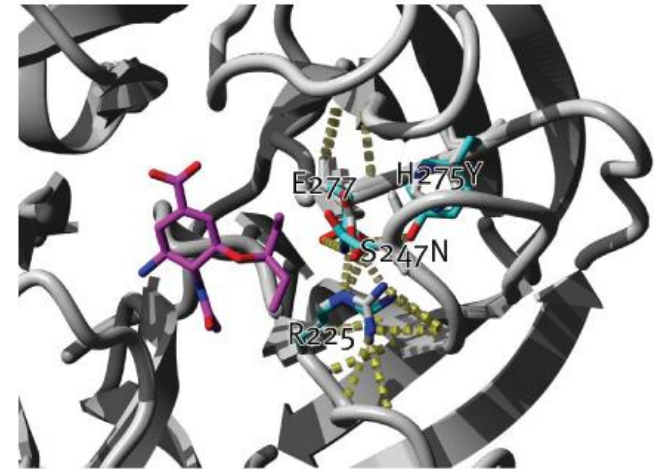
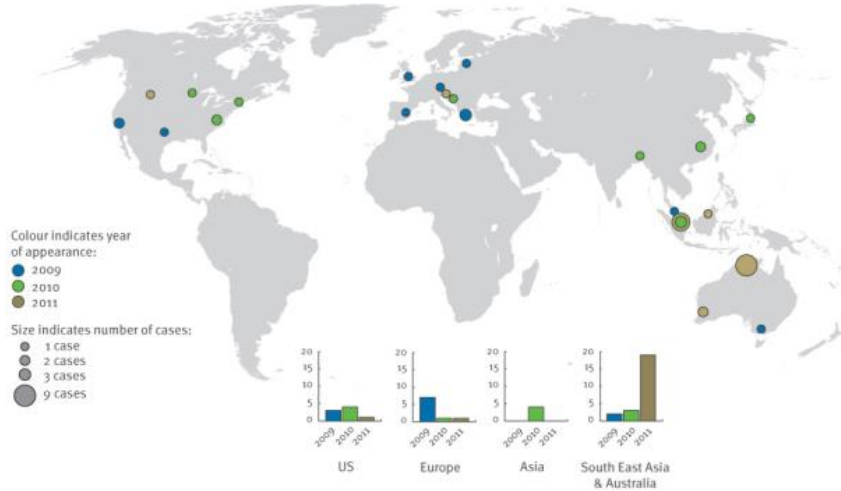
Based on FoldX structural stability calculations H275Y is predicted to be **strongly destabilizing** which could represent a fitness disadvantage (ddG = 4.55 kcal/mol)

[PubMed search for this mutation \(including alternative numbering\)](#)

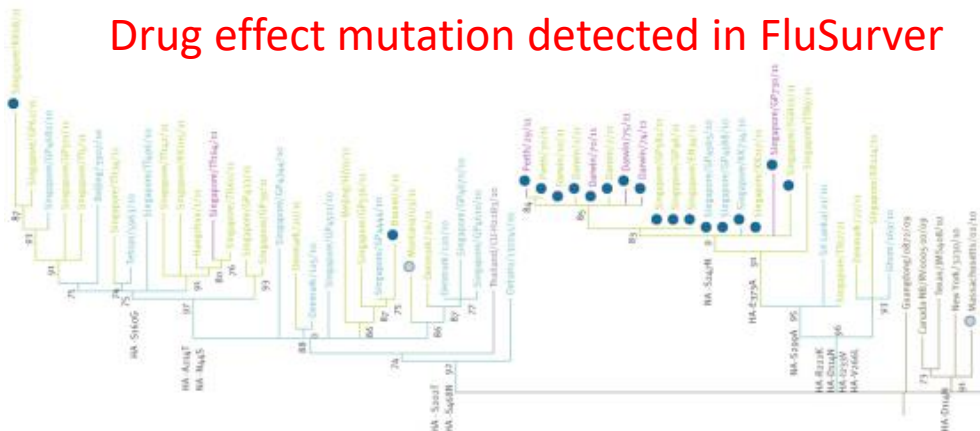
Section IV

EXAMPLE FINDINGS WITH FLUSURVER

New drug sensitivity altering mutation NA S247N



Drug effect mutation detected in FluSurver

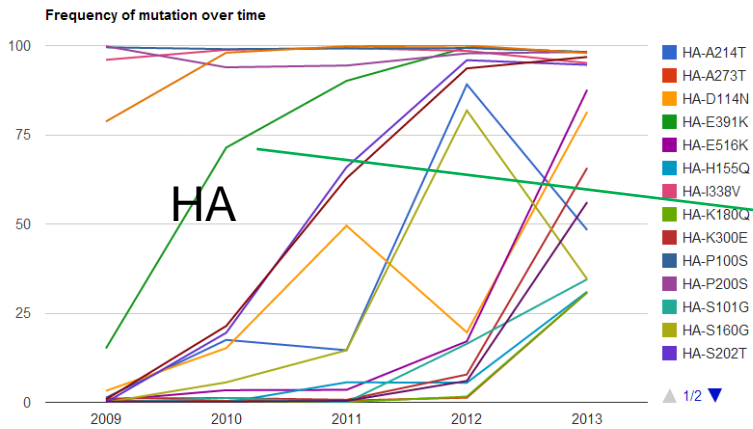
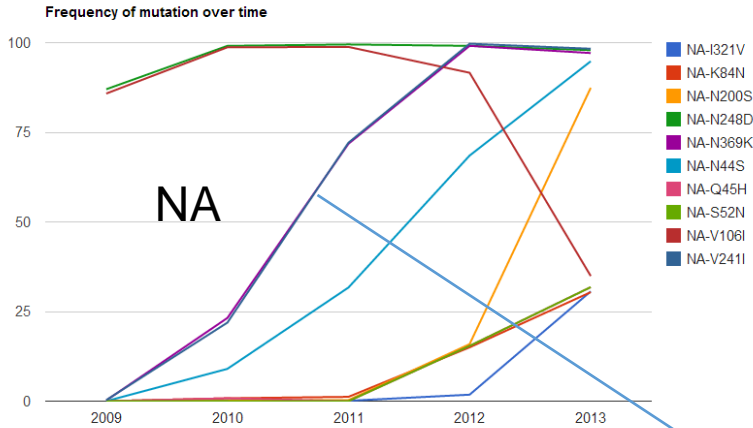


Found circulating in 10% of samples in Singapore and 30% of samples in Northern Australia in early 2011.

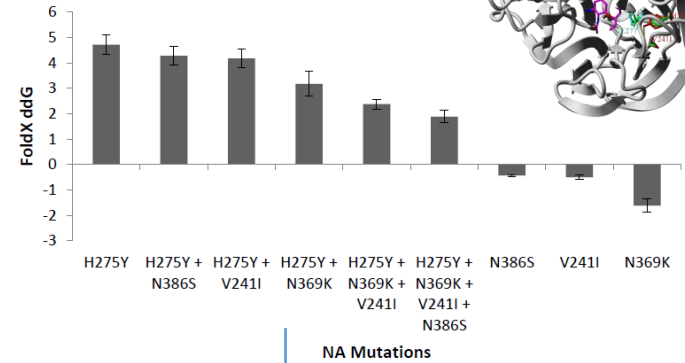
Experimentally measured increase of IC50 for Tamiflu by 6-fold and Relenza by 3-fold but normally administered dose of drugs still sufficient.

Hurt AC, Lee RT, Leang SK, Cui L, Deng YM, Phuah SP, Caldwell N, Freeman K, Komadina N, Smith D, Speers D, Kelso A, Lin RT, Maurer-Stroh S, Barr IG. *Increased detection in Australia and Singapore of a novel influenza A(H1N1)2009 variant with reduced oseltamivir and zanamivir sensitivity due to a S247N neuraminidase mutation.* Euro Surveill. 2011 Jun 9;16(23). pii: 19884.

Mutation frequency pattern highlights relevant changes

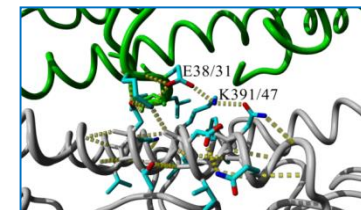


FoldX stability for N1pdm in FluSurver



New H275Y permissive mutations
 Hurt *et al.* J Infect Dis. 2012 Jul 15;206(2):148-57.
 Butler *et al.* PLoS Pathog. 2014 Apr 3;10(4):e1004065.

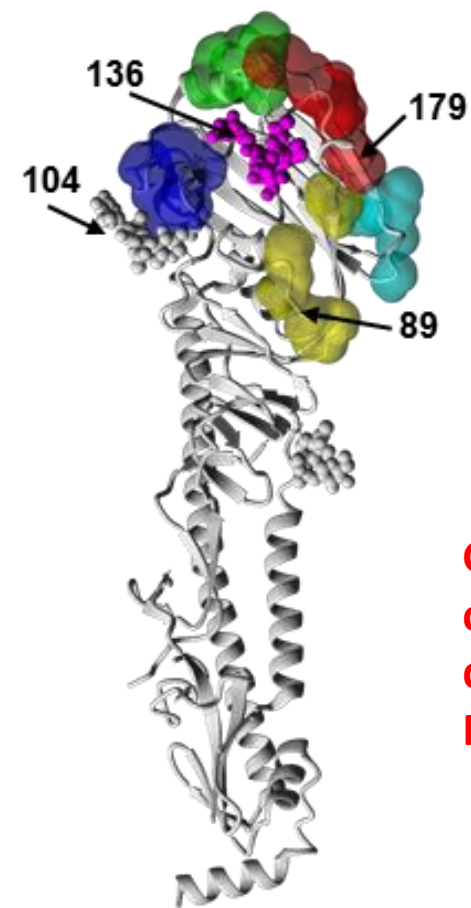
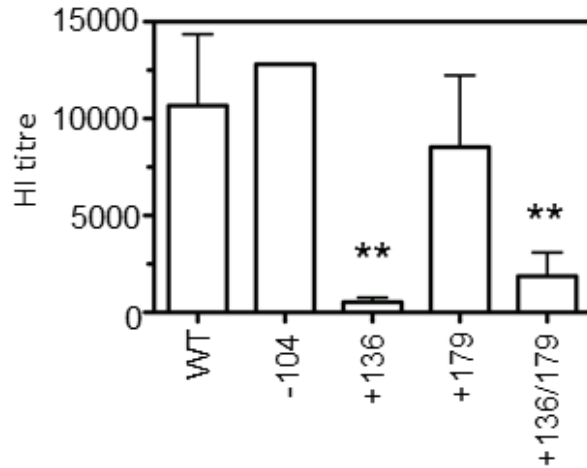
Change in pH-dependency of fusion
 Maurer-Stroh *et al.* PLoS Curr. 2010 Jun 1;2:RRN1162.
 Cotter *et al.* PLoS Pathog. 2014 Jan;10(1):e1003831.



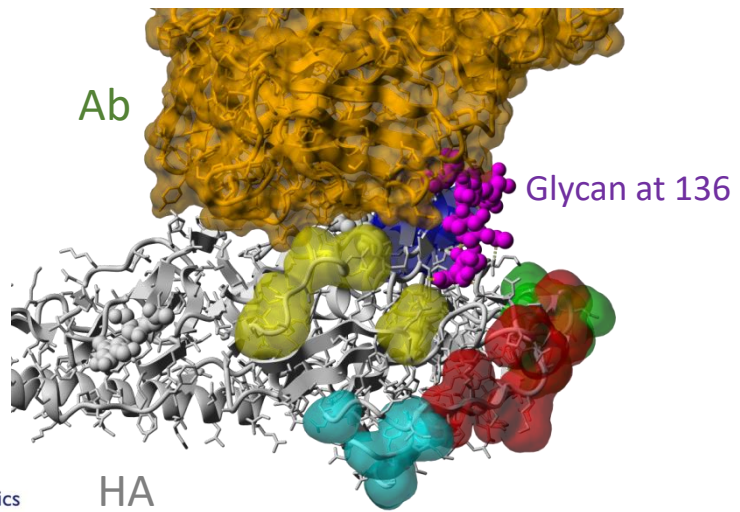
Temporal frequency plot in FluSurver

Addition of Glycosylation to Influenza A Virus Hemagglutinin Modulates Antibody-Mediated Recognition of H1N1 2009 Pandemic Viruses.

Job ER, Deng YM, Barfod KK, Tate MD, Caldwell N, Reddiex S, Maurer-Stroh S, Brooks AG, Reading PC.
J Immunol. 2013 Mar 1;190(5):2169-77.



**Glycosylation
change
detection in
FluSurver**



Addition of a glycan to A(H1N1)pdm HA through a K136N mutation was associated with resistance to neutralizing Abs and showed enhanced growth in A(H1N1)pdm-vaccinated mice, consistent with evasion of Ab-mediated immunity in vivo.

New reference strains (e.g. H7N9, H5N8) constantly added to FluSurver

E.g. H5N8 Emerg Infect Dis. 2015 May;21(5):860-3.

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FluSurver

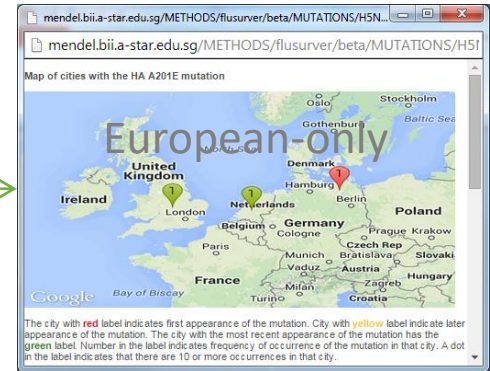
The main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidate mutations for further research and should ideally be combined with experimental testing and verification of any predicted phenotypes. Importantly, any direct diagnostic use, assumed severity or recommendation on patient treatment should not be based solely on these computational predictions. Our curated reference sequences used for annotation transfer of equivalent mutations are mainly comprised of strains that recently infected humans. Therefore, the usage scenario that will give the most fruitful and reliable results are current surveillance sequences with very close relation to used vaccine strains, including some candidates for avian flu and novel reassortant swine flu H3N2v. Please take a look at the [Frequently Asked Questions](#) and [Tutorial](#) if you are new to FluSurver. There is also a [special note for using FluSurver results in publications](#).

Result for comparison with reference selection: autorefall [Back to Reference Selection](#)

Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
HA_A/Ch/Netherlands/14015526/2014_167905	HA A/baikal teal/Korea/Donglim3/2014(H5N8) find closest related sequences	99.295	100.000	4	N54T S197P A201E I390V show in structure
HA_A/dnc/k/England/36254/14_167904	HA A/baikal teal/Korea/Donglim3/2014(H5N8) find closest related sequences	99.295	100.000	4	S197P A201E H289Y I390V show in structure
HA_A/turkey/Germany-MV/R2472/2014_167140	HA A/baikal teal/Korea/Donglim3/2014(H5N8) find closest related sequences	99.467	99.295	3	S197P A201E I390V show in structure
NA_A/Ch/Netherlands/14015526/2014_167905	HA A/baikal teal/Korea/Donglim3/2014(H5N8) find closest related sequences	99.787	99.787	1	A190T show in structure
					NA drug sensitivity positions: 27.0.0
				4	S164P N166S K186N A190T show in structure
					NA drug sensitivity positions: 27.0.0
				1	A190T show in structure
					NA drug sensitivity positions: 27.0.0
				4	I67V V338I R497S K699R show in structure
				4	V338I R497S V511L K699R show in structure

[Saving or import to Excel](#)

[Go back](#)



E.g. 3 HA mutations relative to Korean H5N8 shared among European cases

A201E (A189E)
Strong surface change at common epitope (antibody binding site)

S197P (S185P)
Structural change near receptor binding site but effect not yet reported in literature

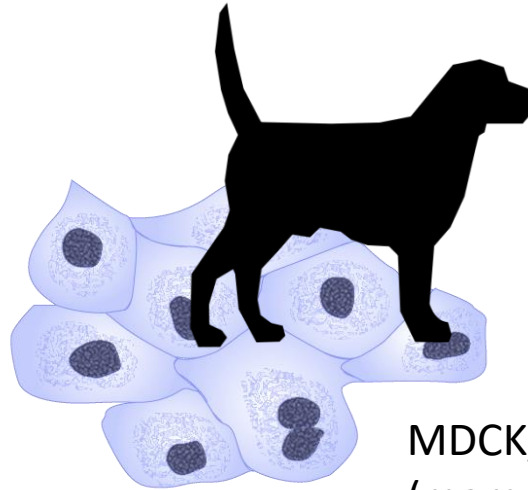
I390V (I45V)
Conservative change at site recognized by "universal" stem antibodies

H5N8 analysis available on GISAID platform

Virus culture/passage bias is a common problem for flu vaccine production!



Original clinical sample



MDCK/SIAT cells
(mammalian host)

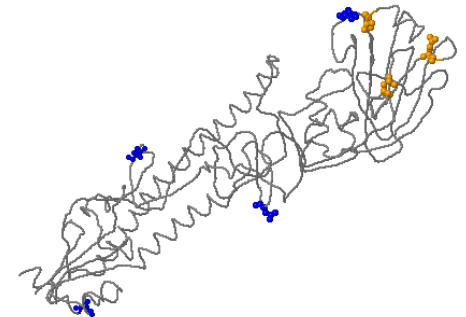
Often like original



Eggs (avian host)
also used for vaccine production!

Egg adapted

+ H172Q, G202V, S235Y



Chen H, Deng Q, Ng SH, Lee RT, Maurer-Stroh S, Zhai W. *Dynamic Convergent Evolution Drives the Passage Adaptation across 48 Years' History of H3N2 Influenza Evolution.* Mol Biol Evol. 2016 Sep 7. pii: msw190.

New: you can choose egg-derived reference H3N2s (default) or cell-derived versions!

Comparison of current and last 3 H3N2 vaccine strains in cell-derived vs egg-derived versions:

The main application scenario for FluSurver is to highlight phenotypically or epidemiologically distinct reference sequences used for annotation transfer of equivalent mutations. **fruitful and reliable results are current surveillance sequences with very close relation to used vaccine strains, including some candidates for avian flu and novel reassortant swine flu H3N2v.** Please take a look at the [Frequently Asked Questions](#) and [Tutorial](#) if you are new to FluSurver. There is also a [special note for using FluSurver results in publications](#).

Additional settings:

- ignore low quality bases for nucleotide input (indicated by lower case, except for all lower case sequences)
- do not show result if alignment coverage is below 50% (useful for analyzing assembled contig files from NGS runs)

Submit Reset (estimated time needed: ~2 seconds per sequence in automatic mode)

Result for comparison with reference selection: **autorefall** [Back to Reference Selection](#)

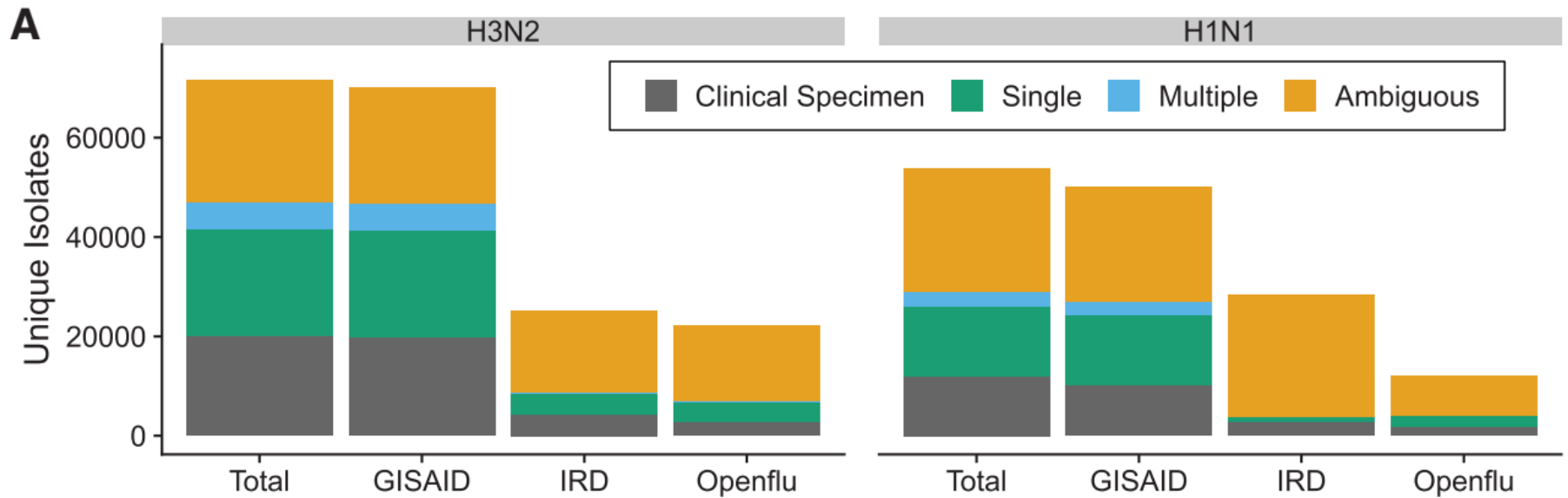
Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
cell_HA_H3N2_Human_2012_Texas50_cell	HA A/Texas/50/2012(H3N2) find closest related sequences	99.647	100.000	2	V202G , F235S show in structure
cell_HA_H3N2_Human_2013_Switzerland9715293	HA A/Switzerland/9715293/2013(H3N2) find closest related sequences	99.470	100.000	3	R156I , V202G , X235S show in structure
cell_HA_H3N2_Human_2014_HongKong4801_cell HA A/Hong	HA A/HongKong/4801/2014(H3N2) find closest related sequences	99.470	100.000	3	S112N , K176T , P210L show in structure
cell_HA_H3N2_Human_2016_SingaporeINFIMH-16-0019_cell	HA A/SingaporeINFIMH-16-0019//2016(H3N2) find closest related sequences	99.647	100.000	2	K176T , P210L show in structure

[Right-click here to save/download mutation report table for archiving or import to Excel](#)

Warning: this reference selection includes sequences of strains without complete genomes, e.g. only HA and NA available/included. Therefore, hits of other segments to different reference strains do not represent reassortments. Please see also [this help section](#) regarding reassortments.

[Back to Reference Selection](#)

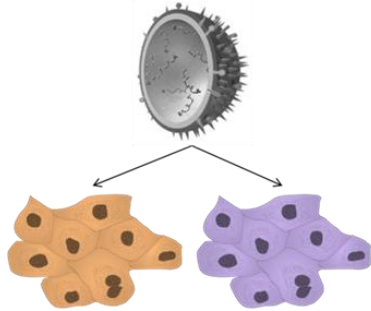
Comparison of database content with passage annotation



DuPai CD, McWhite CD, Smith CB, Garten R, Maurer-Stroh S, Wilke CO.
Influenza passing annotations: what they tell us and why we should listen.
Virus Evol. 2019 Jun 30;5(1):vez016.

Passage bias sites and host specificity mutations

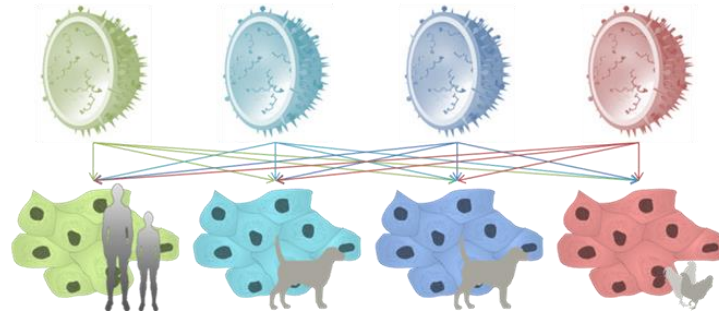
(A) Same virus (H3, H1s, H1p)
passaged in different cell types



Direct passage
bias evidence

~800 strains

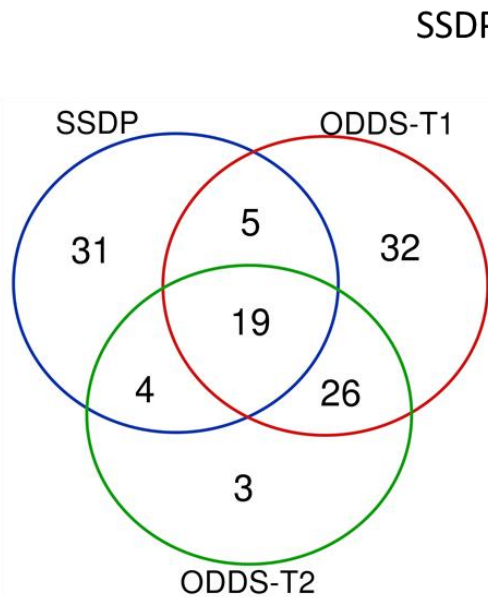
4 Viruses (H3, H1s, H1p, H5) (B)
4 cell types (ORIGINAL, SIAT, MDCK, EGG)



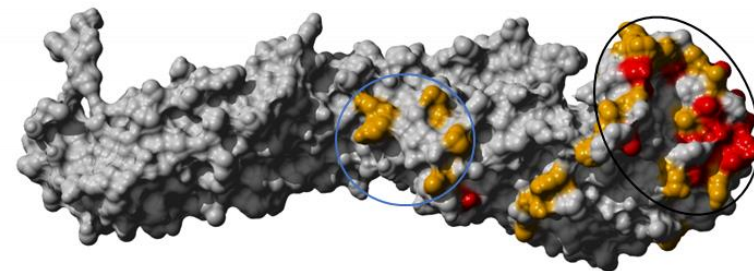
Statistical passage
bias evidence

~80000 sequences
2 time periods

(C)



(D)



19 sites shared by all 3 sets (red),
35 sites shared by 2 sets (orange)

Influenza quasi-species and FluSurver

Q: What is a quasi-species?

A: A group of viruses that are closely related and co-exist in the host but with a twist or two ...

... **TIME** & **PRESSURE**

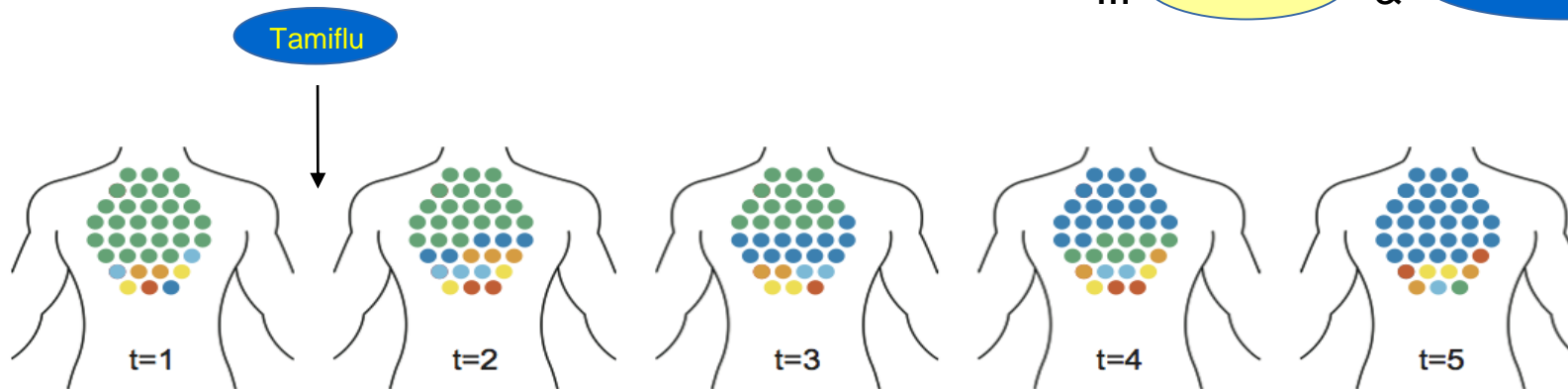
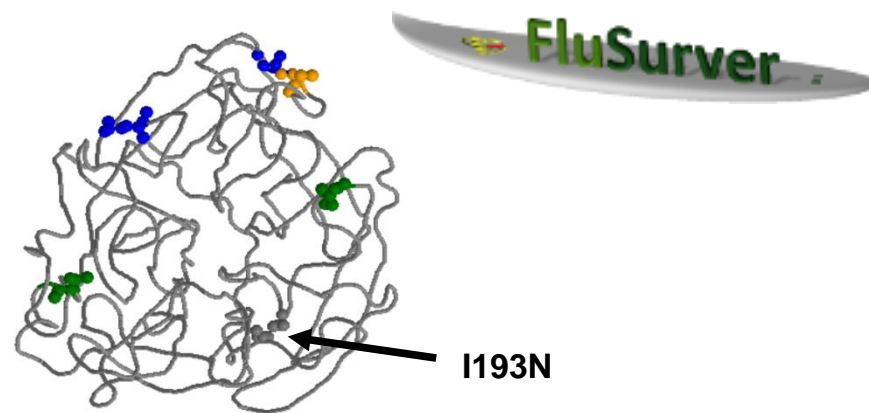


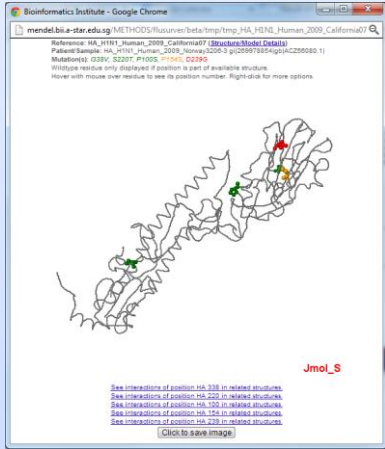
Illustration by Bjorn Koel (Amsterdam UMC)

	T1	T2	T3
Analysis	● ● ●	● ● ●	● ● ●
A(cons) :	-	-	+
B(quasi) :	-	+	+

Early detection



Summary of FluSurfer annotations

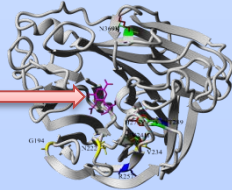


Map mutations to structure

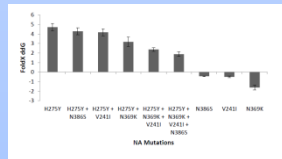
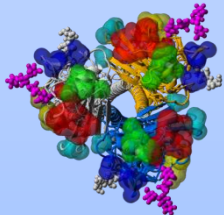
300+ reference homology models

1568	self/oligomerization
975	other small ligand
268	antibody
188	host protein
182	antigen-presenting MHC molecule
132	other viral protein
46	drug
45	nucleic acids
13	host cell receptor
3417	total interactions for 2062 positions

Interactions



Glycosylation site changes



FoldX stability calculations (for high frequency mutations in N1pdm)

Mutation numbering scheme conversion (e.g. H3, H1, H1pdm) and direct PubMed search link



Passage bias (egg/cell adaptation) for ~1300 mutations

Updated Literature-curated mutation effect database
400+ entries

mild drug resistance	30
strong drug resistance	40
virulence	106
antigenic drift / escape mutant	84
host specificity shift	136
other	23

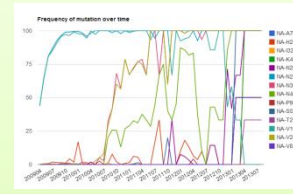
Literature

Structure

Epidemiology

Closest DB hits

Temporal pattern



Genomic co-occurrence

Regional & global occurrence

FluSurver acknowledgements

Many current and former colleagues from the A*STAR Bioinformatics Institute (BII) contribute(d) critically to the FluSurver development and research, including:

Sebastian Maurer-Stroh, Raphael Tze Chuen Lee, Vithiagarun Gunalan, Vachiranee Limviphuvadh, Fernanda L Sirota, Biruhalem Taye, Alvin Han, Han Hao, Dimitar Kenanov, Jianmin Ma, Swe Swe Thet Paing, Narumol Dounghan, Joy Xiang and Frank Eisenhaber.

The FluSurver would be nothing without the valuable feedback and interaction with the influenza research and surveillance community, including especially and in chronological order:

- Genome Institute of Singapore (GIS), Singapore
- INMEGEN Mexico City, Mexico
- Experimental Therapeutics Centre (ETC), Singapore
- Tan Tock Seng Hospital (TTSH), Singapore
- National Public Health Laboratory (NPHL) of the Ministry of Health, Singapore
- IAL Sao Paulo, Brazil
- WHO Collaborating Centre for Reference and Research on Influenza, Australia
- Duke-NUS Emerging Infectious Disease Programme, Singapore
- University of Melbourne, Australia
- Global Initiative for Sharing All Influenza Data 
- Centers for Disease Control (CDC) Atlanta, USA
- Research and Policy for Infectious Disease Dynamics (RAPIDD)
- Health Protection Agency of Canada
- Friedrich Loeffler Institute, Germany
- NEXTFLU T. Bedford and R. Neher


... and thank all of you!



Fishing for Flu Mutations since 2009!

Section IV

FULL REFERENCE FOR BROWSING FLUSURVER RESULTS


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The main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidate mutations for further research and should ideally be combined with experimental testing and verification of any predicted phenotypes. Importantly, any direct diagnostic use, assumed severity or recommendation on patient treatment should not be based solely on these computational predictions. Our curated reference sequences used for annotation transfer of equivalent mutations are mainly comprised of strains that recently infected humans. Therefore, the usage scenario that will give the most fruitful and reliable results are current surveillance sequences with very close relation to used vaccine strains, including some candidates for avian flu and novel reassortant swine flu H3N2v. Please take a look at the [Frequently Asked Questions](#) and [Tutorial](#) if you are new to FluSurver. There is also a [special note for using FluSurver results in publications](#).

Result for comparison with reference selection: H7N7_Human_2003_Netherlands219 [Back to Reference Selection](#)

Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
HA_A/Anhui/1/2013_138739	HA A/Netherlands/219/2003(H7N7) find closest related sequences	96.071	98.418	22	V18I , S20I , V63I , T137A , T150A , D190S , I195V , G202V , T205A , I218V , Q242L , I252M , E286G , N314D , E328R , R347G , T419N , R423K , M436I , N464D , I515M , A550V show in structure
HA_A/Shanghai/1/2013_138737	HA A/Netherlands/219/2003(H7N7) find closest related sequences	96.071	98.418	22	V18I , S20I , V63I , T137A , T150A , A153S , D190N , I195V , T205A , I218V , P237T , I252M , E286G , N292D , H299Y , N314D , E328R , R347G , R423K , M436I , N464D , I515M show in structure
HA_A/Shanghai/2/2013_138738	HA A/Netherlands/219/2003(H7N7) find closest related sequences	96.071	98.418	22	V18I , S20I , V63I , T137A , T150A , D190S , I195V , G202V , T205A , I218V , Q242L , I252M , E286G , N314D , E328R , R347G , T419N , R423K , M436I , N464D , I515M , A550V show in structure

[Right-click here to save/download mutation report table for archiving or import to Excel](#)

[Back to Reference Selection](#)

For each of the query sequences, there are six columns of information generated in the result summary page. From here, users may proceed to look at the query sequence's alignment to the reference strain, get more information on each mutation, generate a structural view of all the mutations in the query sequence ("show in structure") or view a summary of the mutations in a table to download (at end of results).

More details on browsing the results further can be found online at:
<http://flusurver.bii.a-star.edu.sg/help/tutorialpage.html#part2>

FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

The main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidate mutations for further research and should ideally be combined with experimental testing and verification of any predicted phenotypes. Importantly, any direct diagnostic use, assumed severity or recommendation on patient treatment should not be based solely on these computational predictions. Our curated reference sequences used for annotation transfer of equivalent mutations are mainly comprised of strains that recently infected humans. Therefore, the usage scenario that will give the most fruitful and reliable results are current surveillance sequences with very close relation to used vaccine strains, including some candidates for avian flu and novel reassortant swine flu H3N2v. Please take a look at the [Frequently Asked Questions](#) and [Tutorial](#) if you are new to FluSurver. There is also a [special note for using FluSurver results in publications](#).

FluSurver Result for comparison with reference selection: auto [Back to Reference Selection](#)

Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
A/GUNMA/74/2014 EPI_ISL_159395 2014-04-22 A/H1N1 Japan	HA A/California /07/2009(H1N1) find closest related sequences	98.053	<u>99.823</u>	11	P100S , D114H , K180Q , S202I , S220T , A273T , K300E , I338V , E391K , S468N , E516K show in structure
A/HIROSHIMA-C/26/2014 EPI_ISL_162078 2014-05-30 A/H1N1	NA A/California /07/2009(H1N1) find closest related sequences	97.655	<u>100.000</u>	11	I34V , L40I , N44S , N200S , V241I , N248D , H275Y , I321V , N369K , N386K , K432E show in structure NA drug sensitivity positions: 33_0_1 Reduced sensitivity or resistance!
A/HIROSHIMA/57/2014 EPI_ISL_160499 2014-05-19 A/H1N1	HA A/California /07/2009(H1N1) find closest related sequences	97.880	<u>100.000</u>	12	I4T , P100S , D114H , K180Q , S202I , S220T , A273I , K300E , I338V , E391K , S468H , E516K show in structure

Tachyon 11364 hits
Time: 15.854s
Length: 469 Views: Plain | Jalview | Raw Downloads: FASTA | MAFFT | Raw Params: internal, NCBI NR-24070523 sequer

GenBank FASTA BLINK ANIME PhyloPDB UniProt

Hit Seq Filter: Databases: All PDB RefSeq SwissProt/UniProtKB Limit: 250 1000 None

Rank	Score	Hit Seq	Filter	Databases	Limit
1	1.0	gi 251748198 gb ACT10319.1	neuraminidase [Influenza A virus (A/Hong Kong/2369/2009(H1N1))]	gi 254548844 gb ACT67256.1	neuraminidase, partial [Influenza A virus (A/Perth/262/2009(H1N1))]
2	0.9914	gi 300117086 gb ADJ67981.1	neuraminidase, partial [Influenza A virus (A/Hong Kong/FFD/2009(H1N1))]	gi 307071058 gb ADN24730.1	neuraminidase [Influenza A virus (A/Ontario/25913/2009(H1N1))]
3	0.98718	gi 326320245 gb ADZ53143.1	neuraminidase [Influenza A virus (A/Hong Kong/FFD/2009(H1N1))]	gi 294544523 gb ADF10059.1	neuraminidase [Influenza A virus (A/Ontario/10016/2009(H1N1))]
4	0.98294	gi 291219999 gb ADD84685.1	neuraminidase [Influenza A virus (A/Mexico/InDRE797/2010(H1N1))]	gi 294544441 gb ADF10049.1	neuraminidase [Influenza A virus (A/Ontario/10016/2009(H1N1))]
5	0.97872	gi 251833646 gb ACT22016.1	neuraminidase [Influenza A virus (A/Osaka/180/2009(H1N1))]	gi 299781814 gb ADJ40477.1	neuraminidase [Influenza A virus (A/Netherlands/2445b/2009(H1N1))]
6	0.97872	gi 294544923 gb ADF10109.1	neuraminidase [Influenza A virus (A/Ontario/25913/2009(H1N1))]	gi 325451706 gb ADZ13521.1	neuraminidase [Influenza A virus (A/Lyon/48_49/2009(H1N1))]
7	0.97872	gi 294544441 gb ADF10049.1	neuraminidase [Influenza A virus (A/Ontario/10016/2009(H1N1))]	gi 294611208 gb ADF27356.1	neuraminidase [Influenza A virus (A/Taiwan/6663/2009(H1N1))]
8	0.97872	gi 299781814 gb ADJ40477.1	neuraminidase [Influenza A virus (A/Netherlands/2445b/2009(H1N1))]	gi 326320207 gb ADZ53124.1	neuraminidase [Influenza A virus (A/Hong Kong/23369/2009(H1N1))]
9	0.97872	gi 325451706 gb ADZ13521.1	neuraminidase [Influenza A virus (A/Lyon/48_49/2009(H1N1))]	gi 425786025 gb AFX96841.1	neuraminidase [Influenza A virus (A/Viet Nam/12032005/2009(H1N1))]
10	0.97872	gi 294611208 gb ADF27356.1	neuraminidase [Influenza A virus (A/Taiwan/6663/2009(H1N1))]	gi 316986112 gb ADU76312.1	neuraminidase [Influenza A virus (A/England/00380009/2009(H1N1))]
11	0.97872	gi 326320207 gb ADZ53124.1	neuraminidase [Influenza A virus (A/Hong Kong/23369/2009(H1N1))]	gi 316986114 gb ADU76313.1	neuraminidase [Influenza A virus (A/England/00380009/2009(H1N1))]
12	0.97872	gi 425786025 gb AFX96841.1	neuraminidase [Influenza A virus (A/Viet Nam/12032005/2009(H1N1))]	gi 295147036 gb ADP80503.1	neuraminidase [Influenza A virus (A/Seoul/1870/2009(H1N1))]
13	0.97872	gi 316986112 gb ADU76312.1	neuraminidase [Influenza A virus (A/England/00380009/2009(H1N1))]	gi 307071034 gb ADN24718.1	neuraminidase, partial [Influenza A virus (A/Canada-AB/RV2828/2009(H1N1))]
14	0.97872	gi 295147036 gb ADP80503.1	neuraminidase [Influenza A virus (A/Seoul/1870/2009(H1N1))]	gi 326320021 gb ADZ53124.1	neuraminidase [Influenza A virus (A/Hong Kong/23369/2009(H1N1))]
15	0.97872	gi 307071034 gb ADN24718.1	neuraminidase, partial [Influenza A virus (A/Canada-AB/RV2828/2009(H1N1))]	gi 326320021 gb ADZ53124.1	neuraminidase [Influenza A virus (A/Hong Kong/23369/2009(H1N1))]
16	0.97872	gi 326320021 gb ADZ53124.1	neuraminidase [Influenza A virus (A/Hong Kong/23369/2009(H1N1))]	gi 326320021 gb ADZ53124.1	neuraminidase [Influenza A virus (A/Hong Kong/23369/2009(H1N1))]

Find closest reference strain and database hits!

FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

The main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidate mutations for further research and should ideally be combined with experimental testing and verification of any predicted phenotypes. Importantly, any direct diagnostic use, assumed severity or recommendation on patient treatment should not be based solely on these computational predictions. Our curated reference sequences used for annotation transfer of equivalent mutations are mainly comprised of strains that recently infected humans. Therefore, the usage scenario that will give the most fruitful and reliable results are current surveillance sequences with very close relation to used vaccine strains, including some candidates for avian flu and novel reassortant swine flu H3N2v. Please take a look at the [Frequently Asked Questions](#) and [Tutorial](#) if you are new to FluSurver. There is also a [special note for using FluSurver results in publications](#).

FluSurver Result for comparison with reference selection: auto [Back to Reference Selection](#)

Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
A/GUNMA/74/2014 EPI_ISL_159395 2014-04-22 A/H1N1 Japan	HA_A/California /07/2009(H1N1) find closest related sequences	98.053	99.823	11	P100S , D114N , K180Q , S202T , S220T , A273T , K300E , I338V , E391K , S468N , E516K show in structure
A/HIROSHIMA-C/26/2014 NA_HIN1_Human_2009_California07	NA_A/California /07/2009(H1N1)	99.825	100.000	11	I34V , L40I , N44S , N200S , V241I , N248D , H275Y , I321V , N369K , H386K , K432E show in structure NA drug sensitivity positions: 33_0_1 Reduced sensitivity or resistance!
>NA_HIN1_Human_2009_California07 gi 229396469 gb ACQ63272 neuraminidase[Influenza A virus (A/California/07/2009(H1N1))] USA20090409 Length = 469 Score = 999 bits (2559), Expect = 0.0 Identities = 466/469 (99%), Positives = 469/469 (100%) Frame = +3 Query: 21 MNPNQKIITIGSVCHTIGMANLLIQIGNIISIWISHSIQLGNQNIETCNQSVITYENNT 200 MNPNQKIITIGSVCHTIGMANLLIQIGNIISIWISHSIQLGNQNIETCNQSVITYENNT Sbjct: 1 MNPNQKIITIGSVCHTIGMANLLIQIGNIISIWISHSIQLGNQNIETCNQSVITYENNT 60 Query: 201 VVNQTYVNIISNTMFAAGGSVSVSKLAGNSSLCPVSGHAIYSKDNSIRIGSRGDFVFIREP 380 VVNQTYVNIISNTMFAAGGSVSVSKLAGNSSLCPVSGHAIYSKDNSIRIGSRGDFVFIREP Sbjct: 61 VVNQTYVNIISNTMFAAGGSVSVSKLAGNSSLCPVSGHAIYSKDNSVRIGSRGDFVFIREP 120 Query: 381 FISCSPLECRFTFFLTQALLNDRKHSNGTIKDRSPYRTLMSCP IGEVFPSPYNSRFESVAWS 560 FISCSPLECRFTFFLTQALLNDRKHSNGTIKDRSPYRTLMSCP IGEVFPSPYNSRFESVAWS Sbjct: 121 FISCSPLECRFTFFLTQALLNDRKHSNGTIKDRSPYRTLMSCP IGEVFPSPYNSRFESVAWS 180 Query: 561 ASACHDGINWLTIGISGPDNGAVAVLKYNGIITDTIKSWNNILRTQESACVNGSCFT 740 ASACHDGINWLTIGISGPDNGAVAVLKYNGIITDTIKSWNNILRTQESACVNGSCFT Sbjct: 181 ASACHDGINWLTIGISGPDNGAVAVLKYNGIITDTIKSWNNILRTQESACVNGSCFT 240 Query: 741 VHTDGPSDGQASTYKIFRIEKGKIVSEVMNAPNYYEECSYDSEITCVRDNNVHGSN 920 VHTDGPSDGQASTYKIFRIEKGKIVSEVMNAPNYYEECSYDSEITCVRDNNVHGSN Sbjct: 241 VHTDGPSDGQASTYKIFRIEKGKIVSEVMNAPNYYEECSYDSEITCVRDNNVHGSN 300 Query: 921 RFWVSNQMLEYQIGYICSGIFGDNFRPNDKTSOCPVSSNGANGVKGFSFKYGNQWVIG 1100 RFWVSNQMLEYQIGYICSGIFGDNFRPNDKTSOCPVSSNGANGVKGFSFKYGNQWVIG Sbjct: 301 RFWVSNQMLEYQIGYICSGIFGDNFRPNDKTSOCPVSSNGANGVKGFSFKYGNQWVIG 360 Query: 1101 RTKSISSRNQFENIUDPNQWTGTDNNFNIKQDIVGNEWSGYSGSFVQPELTGLDCIRP 1280 RTKSISSRNQFENIUDPNQWTGTDNNFNIKQDIVGNEWSGYSGSFVQPELTGLDCIRP	99.823	100.000	12	I4T , P100S , D114N , K180Q , S202T , S220T , A273T , K300E , I338V , E391K , S468N , E516K show in structure	

Check alignment to reference hit!

FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

Color	Interest level	Remarks
Black	0 (least significant)	No known effects
Green	0	Common
Blue	1	At site of interaction
Magenta	2	Addition or removal of N-glycosylation sites
Orange	2	At site known to be involved in drug-binding, alter host-specificity.
Red	3 (most significant)	At site known to alter virulence, cause drug resistance, reverses premature STOP codon in PB1-F2.

... mutations for further research and should ideally be combined with experimental testing
 recommendation on patient treatment should not be based solely on these computational
 prised of strains that recently infected humans. Therefore, the usage scenario that will
 on to used vaccine strains, including some candidates for avian flu and novel
 w to FluSurver. There is also a [special note for using FluSurver results in publications](#).

selection: auto

I34V, N44S, S82P, N200S, V241I, N248D, H275Y, I321V, N369K,
 N386K, K432E, N449K
[show in structure](#)

12

NA drug sensitivity positions:
 33_0_1
 Reduced sensitivity or resistance!

P100S, D114N, K180Q, S202T, S220T, A273T, K300E, I338V,
 E391K, S468N, E516K
[show in structure](#)

11

I34V, L40I, N44S, V116I, N189S, N200S, V241I, N248D, G249R,
 R257K, H275Y, I321V, N369K, N386S, I389R, K432E
[show in structure](#)

16

NA drug sensitivity positions:
 32_1_1
 Reduced sensitivity or resistance!

[link for archiving or import to Excel](#)

tion

III), Singapore
 tomica (INMEGEN), Mexico

FluSurver

Check list of mutations!

FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidates for further research and should ideally be combined with experimental testing or recommendation on patient treatment should not be based solely on these computational results. The results are mainly comprised of strains that recently infected humans. Therefore, the usage scenario that will be most useful is for those who have a close relation to used vaccine strains, including some candidates for avian flu and novel strains. If you are new to FluSurver, there is also a [special note for using FluSurver results in publications](#).

With reference selection: auto

12	<p>I34V, N44S, S82P, N200S, V241I, N241D, H275Y, I321V, N369K, N386K, K432E, N449K</p> <p>show in structure</p> <p>NA drug sensitivity positions: 33_0_1 Reduced sensitivity or resistance!</p>
11	<p>P100S, D114N, K180Q, S202T, S220T, A273T, K300E, I338V, E391K, S468N, E516K</p> <p>show in structure</p>
16	<p>I34V, L40I, N44S, Y116I, N189S, N200S, V241I, N248D, G249R, R257K, H275Y, I321V, N369K, N386S, I389R, K432E</p> <p>show in structure</p> <p>NA drug sensitivity positions: 32_1_1 Reduced sensitivity or resistance!</p>

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Genetics Institute (IGI), Singapore
 Instituto de Diagnóstico y Referencia Epidemiológica (INDEGEN), Medicina Genómica (INMEGEN), Mexico

FluSurver

NA H275Y

Key to alternative position numbering:

275	FluSurver numbering (absolute as in 2009 H1N1 pandemic)
274	Classical H3N2 strain numbering
275	Classical H1N1 strain numbering

Chosen reference: NA_H1N1_Human_2009_California07
 Position in reference: 275
 AA in reference: H
 AA in query: Y

Mutation NA H275Y already occurred 197 times (2.48% of all samples with NA sequence) in 27 countries. The first strain with this mutation, collected in May 2009, was A/Mexico city/CIA10/2009(H1N1). The mutation most recently occurred in strain A/Rio Grande Do Sul/887/2012(H1N1), collected in June 2012. ([see map](#))

[See detailed global statistics for this position](#)

A mutation at the position equivalent to NA 275 has been reported in the literature to be related to [mild drug resistance](#) and [strong drug resistance](#).

A combination of mutations including the position equivalent to NA 275 has been reported in the literature to be related to [strong drug resistance](#).

As seen in resolved structures of proteins from related strains, the NA position equivalent to your mutation is involved in: [- drug binding](#)

[See all interactions for this position](#)

Based on FoldX structural stability calculations H275Y is predicted to be strongly destabilizing which could represent a fitness disadvantage (ddG = 4.55 kcal/mol)

[PubMed search for this mutation \(including alternative numbering\)](#)

Click on mutation of interest for details!

FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidates

NA H275Y

Key to alternative position numbering:

275	FluSurver numbering (absolute as in 2009 H1N1 pandemic)
274	Classical H3N2 strain numbering
275	Classical H1N1 strain numbering

Chosen reference: NA_H1N1_Human_2009_California07
 Position in reference: 275
 AA in reference: H
 AA in query: Y

Mutation NA H275Y already occurred 197 times (2.48% of all samples with NA sequence) in 27 countries. The first strain with this mutation, collected in May 2009, was A/Mexico city/CIA10/2009(H1N1). The mutation most recently occurred in strain A/Rio Grande Do Sul/887/2012(H1N1), collected in June 2012. [\(see map\)](#)

[See detailed global statistics for this position](#)

A mutation at the position equivalent to NA 275 has been reported in the literature to be related to [mild drug resistance and strong drug resistance](#).

A combination of mutations including the position equivalent to NA 275 has been reported in the literature to be related to [strong drug resistance](#).

As seen in resolved structures of proteins from related strains, the NA position equivalent to your mutation is involved in:
 - [drug binding](#)

[See all interactions for this position](#)

Based on FoldX structural stability calculations H275Y is predicted to be strongly destabilizing which could represent a fitness disadvantage (ddG = 4.55 kcal/mol)

[PubMed search for this mutation \(including alternative numbering\)](#)

Map of cities with the NA H275Y mutation

The city with **red** label indicates first appearance of the mutation. City with **yellow** label indicate later appearance of the mutation. The city with the most recent appearance of the mutation has the **green** label. Number in the label indicates frequency of occurrence of the mutation in that city. A dot in the label indicates that there are 10 or more occurrences in that city.

As there are too many cities with viral isolates carrying this mutation, cities with number of occurrences below 2 are not labeled in the map above.

Map of countries with the NA H275Y mutation

Number of occurrences

Countries without data: [grey box] 1 [light red box] [pink box] [red box] 44

Region	# Occ.	Date of collection(YYYYMMDD)
Sheffield	1	20110105
Catalonia	1	20091126
North Carolina	2	20091016
Kurume	35	20100118
Thailand	4	20100104
Sydney	8	20100916
Denmark	2	20090809
Seoul	4	20091100
Kyoto	4	20091204

Check for geographic occurrence pattern!

FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidates for further research and should ideally be combined with experimental testing of severity or recommendation on patient treatment should not be based solely on these computational results. The database is mainly comprised of strains that recently infected humans. Therefore, the usage scenario that will be most useful is to identify mutations that have a close relation to used vaccine strains, including some candidates for avian flu and novel mutations. If you are new to FluSurver, there is also a [special note for using FluSurver results in publications](#).

With reference selection: auto [Back to Reference Selection](#)

NA H275Y

Key to alternative position numbering:

275	FluSurver numbering (absolute as in 2009 H1N1 pandemic)
274	Classical H3N2 strain numbering
275	Classical H1N1 strain numbering

Chosen reference: NA_H1N1_Human_2009_California07
Position in reference: 275
AA in reference: H
AA in query: Y

Mutation NA H275Y already occurred 197 times (2.48% of all samples with NA sequence) in 27 countries. The first strain with this mutation, collected in May 2009, was A/Mexico city/CIA10/2009(H1N1). The mutation most recently occurred in strain A/Rio Grande Do Sul/887/2012(H1N1), collected in June 2012.

[See detailed global statistics for this position](#)

A mutation at the position equivalent to NA 275 has been reported in the literature to be related to [mild drug resistance](#) and [strong drug resistance](#).

A combination of mutations including the position equivalent to NA 275 has been reported in the literature to be related to [strong drug resistance](#).

As seen in resolved structures of proteins from related strains, the NA position equivalent to your mutation is involved in:

- [drug binding](#)

[See all interactions for this position](#)

Based on FoldX structural stability calculations H275Y is predicted to be strongly destabilizing which could represent a fitness disadvantage (ddG = 4.55 kcal/mol)

[PubMed search for this mutation \(including alternative numbering\)](#)

Mutation statistics for NA at position 275

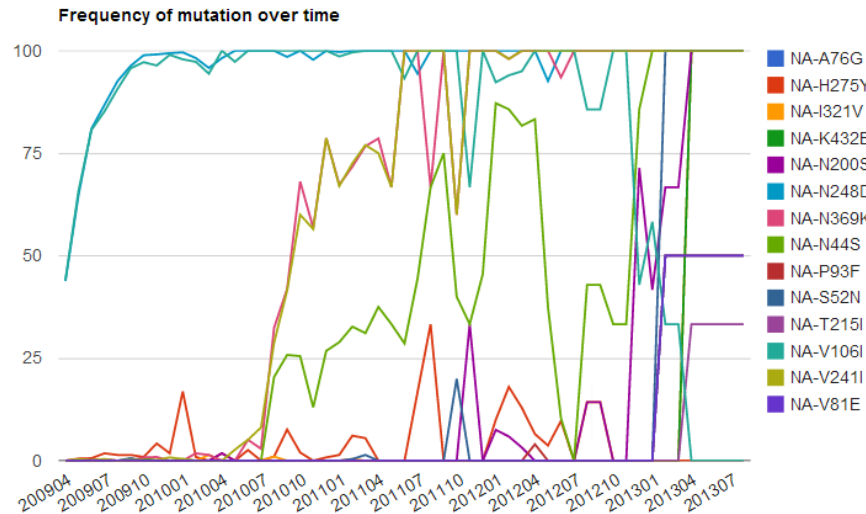
AA	# Occ.	%	Geo. Distribution	Co-occurrences
X	8	0.10		
Y	197	2.48	(geo)	(co-occur)
-	13	0.16		
H	7740	97.26	reference aa	reference aa
ALL	7958	100.00		

Sequences were compared to reference strain A/California/07/2009(H1N1) [AGM53851](#).
Last updated on Sep 02nd 2013 by Raphael Tze Chuen Lee

Above are the occurrences of all amino acid residues at position 275 in NA. For statistics of all position in NA in this subtype click here: [H1N1_NA_mutations_table](#)

Check if there are other mutations at same position!

FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier



The line chart above shows the frequency of mutations in NA over time. Only mutations that were present in more than 30 percent of circulating strains in any of the months were represented in the line chart. Please note that the frequency of mutation in the most recent months tends to fluctuate as the database is still being populated.

Accession	Protein	Strain	WildtypeAA	Position	MutatedAA	Frequency	Date of collection(YYYYMMDD)	Remarks
ACY03001	NA	(A/Italy/137/2009(H1N1))	M	1	L	1	20090700	(co-occur)
ACU88926	NA	(A/Poland/303/2009(H1N1))	N	2	I	4 (geo)	20090710	(co-occur)
AFB77814	NA	(A/Kenya/071/2010(H1N1))	N	2	H	2 (geo)	20101129	(co-occur)
ACR08462	NA	(A/New York/3099/2009(H1N1))	N	2	S	1	20090429	(co-occur)
ACZ96222	NA	(A/Texas/44313703/2009(H1N1))	P	3	S	2 (geo)	20090831	(co-occur)
AGQ02440	NA	(A/Pernambuco/120924/2012(H1N1))	P	3	Q	1	20121002	(co-occur)
ACX566271	NA	(A/Lorestan/1599/2009(H1N1))	N	4	K	5 (geo)	20090727	(co-occur)
ADR32078	NA	(A/Jiangsu/S62/2009(H1N1))	N	4	T	5 (geo)	20091110	(co-occur)
AEH94621	NA	(A/Hualong/SWL1313/2009(H1N1))	N	4	I	2 (geo)	20091118	(co-occur)
AGI54909	NA	(A/South Carolina/29/2009(H1N1))	Q	5	R	3 (geo)	20090723	(co-occur)
ADK90313	NA	(A/Lisboa/60/2009(H1N1))	Q	5	H	2 (geo)	20090914	(co-occur)
ACY30121	NA	(A/Italy/161/2009(H1N1))	Q	5	K	2 (geo)	20090700	(co-occur)
ACY46355	NA	(A/Singapore/ON975/2009(H1N1))	Q	5	P	3 (geo)	20090706	(co-occur)
ADD84600	NA	(A/Xian/Q01/2009(H1N1))	K	6	N	7 (geo)	20090903	(co-occur)
ADG42646	NA	(A/California/VRDL89/2009(H1N1))	K	6	R	4 (geo)	20091017	(co-occur)
ADV17285	NA	(A/Thailand/CU-B2357/2010(H1N1))	K	6	E	3 (geo)	20100420	(co-occur)
ADX96969	NA	(A/Lima/WRAIR8689F/2009(H1N1))	K	6	M	1	20090627	(co-occur)
ADK87312	NA	(A/Qingdao/1215/2009(H1N1))	K	6	T	1	20090912	(co-occur)
AFB77814	NA	(A/Kenya/071/2010(H1N1))	I	7	V	1	20101129	(co-occur)

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ideally be combined with experimental testing
not be based solely on these computational
ans. Therefore, the usage scenario that will
me candidates for avian flu and novel
e for using FluSurver results in publications.

ce Selection

les with NA
cted in May
recently
une 2012.

S, V241I, N248D, H275Y, I321V, N369K,
K, K432E, I449K
how in structure

sensitivity positions:
33, 0, 1
sensitivity or resistance!

S202T, S220T, A273T, K300E, I338V,
K, S468N, E516K
how in structure

N189S, N200S, V241I, N248D, G249R,
I, V, N369K, N386S, I389R, K432E
how in structure

g sensitivity positions:
32, 1, 1
sensitivity or resistance!

Mutation statistics for NA at position 275

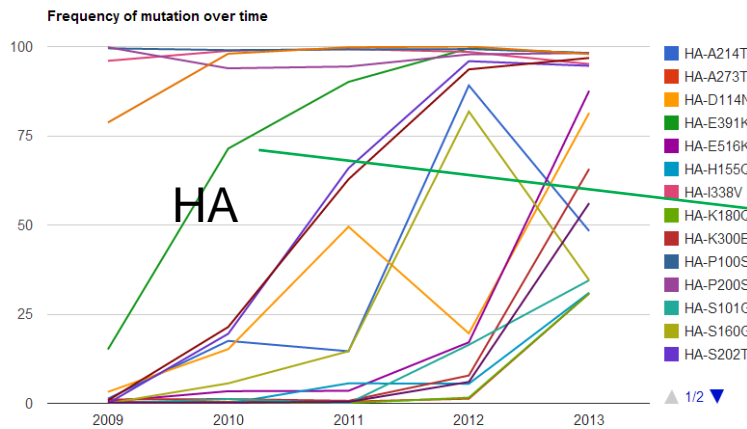
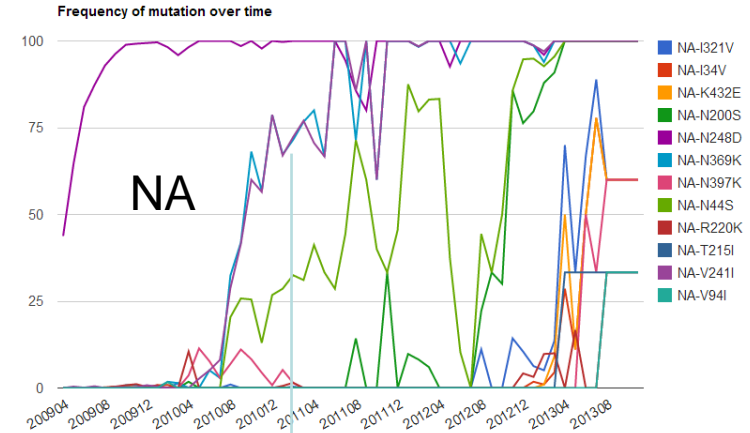
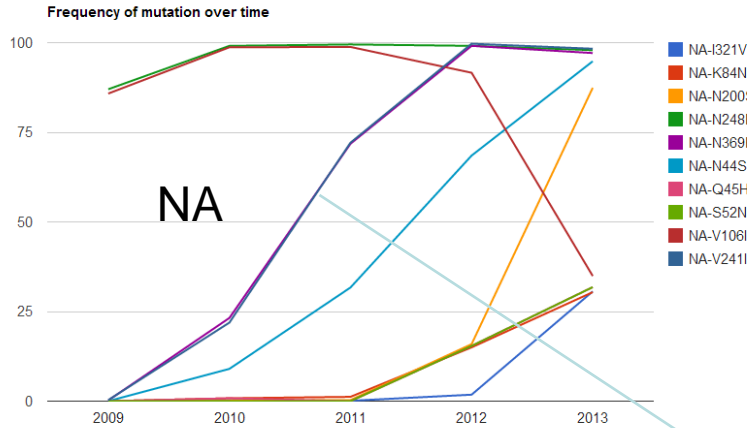
AA	# Occ.	%	Geo Distribution	Co-occurrences
X	8	0.10		
Y	197	2.48	(geo)	(co-occur)
-	13	0.16		
H	7740	97.26	reference aa	reference aa
ALL	7958	100.00		

Sequences were compared to reference strain A/California/07/2009(H1N1) [AGM53851](#).
Last updated on Sep 02nd 2013 by Raphael Tze Chuen Lee

Above are the occurrences of all amino acid residues at position 275 in NA. For statistics of all position
in NA in this subtype click here: [H1N1_NA_mutations_table](#)

Check for temporal mutation frequency changes!

Mutation temporal frequency pattern highlights relevant changes



New H275Y permissive mutations

Hurt *et al.* J Infect Dis. 2012 Jul 15;206(2):148-57.

Butler *et al.* PLoS Pathog. 2014 Apr 3;10(4):e1004065.

Change in pH-dependency of fusion

Maurer-Stroh *et al.* PLoS Curr. 2010 Jun 1;2:RRN1162.

Cotter *et al.* PLoS Pathog. 2014 Jan;10(1):e1003831.

Example H1N1pdm in FluSurver

FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

Version: 0.9.0.0 Date: 03/21/2016

Country	Strain	PB2	PB1	PB1-F2	PA	HA	NP	NA	M1	M2	NS1	NS2	Date of collection(YYYYMMDD)
Taiwan	(A/Taiwan/7338/2009(H1N1))	-	-	-	-	A26T P100S P200S S220T I338V E391K	-	V108I N248D H275Y	-	-	-	-	20091105
Japan	(A/Kurume/R8/2010(H1N1))	-	-	-	-	-	-	V53A V80M S82P V108I N248D H275Y Y282H	-	-	-	-	20100118
South Korea	(A/Daejeon/1871/2009(H1N1))	-	-	-	-	K39R N73S P100S S145P G172E P200S S220T I338V	-	A86T V108I I117M N248D H275Y	-	-	-	-	20091215
United Kingdom	(A/England/94840152/2009(H1N1))	-	-	-	-	P100S P200S S220T I338V	-	V108I N248D H275Y E462K	-	-	-	-	20091119
Japan	(A/Kurume/N8/2010(H1N1))	-	-	-	-	-	-	V80M S82P V108I N248D H275Y	-	-	-	-	20100118
United Kingdom	(A/England/00380015/2009(H1N1))	-	-	-	-	P100S P200S S220T I338V	-	V108I N248D H275Y E462K	-	-	-	-	20091117
USA	(A/California/21/2012(H1N1))	-	-	-	-	S88T P100S K136N S160G P200S S202T A214T S220T D239G N277D I338V F347L E391K S468N V537A	-	A20V G41R N44S V108I V241I N248D H275Y N369K	V80I	S13N	-	-	20120220
Viet Nam	(A/Viet Nam/835/2009(H1N1))	-	-	-	P224S	P100S P200S S220T I338V	V100I	V108I N248D H275Y	-	-	L115F I123V	-	20090727
Mexico	(A/Mexico/INDRE3354/2012(H1N1))	-	-	-	-	S88T P100S S160G P200S S202T A214T S220T N277D I338V E391K S468N V537A	-	G41R N44S S95I V108I V241I N248D H275Y N369K	-	-	-	-	20120208
Japan	(A/Kurume/N1/2010(H1N1))	-	-	-	-	-	-	V80M S82P V108I N248D H275Y	-	-	-	-	20100118
USA	(A/Bethesda/NIH100-D14/2009(H1N1))	R591Q	K736G	-	V14I P224S K716Q	A15T P100S P200S S220T I338V E391K F432L	V100I V270I V444I	V108I N248D H275Y	-	-	I123V	-	20091105
Japan	(A/Kurume/L19/2010(H1N1))	-	-	-	-	-	-	V80M S82P V108I N248D H275Y	-	-	-	-	20100118
China	(A/Haishu/SWL110/2010(H1N1))	-	-	-	-	P100S S179N P200S S220T I338V	-	V108I N248D H275Y	-	-	-	-	20100104
Germany	(A/Munich/INS541/2011(H1N1))	R299K V344M I354L N456S	V845I	-	P224S N321K I330V M548I	P100S D114N P200S S202T S220T I338V E391K S468N	V100I	V108I V241I N248D K280R H275Y I321V N369K	V80I	-	I123V	-	20110218
Canada	(A/Canada-AB/RV2828/2009(H1N1))	-	M92V N158S	-	P224S	P100S P200S S220T T258I I338V	-	V108I N248D H275Y V394I	-	-	-	-	20090804
USA	(A/Texas/33/2012(H1N1))	-	-	-	-	S88T P100S S160G P200S S202T A214T S220T N277D I338V E391K S468N V537A	-	G41R N44S V108I L127W V241I N248D H275Y N369K	V80I	S13N	-	-	20120312
USA	(A/Texas/49/2012(H1N1))	-	-	-	-	S88T P100S S160G P200S S202T A214T S220T N277D I338V E391K S468N V537A	-	G41R N44S S95N V108I V241I N248D H275Y N369K	V80I	S13N	-	-	20120316
United Kingdom	(A/England/00380020/2009(H1N1))	-	-	-	-	P100S P200S S220T I338V	-	V108I N248D H275Y E462K	-	-	-	-	20091120
USA	(A/North Carolina/59/2009(H1N1))	-	-	-	-	P100S V169I P200S S220T P288Q I312V I338V	-	V108I V234I N248D H275Y	-	P25T	-	-	20091107
Spain	(A/Catalonia/NS7362/2009(H1N1))	-	-	-	-	P100S S179N P200S S220T T249A I338V G411D	-	V108I N248D H275Y	-	-	-	-	20091126

A mutation at the position equivalent to NA 275 has been reported in the literature to be related to **mild drug resistance and strong drug resistance**.

A combination of mutations including the position equivalent to NA 275 has been reported in the literature to be related to **strong drug resistance**.

As seen in resolved structures of proteins from related strains, the NA position equivalent to your mutation is involved in:
- **drug binding**

[See all interactions for this position](#)

Based on FoldX structural stability calculations H275Y is predicted to be strongly destabilizing which could represent a fitness disadvantage (ddG = 4.55 kcal/mol)

[PubMed search for this mutation \(including alternative numbering\)](#)

100.000 16

NA drug sensitivity position: **32, 1, 1**
Reduced sensitivity or resistance!

Mutation statistics for NA at position 275

AA	# Occ.	%	Geo Distribution	Co-occurrences
X	8	0.10		
Y	197	2.48	(geo)	(co-occur)
-	13	0.16		
H	7740	97.26	reference aa	reference aa
ALL	7958	100.00		

Sequences were compared to reference strain A/California/07/2009(H1N1) [AGM53851](#).
Last updated on Sep 02nd 2013 by Raphael Tze Chuen Lee

Above are the occurrences of all amino acid residues at position 275 in NA. For statistics of all position in NA in this subtype click here: [H1N1 NA mutations table](#)

Check for co-occurring mutations!

FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

NA H275Y

Key to alternative position numbering:

275	FluSurver numbering (absolute as in 2009 H1N1 pandemic)
274	Classical H3N2 strain numbering
275	Classical H1N1 strain numbering

Chosen reference: NA_H1N1_Human_2009_California07
 Position in reference: 275
 AA in reference: H
 AA in query: Y

Mutation NA H275Y already occurred 197 times (2.48% of all samples with NA sequence) in 27 countries. The first strain with this mutation, collected in May 2009, was A/Mexico city/CIA10/2009(H1N1). The mutation most recently occurred in strain A/Rio Grande Do Sul/887/2012(H1N1), collected in June 2012. ([see map](#))

[See detailed global statistics for this position](#)

A mutation at the position equivalent to NA 275 has been reported in the literature to be related to [mild drug resistance and strong drug resistance](#).

A combination of mutations including the position equivalent to NA 275 has been reported in the literature to be related to [strong drug resistance](#).

As seen in resolved structures of proteins from related strains, the NA position equivalent to your mutation is involved in: [- drug binding](#)

[See all interactions for this position](#)

Based on FoldX structural stability calculations H275Y is predicted to be strongly destabilizing which could represent a fitness disadvantage (ddG = 4.55 kcal/mol)

[PubMed search for this mutation \(including alternative numbering\)](#)

Known effect(s) of mutations at position equivalent to your mutation:

Protein: NA
 Influenza type: Human H1N1 (2006)
 Mutation (as in paper): H274Y
 neutral AA: H
 neg. eff. AA: Y
 Effect: strong drug resistance (drug name in comments)

Comment:
 Tamiflu but not Relenza resistance (Table 3)
[Literature reference](#)
 (Mutation H274Y in the paper is at an equivalent position of the mutation in your query)

[show in structure](#)

100.000 12 NA drug sensitivity positions:

NCBI Resources How To

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 National Institutes of Health
 PubMed
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Display Settings: Abstract

Antimicrob Agents Chemother. 2008 Sep;52(9):3284-92. doi: 10.1128/AAC.00555-08. Epub 2008 Jul 14.

Surveillance for neuraminidase inhibitor resistance among human influenza A and B viruses circulating worldwide from 2004 to 2008.

Sheu TG, Devde VM, Okomo-Adhiambo M, Garten RJ, Xu X, Bright RA, Butler EN, Wallis TR, Klimov AI, Gubareva LV. Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333, USA.

[mutation report table for archiving or import to Excel](#)

PubMed.gov
 US National Library of Medicine
 National Institutes of Health
 PubMed
 influenza AND (neuraminidase OR NA) AND (H275Y OR H274Y)
 RSS Save search Advanced

Show additional filters Display Settings: Summary, 20 per page. Sorted by Pub Date Send to: ☺

Article types
 Clinical Trial
 Review
 More ...

Text availability
 Abstract available
 Free full text available
 Full text available

Publication dates
 5 years
 10 years
 Custom range...

Results: 1 to 20 of 239

1. [Neuraminidase inhibitor susceptibility surveillance of influenza viruses circulating worldwide during the 2011 Southern Hemisphere season.](#)
 Okomo-Adhiambo M, Sleeman K, Lysén C, Nguyen HT, Xu X, Li Y, Klimov AI, Gubareva LV. *Influenza Other Respi Viruses*. 2013 Sep;7(5):645-58. doi: 10.1111/irv.12113. Epub 2013 Apr 10. PMID: 23575174 [PubMed - in process] [Related citations](#)

2. [Functional and structural analysis of influenza virus neuraminidase n3 offers further insight into the mechanisms of oseltamivir resistance.](#)
 Li Q, Qi J, Wu Y, Kiyota H, Tanaka K, Suhara Y, Ohnri H, Suzuki Y, Vavricka CJ, Gao GF. *J Virol*. 2013 Sep;87(18):10016-24. doi: 10.1128/JVI.01129-13. Epub 2013 Jul 3. PMID: 23824808 [PubMed - in process] [Related citations](#)

Check for associated literature!

FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting changes

NA H275Y

Key to alternative position numbering:

275	FluSurver numbering (absolute as in 2009 H1N1 pandemic)
274	Classical H3N2 strain numbering
275	Classical H1N1 strain numbering

Chosen reference: NA_H1N1_Human_2009_California07
 Position in reference: 275
 AA in reference: H
 AA in query: Y

Mutation NA H275Y already occurred 197 times (2.48% of all samples with NA sequence) in 27 countries. The first strain with this mutation, collected in May 2009, was A/Mexico city/CIA10/2009(H1N1). The mutation most recently occurred in strain A/Rio Grande Do Sul/887/2012(H1N1), collected in June 2012. ([see map](#))

[See detailed global statistics for this position](#)

A mutation at the position equivalent to NA 275 has been reported in the literature to be related to [mild drug resistance](#) and [strong drug resistance](#).

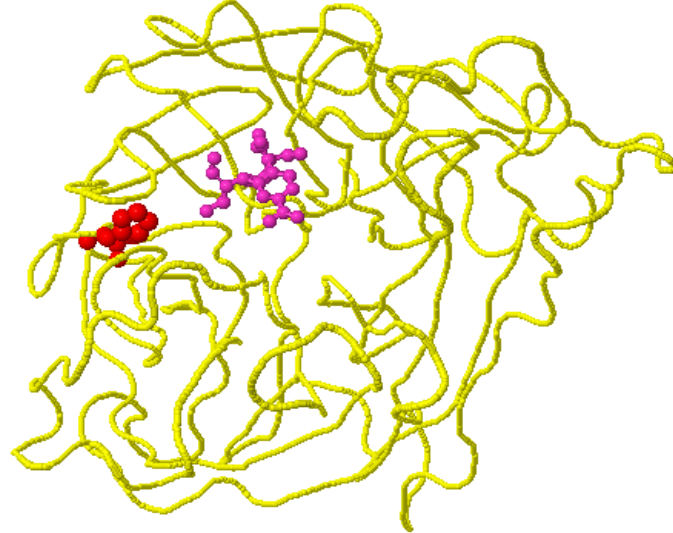
A combination of mutations including the position equivalent to NA 275 has been reported in the literature to be related to [strong drug resistance](#).

As seen in resolved structures of proteins from related strains, the NA position equivalent to your mutation is involved in:
 - [drug binding](#)

[See all interactions for this position](#)

Based on FoldX structural stability calculations H275Y is predicted to be strongly destabilizing which could represent a fitness disadvantage (ddG = 4.55 kcal/mol)

[PubMed search for this mutation \(including alternative numbering\)](#)



JSmol

Spin ON Spin OFF Save IMAGE

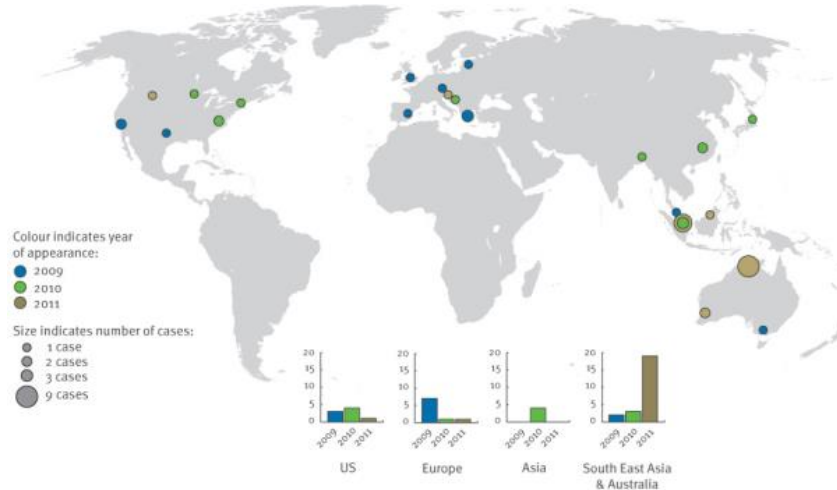
Description:
 The mutation position (**red atoms**) corresponds to position 273 on viral chain A (**yellow backbone**) and is within 5 Å from drug RA2 (**pink atoms**).

[See all 18 interactions for this position](#)

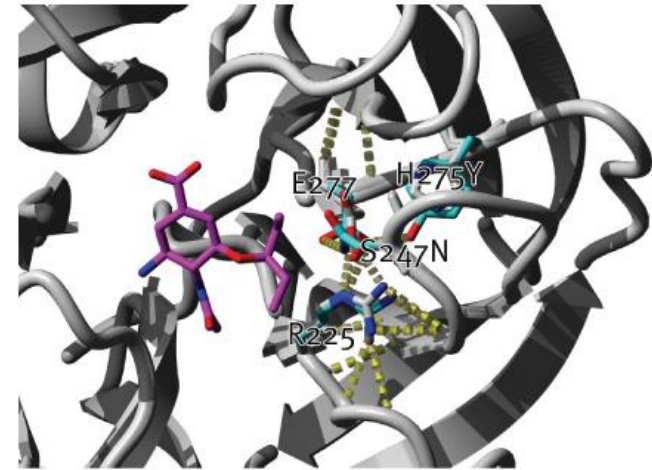
PDB ID	1B9V
Subtype	Not available
Strain	B/LEE/40
PMID of reference paper	10547289
Structure title	NOVEL AROMATIC INHIBITORS OF INFLUENZA VIRUS NEURAMINIDASE MAKE SELECTIVE INTERACTIONS WITH CONSERVED RESIDUES AND WATER MOLECULES IN THE ACTIVE SITE

Check for structural interactions!

Example of new drug sensitivity altering mutation NA S247N discovered with the help of FluSurver



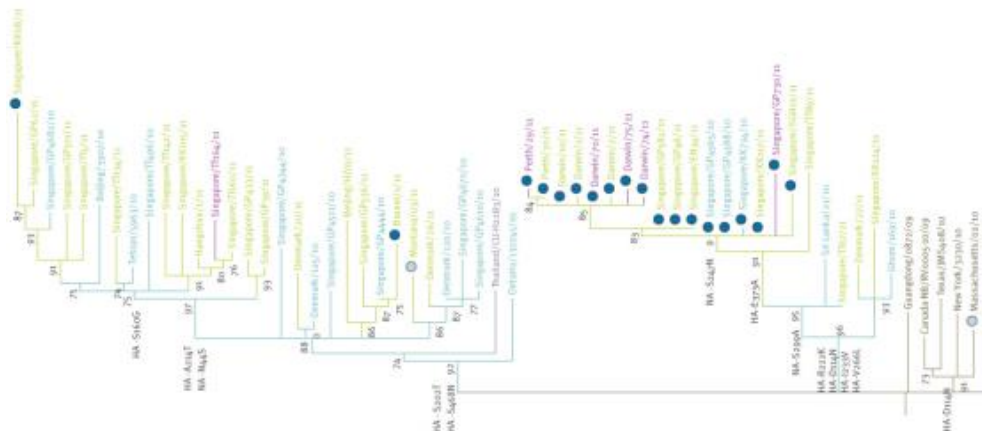
Global occurrence of new variant



Structural context of mutation

Found circulating in 10% of samples in Singapore and 30% of samples in Northern Australia in early 2011.

Experimentally measured increase of IC50 for Tamiflu by 6-fold and Relenza by 3-fold but **normally administered dose of drugs still sufficient.**



Phylogenetic context of new variant

*Collaboration between Bioinformatics Institute, A*STAR with NPHL/Ministry of Health Singapore and WHO Collaborating Centre for Reference and Research on Influenza.*

Euro Surveill. 2011;16(23):pii=19884.

FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidates

NA H275Y

Key to alternative position numbering:

275	FluSurver numbering (absolute as in 2009 H1N1 pandemic)
274	Classical H3N2 strain numbering
275	Classical H1N1 strain numbering

Chosen reference: NA_H1N1_Human_2009_California07
 Position in reference: 275
 AA in reference: H
 AA in query: Y

Mutation NA H275Y already occurred 197 times (2.48% of all samples with NA sequence) in 27 countries. The first strain with this mutation, collected in May 2009, was A/Mexico city/CIA10/2009(H1N1). The mutation most recently occurred in strain A/Rio Grande Do Sul/887/2012(H1N1), collected in June 2012. ([see map](#))

[See detailed global statistics for this position](#)

A mutation at the position equivalent to NA 275 has been reported in the literature to be related to [mild drug resistance](#) and [strong drug resistance](#).

A combination of mutations including the position equivalent to NA 275 has been reported in the literature to be related to [strong drug resistance](#).

As seen in resolved structures of proteins from related strains, the NA position equivalent to your mutation is involved in:
 - [drug binding](#)

[See all interactions for this position](#)

Based on FoldX structural stability calculations H275Y is predicted to be strongly destabilizing which could represent a fitness disadvantage (ddG = 4.55 kcal/mol)

[PubMed search for this mutation \(including alternative numbering\)](#)

Comparison with reference selection: auto [Back to Reference Selection](#)

100.000	12	I34V, N44S, S82P, N200S, V241I, N248D, H275Y , I21V, N369K, N386S, K432E, N449K show in structure	NA drug sensitivity positions: 33, 0, 1 Reduced sensitivity or resistance!
99.647	11	P100S, D114N, K180Q, S202T, S220T, A273T, K300E, I338V, E391K, S468N, E516K show in structure	
100.000	16	I34V, L40I, N44S, V116I, N189S, N200S, V241I, N248D, G249R, R257K, H275Y, I321V, N369K, N386S, I389R, K432E show in structure	NA drug sensitivity positions: 32, 1, 1 Reduced sensitivity or resistance!

[mutation report table for archiving or import to Excel](#)

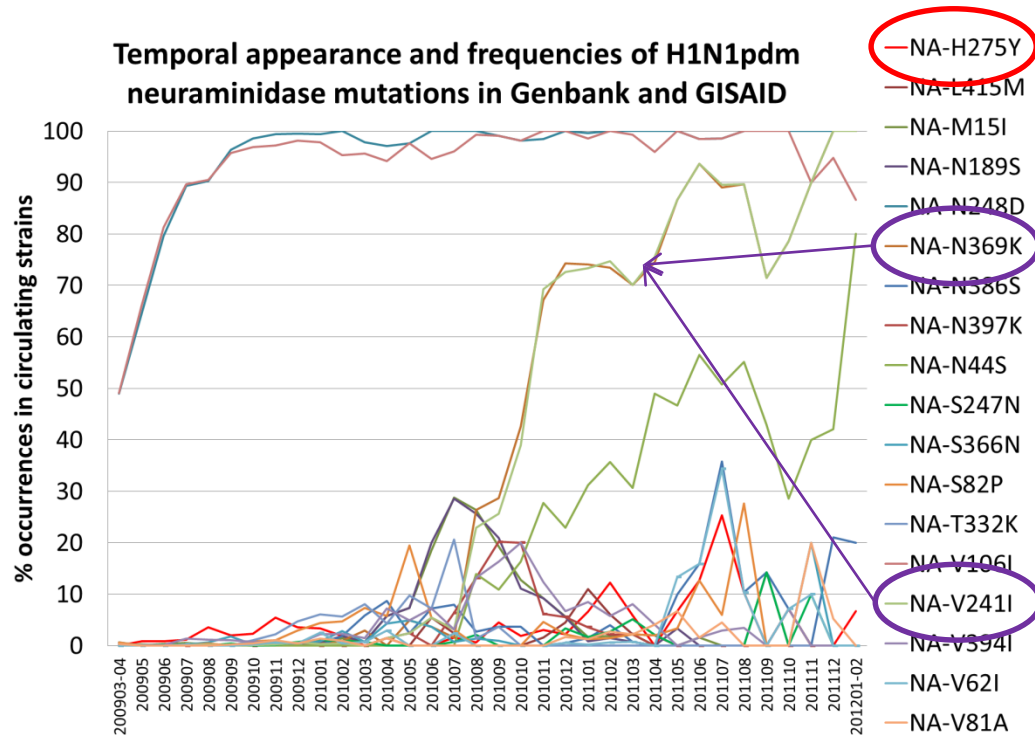
[Back to Reference Selection](#)

Bioinformatics Institute (BII), Singapore
 Instituto Nacional de Medicina Genómica (INMEGEN), Mexico
 served.

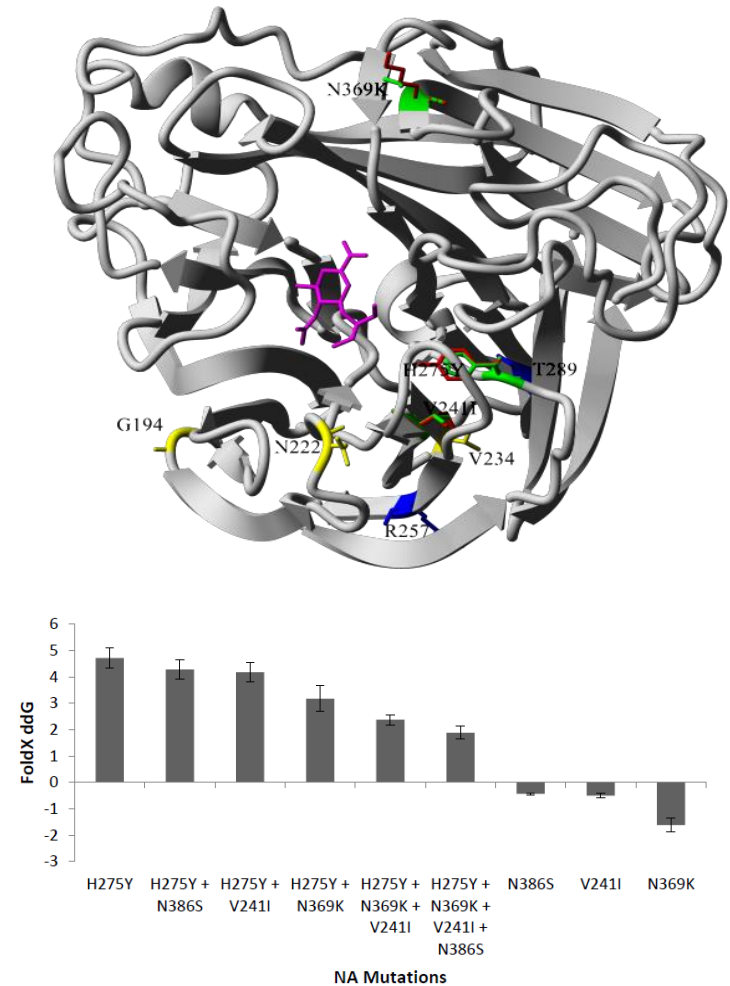
FluSurver

Check for stability
or passage effect
(if available)!

Example of frequency rise associated with stability changes leading to permissive mutations



FoldX predicts increase in structural stability for mutations that were increasing in frequency and were fixed in Newcastle strains.

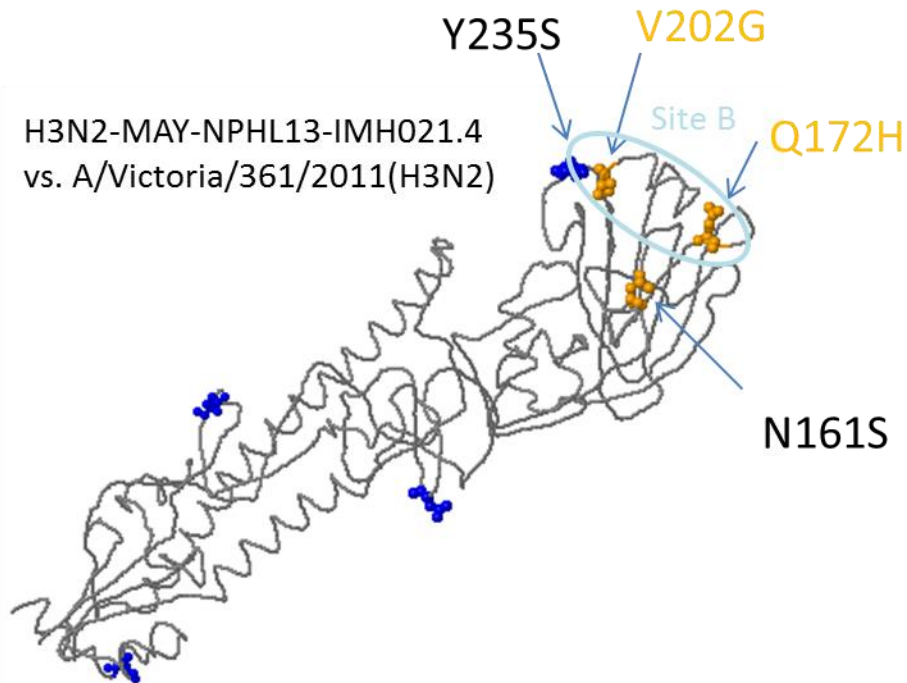


Hurt AC, Hardie K, Wilson NJ, Deng YM, Osbourn M, Leang SK, Lee RT, Iannello P, Gehrig N, Shaw R, Wark P, Caldwell N, Givney RC, Xue L, Maurer-Stroh S, Dwyer DE, Wang B, Smith DW, Levy A, Booy R, Dixit R, Merritt T, Kelso A, Dalton C, Durrheim D, Barr IG.

Characteristics of a widespread community cluster of H275Y oseltamivir-resistant A(H1N1)pdm09 influenza in Australia.

J Infect Dis. 2012 Jul 15;206(2):148-57.

H3N2 strains have HA passage bias mutations in antigenic sites



FluSurfer

Substrate as in 2009 H1N1 pandemic: HA1 156
Classical H3N2 strain numbering: HA1 152
Classical H1N1 strain numbering: HA_H3N2_Human_2011_Victoria361
Chosen reference: 202
Position in reference: V
AA in reference: G
AA in query: G

Mutation HA V202G already occurred 1164 times (91.32% of all samples with HA sequence) in 22 countries. The first strain with this mutation, collected in October 2011, was A/Singapore/GP168/2011(H3N2). This mutation most recently occurred in strain A/Guinea/3419/2013(H3N2), collected in April 2013. [See detailed global statistics for this position](#)

A mutation at the position equivalent to HA 202 has been reported in the literature to be related to [antigenic drift / escape mutant](#)

A combination of mutations including the position equivalent to HA 202 has been reported in the literature to be related to [antigenic drift / escape mutant and substance / antigenic drift / escape mutant](#)

As seen in resolved structures of proteins from related strains, the HA position equivalent to your mutation is involved in:

- [host cell receptor binding](#)
- [antibody recognition sites](#)
- [viral oligomerization interfaces](#)
- [binding small ligand\(s\)](#)

[See all interactions for this position](#)

Passage bias info available:
In subtype H3, G at this position is preferred over V in MDCK cells with odds ratio of 129.53. In subtype H3, G at this position is preferred over V in SIAT cells with odds ratio of 95.05.

PubMed search for this mutation (including alternative numbering)

As seen in resolved structures of proteins from related strains, the HA position equivalent to your mutation is involved in:

- [host cell receptor binding](#)
- [antibody recognition sites](#)
- [viral oligomerization interfaces](#)
- [binding small ligand\(s\)](#)

V202G

[See all interactions for this position](#)

Passage bias info available:

In subtype H3, G at this position is preferred over V in MDCK cells with odds ratio of 129.53. In subtype H3, G at this position is preferred over V in SIAT cells with odds ratio of 95.05.

Same isolate but different passage

(A/SINGAPORE/22/2012 NPHL: GP1187-2012)

GISAID ID	Submitter	Passage	Mutations relative to Victoria/361
EPI_ISL_128750	WHO CC Melbourne via NPHL	MDCK0, MDCK1	H9Y, Q49R, N161S, Q172H, V202G, Y235S , N294K
EPI_ISL_135838	US CDC via WHO CC Melbourne	E4/E1	H9Y, Q49R, N161S, N294K

Q172H

As seen in resolved structures of proteins from related strains, the HA position equivalent to your mutation is involved in:

- [host cell receptor binding](#)
- [antibody recognition sites](#)
- [binding small ligand\(s\)](#)
- is involved in [binding host protein\(s\)](#)
- [viral oligomerization interfaces](#)

[See all interactions for this position](#)

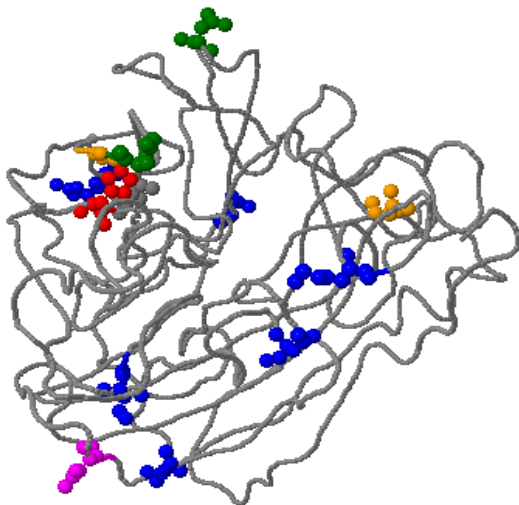
Passage bias info available:

In subtype H3, H at this position is preferred over Q in SIAT cells with odds ratio of 67.59.

FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

Reference: NA_H1N1_Human_2009_California07 ([Structure/Model Details](#))
 Patient/Sample: A/Norway/2227/2015 | EPI_ISL_189209 | 2015-06-23 | A/H1N1 |
 Mutation(s): I34V, L40I, V241I, N189S, K432E, R257K, I321V, I389R, N369K, N248D, N200S, N386S, N44S, V116I, G249R, H275Y

Wildtype residue only displayed if position is part of available structure.
 Hover with mouse over residue to see its position number. Right-click for more options.



FluSurver-JSmol

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[See interactions of position NA 189 in related structures.](#)
[See interactions of position NA 432 in related structures.](#)
[See interactions of position NA 257 in related structures.](#)
[See interactions of position NA 321 in related structures.](#)
[See interactions of position NA 389 in related structures.](#)
[See interactions of position NA 369 in related structures.](#)

Update mutations for further research and should ideally be combined with experimental testing
 recommendation on patient treatment should not be based solely on these computational
 comprised of strains that recently infected humans. Therefore, the usage scenario that will
 relation to used vaccine strains, including some candidates for avian flu and novel
 new to FluSurver. There is also a [special note for using FluSurver results in publications.](#)

Reference selection: auto

I34V, N44S, S82P, N200S, V241I, N248D, H275Y, I321V, N369K,
 N386K, K432E, N449K
[show in structure](#)

12

NA drug sensitivity positions:
 33, 0, 1
 Reduced sensitivity or resistance!

P100S, D114N, K180Q, S202T, S220T, A273T, K300E, I338V,
 E391K, S468N, E516K
[show in structure](#)

11


I34V, L40I, N44S, V116I, N189S, N200S, V241I, N248D, G249R,
 R257K, H275Y, I321V, N369K, N386S, I389R, K432E
[show in structure](#)

16

NA drug sensitivity positions:
 32, 1, 1
 Reduced sensitivity or resistance!

[Download table for archiving or import to Excel](#)

Site: [BII](#), Singapore
 Genomica (INMEGEN), Mexico



View all mutations together in
 structure or homology model
 of reference strain!

FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

Reference: NA_H1N1_Human_2009_California07 [Structure/Model Details](#)
 Patient/Sample: A/Norway/2227/2015 | EPI_ISL_189209 | 2015-06-25 | H1N1 |
 Mutation(s): I34V, L40I, V241I, N189S, K432E, R257K, I321V, I389R, N369K, N240D, N200S, N386S, N44S, V116I, G249R, H275Y

Wildtype residue only displayed if position is part of available structure.
 Hover with mouse over residue to see its position number. Right-click for more options.

Update mutations for further research and should ideally be combined with experimental testing
 recommendation on patient treatment should not be based solely on these computational
 comprised of strains that recently infected humans. Therefore, the usage scenario that will
 used vaccine strains, including some candidates for avian flu and novel
 new to FluSurver. There is also a [special note for using FluSurver results in publications](#).

Information of the template of 3NSS used to model NA_H1N1_Human_2009_California07

PDB ID	3NSS
Subtype	H1N1
Strain	A/CALIFORNIA/04/2009
Structure Title	THE 2009 PANDEMIC H1N1 NEURAMINIDASE N1 LACKS THE 150-CAVITY IN ITS ACTIVE SITES
PMID of Reference	Not Available
Viral Protein	NEURAMINIDASE
Corresponding Chain	A

Information of the alignment of NA_H1N1_Human_2009_California07 with 3NSS

Identity	Alignment Length	E-Value	Bit Score
100.00	388	0.0	797

Alignment of NA_H1N1_Human_2009_California07 with 3NSS used for structural modeling

```

      _aln_pos      10      20      30      40      50      60      70      80      90      100     110     120     130     140     150
      3NSS          SVELAGNSLQFVSGWAIYKSDNSVRIGSGKGVFVIREFFIISCSFLECRITFFLIQGALLNDKHSNGTIKDRSPYRTLMSCPIGEVSPFYNRSFESVAWSAACHDGINWLTIGISGFDNGAVAVLKYNGIITDIKSNWNILRTQESQC
NA_H1N1_2009_CALIFORNIA07 SVELAGNSLQFVSGWAIYKSDNSVRIGSGKGVFVIREFFIISCSFLECRITFFLIQGALLNDKHSNGTIKDRSPYRTLMSCPIGEVSPFYNRSFESVAWSAACHDGINWLTIGISGFDNGAVAVLKYNGIITDIKSNWNILRTQESQC
      _consrvd      .....

      _aln_pos      160     170     180     190     200     210     220     230     240     250     260     270     280     290     300
      3NSS          ACVNGSCFTVMTDGPSSNGQSYKIFRIEGRKIVKSVEMDAPVHYHEECSCVFDSSSEITCVCRDNNHGSNRFWISFMQLEVQIGVICSIFGDNFRFRFKIGSCGFVSNGANGVGQFFKVGNGVWIGRKAISRSNGFEMINDFNGWT
NA_H1N1_2009_CALIFORNIA07 ACVNGSCFTVMTDGPSSNGQSYKIFRIEGRKIVKSVEMDAPVHYHEECSCVFDSSSEITCVCRDNNHGSNRFWISFMQLEVQIGVICSIFGDNFRFRFKIGSCGFVSNGANGVGQFFKVGNGVWIGRKAISRSNGFEMINDFNGWT
      _consrvd      .....

      _aln_pos      310     320     330     340     350     360     370     380     390
      3NSS          GTDNNFSIKQDIVGNEWSYSGSFVQHPFELTGLDCIRPCFWVELIRGRPEENTIWTSGSSISFCGVNSDITVGNWFDGAELEPFTIID
NA_H1N1_2009_CALIFORNIA07 GTDNNFSIKQDIVGNEWSYSGSFVQHPFELTGLDCIRPCFWVELIRGRPEENTIWTSGSSISFCGVNSDITVGNWFDGAELEPFTIID
      _consrvd      .....
  
```

FluSurver-JSmol

Spin ON Spin OFF Save IMAGE

[See interactions of position NA 189 in related structures.](#)
[See interactions of position NA 432 in related structures.](#)
[See interactions of position NA 257 in related structures.](#)
[See interactions of position NA 321 in related structures.](#)
[See interactions of position NA 389 in related structures.](#)
[See interactions of position NA 369 in related structures.](#)

Check source and template similarity of structure/homology model!

FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

Check drug summary table!

The main application scenario for FluSurver is the search and verification of any predicted phenotypic effects of mutations. Our curated reference sequences are intended to give the most fruitful and reliable results. Please take a special note for using FluSurver results in publications.



Known effect(s) of mutations at position equivalent to your mutation:

Protein: NA
 Influenza type: Human H1N1 (2006)
 Mutation (as in paper): H274Y
 neutral AA: H
 neg. eff. AA: Y
 Effect: strong drug resistance (drug name in comments)

Comment:
 Tamiflu but not Relenza resistance (Table 3)

Literature reference
 (Mutation H274Y in the paper is at an equivalent position of the mutation in your query)

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Advanced

Display Settings: Abstract

Antimicrob. Agents Chemother. 2008 Sep;52(9):3284-92. doi: 10.1128/AAC.00555-08. Epub 2008 Jul 14.

Surveillance for neuraminidase inhibitor resistance among human influenza A and worldwide from 2004 to 2008.

Sheu TG, Deyde VM, Okomo-Adhiambo M, Garten RJ, Yu X, Bright RA, Butler EN, Wallis TR, Klimov AI, Gubareva U. Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Summary of critical drug sensitivity positions				
Residue	Type	Ref.num.	Effect annotation	Close to drug in 3D structure (<5Å)
V116	wt	116 (N2)	sensitive	-
R118	wt	118 (N2)	no known effect (common wildtype AA)	3D
E119	wt	119 (N2)	sensitive	3D
L134	wt	134 (N2)	no known effect (common wildtype AA)	3D
Q136	wt	136 (N2)	sensitive	-
D151	wt	151 (N2)	sensitive	3D
Y155	wt	155 (N2)	sensitive	-
R156	wt	156 (N2)	no known effect (common wildtype AA)	3D
S180	wt	179 (N2)	no known effect (common wildtype AA)	3D
I223	wt	222 (N2)	sensitive	3D
L224	wt	223 (N2)	no known effect (common wildtype AA)	3D
R225	wt	224 (N2)	sensitive	3D
T226	wt	225 (N2)	no known effect (common wildtype AA)	3D
Q227	wt	226 (N2)	sensitive	-
E228	wt	227 (N2)	sensitive	3D
G245	wt	244 (N2)	no known effect (common wildtype AA)	3D
P246	wt	245 (N2)	no known effect (common wildtype AA)	3D
S247	wt	246 (N2)	sensitive	3D
N248D	mt	247 (N2)	no known effect (mt)	3D
H275Y	mt	274 (N2)	effect	3D
E277	wt	276 (N2)	sensitive	3D
R293	wt	292 (N2)	sensitive	3D
N344	wt	347 (N2)	no known effect (common wildtype AA)	3D
G345	wt	348 (N2)	no known effect (common wildtype AA)	3D
G348	wt	351 (N2)	no known effect (common wildtype AA)	3D
R368	wt	371 (N2)	sensitive	3D
G401	wt	405 (N2)	no known effect (common wildtype AA)	3D

DISCLAIMER: This table is not suitable to unambiguously determine drug resistance but should rather serve to help selecting candidate positions/mutations that may have an effect for further experimental testing. Vicinity of a mutation to the drug in 3D structures does not automatically imply an effect on the drug and requires further careful modeling and/or experimental testing. Most of the available effect annotations refer to specific subtypes and may hence not apply exactly to your query. Please read the annotation carefully and follow up the provided links to the original literature to judge whether a similar effect on drug sensitivity for your query may be plausible.

Search and should ideally be combined with experimental testing. Statement should not be based solely on these computational predictions. Therefore, the usage scenario that will be most useful, including some candidates for avian flu and novel influenza A, is a special note for using FluSurver results in publications.

to Reference Selection

S82P, N200S, V241I, N248D, H275Y, I321V, N369K, N386K, K432E, N449K
[show in structure](#)

NA drug sensitivity positions:
 33, 0, 1
 Reduced sensitivity or resistance!

N141H, K180Q, S202T, S220T, A273T, K300E, I338V, E391K, S468N, E516K
[show in structure](#)

N44S, V116S, N189S, N200S, V241I, N248D, G249R, H275Y, I321V, N369K, N386S, I389R, K432E
[show in structure](#)

NA drug sensitivity positions:
 32, 1, 1
 Reduced sensitivity or resistance!



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Description:
 The residue position (red atoms) corresponds to position 273 on viral chain A (yellow backbone) and is within 5 Å from drug RA2 (pink atoms).

See all 18 interactions for this position

POB ID:	I189V
Subtype:	not available
Strain:	B/E/E/40
PDB ID of reference paper:	1G547Z09
Structure title:	NOVEL AROMATIC INHIBITORS OF INFLUENZA VIRUS NEURAMINIDASE HAVE SELECTIVE INTERACTIONS WITH CONSERVED RESIDUES AND WATER MOLECULES IN THE ACTIVE SITE

Also useful for analysis of other segments!

Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
RVM4541200051[H3 clade 3B]N2]	M2 A/Wisconsin/67/2005(H3N2) find closest related sequences	98.780	84.536	1	V271 show in structure

M2 drug sensitivity positions:
[16_0_2](#)
Reduced sensitivity or resistance!

Known effect(s) of mutations at position equivalent to your mutation:

Protein: M2

Influenza type: Duck (live poultry market) H3N2

Mutation (as in paper): V271

neutral AA: V

neg. eff. AA: **I**

Effect: mild drug resistance (drug name comments)

Comment:

conferred Amantadine resistance (Table 1).

[Literature reference](#)

(Mutation V271 in the paper is at an equivalent position of the mutation in your query)

Summary of critical drug sensitivity positions

Residue	Type	Ref.num.	Effect annotation	Close to drug in 3D structure (<5Å)
L26	wt	26	sensitive	3D
V271	mt	27	effect	3D
A30	wt	30	sensitive	3D
N31	wt	31	effect	3D
I33	wt	33	no known effect (common wildtype AA)	3D
G34	wt	34	sensitive	3D
I35	wt	35	no known effect (common wildtype AA)	3D
H37	wt	37	no known effect (common wildtype AA)	3D
L38	wt	38	no known effect (common wildtype AA)	3D
L40	wt	40	no known effect (common wildtype AA)	3D
W41	wt	41	no known effect (common wildtype AA)	3D
I42	wt	42	no known effect (common wildtype AA)	3D
L43	wt	43	no known effect (common wildtype AA)	3D
D44	wt	44	no known effect (common wildtype AA)	3D
R45	wt	45	no known effect (common wildtype AA)	3D

Known effect(s) of mutations at position equivalent to your mutation:

Protein: M2

Influenza type: Human H1N1 (2007)

Mutation (as in paper): S31N

neutral AA: S

neg. eff. AA: **N**

Effect: strong drug resistance (drug name in comments)

Comment:

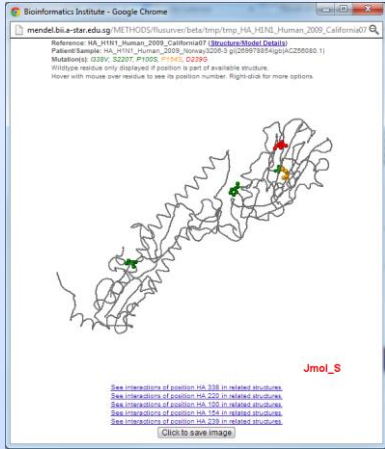
Amantadine resistance (Table)

[Literature reference](#)

(Mutation S31N in the paper is at an equivalent position of the mutation in your query)

If WT residues in reference strains are associated with resistance it will be shown in drug summary table!

Summary of FluSurver annotations

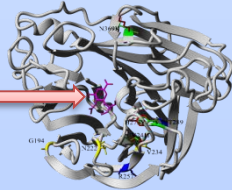


Map mutations to structure

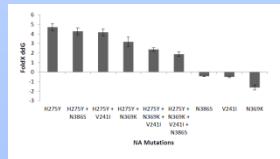
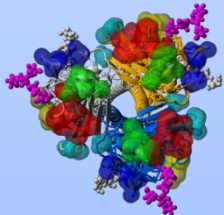
300+ reference homology models

1568	self/oligomerization
975	other small ligand
268	antibody
188	host protein
182	antigen-presenting MHC molecule
132	other viral protein
46	drug
45	nucleic acids
13	host cell receptor
3417	total interactions for 2062 positions

Interactions



Glycosylation site changes



FoldX stability calculations (for high frequency mutations in N1pdm)

Mutation numbering scheme conversion (e.g. H3, H1, H1pdm) and direct PubMed search link



Passage bias (egg/cell adaptation) for ~1300 mutations

Updated Literature-curated mutation effect database
~400 entries

mild drug resistance	30
strong drug resistance	40
virulence	106
antigenic drift / escape mutant	84
host specificity shift	136
other	23

Literature

Structure

Epidemiology

Closest DB hits

Temporal pattern



Genomic co-occurrence

Regional & global occurrence

