ISSN 2518-1629 (Online),
ISSN 2224-5308 (Print)

ҚАЗАҚСТАН РЕСПУБЛИКАСЫ
ҰЛТТЫҚ ҒЫЛЫМ АКАДЕМИЯСЫНЫҢ
Өсімдіктердің биологиясы және биотехнологиясы институтының

Х А Б А Р Л А Р Ы

ИЗВЕСТИЯ

НАЦИОНАЛЬНОЙ АКАДЕМИИ НАУК
РЕСПУБЛИКИ КАЗАХСТАН
Института биологии и биотехнологии растений

N E W S

OF THE NATIONAL ACADEMY OF SCIENCES
OF THE REPUBLIC OF KAZAKHSTAN
of the Institute of Plant Biology and Biotechnology

БИОЛОГИЯ ЖӘНЕ МЕДИЦИНА СЕРИЯСЫ

♦

СЕРИЯ БИОЛОГИЧЕСКАЯ И МЕДИЦИНСКАЯ

♦

SERIES OF BIOLOGICAL AND MEDICAL

4 (328)

ШІЛДЕ – ТАМЫЗ 2018 ж.
ИЮЛЬ – АВГУСТ 2018 г.
JULY – AUGUST 2018

1963 ЖЫЛДЫҢ ҚАҢТАР АЙЫНАН ШЫҒА БАСТАҒАН
ИЗДАЕТСЯ С ЯНВАРЯ 1963 ГОДА
PUBLISHED SINCE JANUARY 1963

ЖЫЛЫНА 6 РЕТ ШЫҒАДЫ
ВЫХОДИТ 6 РАЗ В ГОД
PUBLISHED 6 TIMES A YEAR

АЛМАТЫ, ҚР ҰҒА
АЛМАТЫ, НАН РК
ALMATY, NAS RK

«ҚР ҰҒА Хабарлары. Биология және медициналық сериясы».
ISSN 2518-1629 (Online),
ISSN 2224-5308 (Print)
Меншіктенуші: «Қазақстан Республикасының Ұлттық ғылым академиясы» РҚБ (Алматы қ.)
Қазақстан республикасының Мәдениет пен ақпарат министрлігінің Ақпарат және мұрағат комитетінде 01.06.2006 ж. берілген **№5546-Ж** мерзімдік басылым тіркеуіне қойылу туралы куәлік

Мерзімділігі: жылына 6 рет.
Тиражы: 300 дана.

Редакцияның мекенжайы: 050010, Алматы қ., Шевченко көш., 28, 219 бөл., 220, тел.: 272-13-19, 272-13-18,
www:nauka-nanrk.kz / biological-medical.kz

Типографияның мекенжайы: «Аруна» ЖК, Алматы қ., Муратбаева көш., 75.

«Известия НАН РК. Серия биологическая и медицинская».
ISSN 2518-1629 (Online),
ISSN 2224-5308 (Print)
Собственник: РОО «Национальная академия наук Республики Казахстан» (г. Алматы)
Свидетельство о постановке на учет периодического печатного издания в Комитете информации и архивов Министерства культуры и информации Республики Казахстан **№5546-Ж**, выданное 01.06.2006 г.

Периодичность: 6 раз в год
Тираж: 300 экземпляров

Адрес редакции: 050010, г. Алматы, ул. Шевченко, 28, ком. 219, 220, тел. 272-13-19, 272-13-18,
www:nauka-nanrk.kz / biological-medical.kz

Адрес типографии: ИП «Аруна», г. Алматы, ул. Муратбаева, 75

News of the National Academy of Sciences of the Republic of Kazakhstan. Series of biology and medicine.
ISSN 2518-1629 (Online),
ISSN 2224-5308 (Print)
Owner: RPA "National Academy of Sciences of the Republic of Kazakhstan" (Almaty)
The certificate of registration of a periodic printed publication in the Committee of information and archives of the Ministry of culture and information of the Republic of Kazakhstan N 5546-Ж, issued 01.06.2006

Periodicity: 6 times a year
Circulation: 300 copies

Editorial address: 28, Shevchenko str., of. 219, 220, Almaty, 050010, tel. 272-13-19, 272-13-18,
http://nauka-nanrk.kz / biological-medical.kz

Address of printing house: ST "Aruna", 75, Muratbayev str, Almaty

N E W S
OF THE NATIONAL ACADEMY OF SCIENCES OF THE REPUBLIC OF KAZAKHSTAN
SERIES OF BIOLOGICAL AND MEDICAL
ISSN 2224-5308
Volume 4, Number 328 (2018), 119 – 126

UDC 616.921.5+621.3.011.716

I. S. Korotetskiy[1], R. K. Karipbaeva[2], S. V. Shilov[1]

[1]Scientific Center for Anti-Infectious Drugs JSC, Almaty, Kazakhstan,
[2]Al-Farabi Kazakh National University, Almaty, Kazakhstan.
E-mail: laeda1@mail.ru, rasima.24.02@mail.ru, sergey_0603@mail.ru

MODELLING THE PROBABILITY OF EMERGENCE OF MULTIPLE DRUG RESISTANCE IN INFLUENZA VIRUS

Abstract. Antiviral drug resistance in influenza virus poses a serious threat to public health, particularly during the epidemic period. In this article we evaluated the probability of emergence of multiple drug resistance to adamantane and the oseltamivir in influenza virus. 35,061 amino acid sequences of both the neuraminidase and M2 matrix protein genes were selected for analysis in the international NCBI database. In order to search for and count the sites responsible for the formation of susceptibility to antiviral drugs, the scripts were developed and written in the Python 3.6 programming language. Evaluation of the possibility of simultaneous existence of amino acid substitutions in the M2 and NA genes leading to the formation of resistance showed that these paired mutations are antagonistic to each other, and theoretically the occurrence of such virus strains is unlikely. The findings can serve as a basis for the practical application of complex therapy with the drugs based on adamantane derivatives and neuraminidase inhibitors against influenza virus.

Key words: influenza virus, antiviral resistance, amino acid substitutions, fitness cost, genetic linkage.

Introduction. Evolution of antibiotic resistance is usually the result of small changes that allow the microbes or other organisms to survive under special circumstances when the organism encounters an extremely strong selection pressure due to the presence of any antibiotic drug. In other cases, this is the result of the transfer of pre-existing antibiotic resistance genes from one microbe to another and selection of such microorganisms in an antibiotic-containing medium. Even in the first example, evolution does not create a truly new function. Such changes often make microorganisms less adapted to normal growth conditions – their efficiency declines, manifesting itself in reduced virulence, transmission, and growth rate, while these mutants are able to survive treatment with antibiotics. This effect is widely recognized and called the fitness cost of antibiotic resistance or “fitness cost”.

Energy costs of drug resistance are real, and biological realities such as “fitness cost” and other limitations of the evolution of microorganisms play a vital role in shaping strategies used to combat resistance to antibiotics, antiviral resistance, etc. In fact, if it weren’t for the “fitness cost”, in many cases drug-resistant bacteria and viruses would multiply without restriction, and soon replace susceptible strains. However, in practice, because of the “fitness cost”, resistant strains are replaced by susceptible strains when the drug is removed from the medium, and the selection pressure is weakened. Thereby, the susceptible strain will eventually defeat the resistant one in a drug-free medium. It can take several days, or several decades, depending on the relative difference in the “fitness cost”. The difference in the “fitness cost” between susceptible and resistant strains can also be leveled by compensatory mutations, but will never be zero [1, 2].

A number of drug resistance mutations are incompatible with each other because of the cumulative effect of the associated negative effects on the body, as well as in relation to the need to maintain a certain general genomic context for the states of many other polymorphic alleles in the genome, including compensatory mutations.

There is a large number of works devoted to the study of the "fitness cost" concept in various bacteria. However, there are very few similar studies on viral infection models. In this article, we have tried to evaluate the probability of emergence of multiple drug resistance to adamantane and oseltamivir in influenza virus.

There are currently two classes of the most common antiviral drugs used in the treatment of the influenza virus infection: adamantane derivatives (amantadine, rimantadine) and neuraminidase inhibitors (oseltamivir) [3].

The study into the genetic basis of resistance showed that all rimantadine-resistant strains have mutations in the transmembrane domain of the M2 protein, namely at positions 26, 27, 30, 31, and 34 [4, 5]. In this case, a structure of the mutant transmembrane domain of the M2 protein changes, which leads to a change in the structure of the viral ion channel [6, 7].

The frequency of appearance of a virus resistant to neuraminidase inhibitors remains low compared to the resistance to adamantanes. However, every year the share of oseltamivir-resistant variants increases throughout the world [8]. Genetic studies of influenza virus strains have revealed a histidine to tyrosine amino acid substitution (H274Y mutation) in the neuraminidase protein, leading to the formation of resistance to the oseltamivir.

Therapy for the disease with several drugs that act at different stages of the viral life cycle is now considered to be one of the most effective approaches. And, perhaps, the complex therapy may reduce the likelihood that any single mutation will lead to the emergence of resistance.

Materials and methods. *Objects of the study.* The amino acid sequences of the neuraminidase protein and matrix protein M2 of the influenza A virus, obtained from the international NCBI database [9], were used in this study. Information on the frequencies of amino acid substitutions in 53,761 genomes of the influenza virus was analyzed. The data were used to examine the dynamics of mutation accumulation in the global population of the influenza virus.

Search and analysis of amino acid substitutions leading to the emergence of resistant virus strains. The search for mutations responsible for the formation of resistance to adamantane in the M2 protein gene was carried out at positions 26, 27, 30, 31, and 34, initiating at the first start codon.

The search for mutations responsible for the formation of resistance to the oseltamivir in the neuraminidase protein was carried out at position -2 from the location of the EEC/SSC/RY/H/F pattern.

The mutations associated with drug resistance were established according to the NCBI database records [9].

To determine the conservative pattern in the neuraminidase gene, multiple amino acid sequence alignment was performed using the MEGA 7 [10] and Lasergen software (version 12, DNASTAR, Inc, Madison, WI).

Determination of mutation frequencies. The frequencies of single mutations responsible for the formation of mono resistance have been calculated. The mutation frequency was calculated as the ratio of the number of each mutation to the total number of amino acid sequences according to formula (1):

$$f = n/N, \qquad (1)$$

where f – mutation frequency, n – number of mutations, N – total number of amino acid sequences.

To analyze the character of amino acid substitutions, the Grantham's distance was used (figure).

With a physicochemical distance above 57.9, the substitution is assumed to be conservative, or radical in the opposite case [11].

Calculation of linkage disequilibrium (LD) parameter for the pairs of mutations. For each pair of mutations, a parameter LD, characterizing the disequilibrium concatenation of the signs, was calculated by the formulae (2)-(4) [12]:

$$LD = \sum_{i=1}^{k} \sum_{j=1}^{l} p(A_i) p(B_j) \times \left| \frac{D_{ij}}{D_{ij}^{\max}} \right|, \qquad (2)$$

$$D_{ij} = p(A_i B_j) - p(A_i) p(B_j), \qquad (3)$$

$$D_{ij}^{\max} = \begin{cases} \min\left[p(A_i)p(B_j),(1-p(A_i))(1-p(B_j))\right] & D_{ij} < 0 \\ \min\left[p(A_i)(1-p(B_j)),(1-p(A_i))p(B_j)\right] & D_{ij} \geq 0 \end{cases}, \quad (4)$$

where *pA* and *pB* are the allele frequencies at loci *A* and *B*, *pAB* is the frequency of gametes carrying a pair of alleles A and B at two loci.

	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
A	100	9	41	50	45	73	59	54	50	54	59	45	86	54	45	54	73	68	32	45
C		100	27	23	4	27	18	9	4	9	9	36	23	27	18	45	32	9	0	9
D			100	77	18	54	59	23	50	18	27	86	50	68	54	68	59	27	14	27
E				100	36	54	82	36	73	36	41	77	54	86	73	64	68	41	27	41
F					100	27	54	86	50	86	86	27	45	45	54	27	50	77	82	86
G						100	54	36	41	36	41	64	77	59	41	73	73	50	14	32
H							100	54	82	54	59	68	64	86	86	59	77	59	45	59
I								100	50	95	95	32	54	50	54	32	59	86	68	82
K									100	50	54	54	50	73	86	41	64	54	50	59
L										100	91	27	54	45	50	32	54	82	68	82
M											100	32	59	50	54	36	59	86	68	82
N												100	54	77	59	77	68	36	18	32
P													100	64	50	64	82	68	32	50
Q														100	77	68	77	54	41	54
R															100	50	64	54	50	64
S																100	73	41	18	32
T																	100	68	41	54
V																		100	59	73
W																			100	82
Y																				100

Grantham's physicochemical distance matrix for amino acid substitutions

Bioinformatics calculations. To search for amino acid substitutions in the examined genes responsible for the emergence of drug resistance and calculate frequencies of both mono- and paired mutations, we have used own scripts written in the Python 3.6.

Results. *Finding whole genome amino acid sequences of influenza A virus from the NCBI database.* The whole genome amino acid sequences of the NA and M2 proteins were obtained from the NCBI database to carry out an analysis. The appropriate filters were used to collect relevant data, which make it possible to get rid of laboratory isolates, mixed strains, and duplicating sequences.

In total, 53,761 whole genome sequences of the NA and M2 genes of the influenza A virus circulating in the world between 1902 and 2017 were obtained from the database. In view of the fact that the strains are often deposited in the NCBI without the first start codon, or, conversely, have an additional sequence before it, the sequences obtained were optimized in the subsequent experiments. Using own scripts written in Python 3.6, all sequences of the M2 and NA proteins were aligned with the first start codon. In addition, the strains, which simultaneously included genome sequences of the M2 and NA proteins, meeting the requirements as described above, were sorted.

As a result of all manipulations, 35,061 amino acid sequences of both the neuraminidase and M2 matrix protein genes were selected for further analysis.

Analysis of amino acid substitutions leading to the emergence of resistant strains of influenza virus. Using the obtained amino acid sequences, the search and counting of sites responsible for the formation of resistance to adamantane and to the oseltamivir were carried out in subsequent experiments. In view of the fact that, despite the optimization, the amount of data analyzed was extremely large, direct search and counting of sites were not possible. At the same time, the existing software (both commercial and free) did not allow to carry out the required manipulations. We have developed and written own scripts in the Python 3.6, which enables us to perform a search and counting of sites for the given parameters quickly and optimally.

According to the published data, the formation of resistance to adamantane causes by amino acid substitutions in the matrix protein of the influenza virus at positions 26, 27, 30, 31, and 34 relative to the start codon. All amino acid substitutions in the M2 protein and their absolute number are shown in table 1.

Table 1 – Amino acid substitutions in the M2 protein gene

Substitution	Number	Phenotype	Substitution	Number	Phenotype
26A	1	n/d	30A	35007	S
26F	51	R	30E	1	n/d
26I	346	R	30I	11	n/d
26L	34645	S	30N	1	n/d
26N	3	n/d	30S	22	n/d
26P	1	n/d	30T	16	R
26R	1	n/d	30V	3	R
26S	8	n/d	31K	1	n/d
26V	5	n/d	31A	1	n/d
A27	1144	R	31R	2	n/d
27E	1	n/d	31I	6	n/d
27F	38	n/d	31N	20579	R
27G	20	n/d	31G	4	n/d
27I	1585	R	31L	11	n/d
27L	5	n/d	31D	7	n/d
27M	3	n/d	31S	14450	S
27S	2	R	34G	35039	S
27T	345	R	34I	15	n/d
27V	31918	S	34E	3	R
			34W	4	n/d

Notes: S – susceptibility phenotype; R – resistance phenotype; n/d – no data.

However, during the analysis, a number of amino acid substitutions were recorded in the matrix protein gene, which, according to the literature data, did not clearly differentiate into mutations leading to susceptibility or resistance, but nonetheless affecting the phenotype to some extent.

In order to take into account the influence of these substitutions on the formation of resistance in influenza virus and calculate the linkage disequilibrium parameter, an analysis was made to determine the character of the amino acid substitutions for the M2 protein. To determine the nature of the mutations, which were not described in the literature, the Grantham's physicochemical distance matrix was used. The results are shown in table 2.

In addition to the mutation at position 274 resulting in resistance to oseltamivir, a number of substitutions are known for the neuraminidase protein. However, some of them are related to compensatory mutations, while the other part is specific only for certain genetic groups of the influenza virus and cannot provide an adequate picture of resistance formation. As a result, only an amino acid substitution at position 274 in the neuraminidase protein was used in the final analysis. However, in view of the fact that the neuraminidase protein sequences differ in length due to the presence of insertions/deletions that are responsible for pathogenicity, the search for position 274, initiating at the start codon, will not provide adequate amino acid content in this site. Therefore, in preliminary studies, a conservative pattern was searched for, which would be located in the immediate vicinity of the necessary site.

The search for a conservative pattern was carried out using the MEGA 7 and Lasergen 12 software. A rather conservative EEC/SSC/RY/H/F pattern, located two amino acids after the site responsible for the formation of resistance to the oseltamivir, was found.

Using the found pattern and own scripts, the number of sites responsible for the formation of susceptibility/resistance was determined (table 3).

Table 2 – Determination of the character of amino acid substitutions in the M2 protein gene

Amino acid substitution	Number of substitutions	Character of substitutions
26A	1	R
26N	3	R
26P	1	R
26R	1	R
26S	8	R
26V	5	S
27E	1	R
27F	38	S
27G	20	R
27L	5	S
27M	3	S
30E	1	R
30I	11	R
30N	1	R
30S	22	R
31K	1	R
31A	1	R
31R	2	R
31I	6	R
31G	4	S
31L	11	R
31D	7	S
34I	15	R
34W	4	R
Notes: S – susceptibility phenotype; R – resistance phenotype.		

Table 3 – Amino acid substitutions in the neuraminidase protein gene

Substitution	Number of substitutions	Phenotype
274H	34615	S
274Y	446	R
Notes: S – susceptibility phenotype; R – resistance phenotype.		

In subsequent experiments, in order to calculate the linkage disequilibrium parameter, it was required to determine a possibility of the simultaneous existence of amino acid substitutions in the M2 and NA genes leading to the formation of resistance within the same organism. Therefore, only mutations leading to the resistance phenotype were used for the analysis. In other words, the frequencies of mutations, both described in the literature and calculated according to the Grantham's distance, were summed up within the same site. Based on the values obtained, the frequencies of mutations responsible for resistance to adamantanes at positions 26, 27, 30, 31, and 34 for protein M2 and to oseltamivir at position 274 for the neuraminidase protein were calculated. The values of theoretical and practical frequencies of paired mutations were further calculated. Practical frequencies were obtained on the basis of direct counting of substitutions in the M2 and NA genes (table 4).

Using the obtained frequency values, the linkage disequilibrium (LD) parameter was calculated for paired mutations.

Table 4 – Frequencies of paired mutations

Paired mutations	Practical values	Theoretical values
26-274	0,0	1,50E-04
27-274	1,7E-04	1,12E-03
30-274	0,0	1,96E-05
31-274	3,68E-03	7,47E-03
34-274	0,0	7,98E-06

The linkage disequilibrium (LD) parameter is a non-random distribution of allele frequencies at different loci, which can be due not only to the close genetic linkage but also to the adaptive advantage of the particular combination of alleles, whose frequency accordingly increases in comparison with the frequency expected with a random distribution.

The LD parameter can take both positive and negative values. Positive linkage values indicate that two loci occur together in the same haplotype more often than expected, while negative LD exists when alleles occur together in the same haplotype less often than expected. The data are shown in table 5.

Table 5 – Linkage disequilibrium parameter for paired mutations in the M2 and NA proteins

Paired mutations	LD value
26-274	-1,50E-04
27-274	-9,70E-04
30-274	-2,00E-05
31-274	-3,95E-03
34-274	-8,16E-06
LD_{common}	-5,12E-03

The resulting negative LD values indicate that these paired mutations are antagonistic to each other. The common LD parameter also has a negative value. Theoretically, the emergence of influenza virus strain, which simultaneously possesses such pairs of amino acid substitutions in the NA and M2 genes, is extremely unlikely. However, the LD parameter has a low negative value, tending to zero, which in turn may indicate a lack of analyzed data or a relative general neutrality of the simultaneous presence of two mutations resulting in the formation of multiple drug resistance.

Conclusions. The concept of energy relevance is a characteristic of any living organism. The acquisition or loss of structures, including genetic ones, inevitably leads to a change in the energy status of the organism. Restoring this balance entails changes in the structure of the genome or epigenome. However, this can be problematic for viruses due to the limited size of their genome and lead to irreversible fatal consequences.

Based on the data presented in the NCBI database, as well as the analysis carried out, it was suggested that resistance to adamantane and neuraminidase inhibitors (oseltamivir) cannot exist simultaneously due to the energy irrelevance. In this article, the effect of compensatory mutations on the decrease of the “fitness cost” was not taken into account; however, the findings can serve as a basis for subsequent studies.

Theoretical calculations obtained in the framework of this work undoubtedly require a comprehensive experimental verification and evaluation. However, if the results are confirmed, the data may serve as a basis for reviewing or clarifying existing regimens for influenza virus treatment.

Acknowledgment. The authors are very grateful to Professor Oleg N. Reva, from the Center for Computational Biology and Bioinformatics, University of Pretoria (South Africa), for valuable recommendations and suggestions.

REFERENCES

[1] Cohen T., Sommers B., Murray M. (2003) The effect of drug resistance on the fitness of Mycobacterium tuberculosis, The LANCET Infectious Diseases, 3(1):13-21. DOI: 10.1016/S1473-3099(03)00483-3 (in Eng.)

[2] Cohen T., Murray M. (2004) Modeling epidemics of multidrug-resistant M. tuberculosis of heterogeneous fitness, Nature Medicine, 10:1117-1121. DOI: 10.1038/nm1110 (in Eng.)

[3] Ison M.G. (2011) Antivirals and resistance: influenza virus, Current Opinion in Virology, 1(6):563-573. DOI: 10.1016/j.coviro.2011.09.002 (in Eng.)

[4] Dong G., Peng Ch., Luo J., Wang Ch., Han L., Wu B., Ji G., He H. (2015) Adamantane-Resistant Influenza A Viruses in the World (1902–2013): Frequency and Distribution of M2 Gene Mutations, PLOS One, 10(3):e0119115. DOI: 10.1371/journal.pone.0119115 (in Eng.)

[5] Abed Y., Goyette N., Boivin G. (2005) Generation and Characterization of Recombinant Influenza A (H1N1) Viruses Harboring Amantadine Resistance Mutations, Antimicrobial Agents Chemotherapy, 49(2):556-559. doi:10.1128/AAC.49.2.556-559.2005 (in Eng.)

[6] Yi M., Cross T.A., Zhou H.-X. (2009) Conformational heterogeneity of the M2 proton channel and a structural model for channel activation, PNAS, 106(32):13311-13316. DOI: 10.1073/pnas.0906553106 (in Eng.)

[7] Wang J.-F., Wei D.-Q., Chou K.-C. (2009) Insights from investigating the interactions of adamantine-based drugs with the M2 proton channel from the H1N1 swine virus, Biochemical and Biophysical Research Communications, 388(2):413-417. DOI: 10.1016/j.bbrc.2009.08.026 (in Eng.)

[8] Walaza S., Cohen C. (2015) Recommendations pertaining to the use of influenza vaccines and influenza antiviral drugs: Influenza 2015, South African Medical Journal, 105(2): 90-91. DOI: 10.7196/samj.9367 (in Eng.)

[9] Influenza Virus Database. https://www.ncbi.nlm.nih.gov/genomes/FLU/Database/nph –select.cgi?go=database.

[10] Kumar S., Stecher G., Tamura K. (2016) MEGA7: Molecular Evolutionary Genetics Analysis version 7.0 for Bigger Datasets, Molecular Biology and Evolution, 33(7):1870-1874. DOI: 10.1093/molbev/msw054 (in Eng.)

[11] Butvilovsky A.V., Chernous E.A. (2008) Methods for determining the character of amino acid substitutions: educational manual. [Metody opredelenija haraktera aminokislotnyh zamen: uchebno-metodicheskoe posobie.] BSMU, Minsk. [BGMU, Minsk.] ISBN: 978–985–462–817–2 (in Rus.)

[12] Yang J., Shikano T., Li M.-H., Merilä J. (2014) Genome-wide linkage disequilibrium in nine-spined stickleback populations, G3: Genes, Genomes, Genetics, 4(10):1919-1929. DOI: 10.1534/g3.114.013334 (in Eng.)

И. С. Коротецкий[1], Р. К. Карипбаева[2], С. В. Шилов[1]

[1]«Инфекцияға қарсы препараттар ғылыми орталығы» АҚ, Алматы, Қазақстан,
[2]Әл-Фараби атындағы Қазақ ұлттық университеті, Алматы, Қазақстан

ГРИПП ВИРУСЫНДАҒЫ КӨПТЕГЕН ДӘРІГЕ ТҰРАҚТЫЛЫҚТЫҢ ПАЙДА БОЛУ МҮМКІНДІГІН МОДЕЛДЕУ

Аннотация. Тұмау вирусының дәрілік заттарға қарсы вирусқа қарсы тұрақтылығы қоғамдық денсаулық үшін, әсіресе эпидемия кезеңінде елеулі қатер болып табылады. Осы мақалада біз грипп вирусындағы адамантандық қатардағы препараттар мен осельтамивир препаратына кұптеген дәрілік тұрақтылығының пайда болу мүмкіндігін бағаладық. Талдау үшін NCBI халықаралық базасында нейраминидаз және М2 матрикстік ақуыз ретінде гендердің 35061 аминқышқылдарының бірізділігі бойынша іріктедік. Вирусқа қарсы препараттарға сезімталдықты қалыптастыруға жауапты сайттарды іздеу және санау үшін Python 3.6 бағдарламалау тілінде скрипттер әзірленіп, жазылды.

Тұрақтылықты қалыптастыруға әкелетін М2 және НА гендеріндегі амин қышқылының алмастыруларының бір мезгілде болу мүмкіндігін бағалау бұл мутациялардың жұптары бір-біріне антагонист болып табылады және теориялық түрде мұндай штаммдардың пайда болуы екіталай.

Алынған нәтижелер грипп вирусына қатысты нейраминидаз ингибиторлары және адамантан туындылары препараттарымен кешенді терапияны практикалық қолдану үшін негіз бола алады.

Түйін сөздер: грипп вирусы, вирусқа қарсы тұрақтылық, аминқышқылдық алмасулар, fitness cost, тіркеспе гендер.

И. С. Коротецкий[1], Р. К. Карипбаева[2], С. В. Шилов[1]

[1]АО «Научный центр противоинфекционных препаратов», Алматы, Казахстан,
[2]Казахский национальный университет им. аль-Фараби, Алматы, Казахстан

МОДЕЛИРОВАНИЕ ВОЗМОЖНОСТИ ВОЗНИКНОВЕНИЯ МНОЖЕСТВЕННОЙ ЛЕКАРСТВЕННОЙ УСТОЙЧИВОСТИ У ВИРУСА ГРИППА

Аннотация. Антивирусная резистентность вируса гриппа к лекарственным препаратам является серьезной угрозой для общественного здравоохранения, особенно в эпидемический период. В этой статье мы провели оценку возможности возникновения множественной лекарственной устойчивости к препаратам адамантанового ряда и препарату осельтамивир у вируса гриппа. Для анализа было отобрано по 35061 аминокислотных последовательностей генов как нейраминидазы, так и матриксного белка M2 в международной базе NCBI. Для поиска и подсчета сайтов, отвечающих за формирование чувствительности к противовирусным препаратам, были разработаны и написаны скрипты на языке программирования Python 3.6. Оценка возможность одновременного существования аминокислотных замен в генах M2 и NA, ведущих к формированию устойчивости показала, что данные пары мутаций являются антагонистическими по отношению друг к другу, и теоретически возникновение таких штаммов вируса маловероятно. Полученные результаты могут служить основанием для практического применения комплексной терапии препаратами производных адамантана и ингибиторами нейраминидазы в отношении вируса гриппа.

Ключевые слова: вирус гриппа, противовирусная резистентность, аминокислотные замены, fitness cost, сцепленность генов

Authors' information:

Korotetskiy Ilya – PhD, Scientific Center for Anti-Infectious Drugs, Almaty, Kazakhstan JSC, laeda1@mail.ru

Shilov Sergey – master, Scientific Center for Anti-Infectious Drugs, Almaty, Kazakhstan JSC, sergey_0603@mail.ru

Karipbaeva Rasima – bachelor, Al-Farabi Kazakh National University, Almaty, Kazakhstan, rasima.24.02@mail.ru

Publication Ethics and Publication Malpractice in the journals of the National Academy of Sciences of the Republic of Kazakhstan

For information on Ethics in publishing and Ethical guidelines for journal publication see http://www.elsevier.com/publishingethics and http://www.elsevier.com/journal-authors/ethics.

Submission of an article to the National Academy of Sciences of the Republic of Kazakhstan implies that the described work has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis or as an electronic preprint, see http://www.elsevier.com/postingpolicy), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. In particular, translations into English of papers already published in another language are not accepted.

No other forms of scientific misconduct are allowed, such as plagiarism, falsification, fraudulent data, incorrect interpretation of other works, incorrect citations, etc. The National Academy of Sciences of the Republic of Kazakhstan follows the Code of Conduct of the Committee on Publication Ethics (COPE), and follows the COPE Flowcharts for Resolving Cases of Suspected Misconduct (http://publicationethics.org/files/u2/New_Code.pdf). To verify originality, your article may be checked by the Cross Check originality detection service http://www.elsevier.com/editors/plagdetect.

The authors are obliged to participate in peer review process and be ready to provide corrections, clarifications, retractions and apologies when needed. All authors of a paper should have significantly contributed to the research.

The reviewers should provide objective judgments and should point out relevant published works which are not yet cited. Reviewed articles should be treated confidentially. The reviewers will be chosen in such a way that there is no conflict of interests with respect to the research, the authors and/or the research funders.

The editors have complete responsibility and authority to reject or accept a paper, and they will only accept a paper when reasonably certain. They will preserve anonymity of reviewers and promote publication of corrections, clarifications, retractions and apologies when needed. The acceptance of a paper automatically implies the copyright transfer to the National Academy of Sciences of the Republic of Kazakhstan.

The Editorial Board of the National Academy of Sciences of the Republic of Kazakhstan will monitor and safeguard publishing ethics.

Правила оформления статьи для публикации в журнале смотреть на сайте:

www:nauka-nanrk.kz

ISSN 2518-1629 (Online), ISSN 2224-5308 (Print)

http://www.biological-medical.kz/index.php/ru/

Редактор *М. С. Ахметова, Т. М. Апендиев, Д. С. Аленов*
Верстка на компьютере *Д. Н. Калкабековой*

Подписано в печать 11.07.2018.
Формат 60x881/8. Бумага офсетная. Печать – ризограф.
9,2 п.л. Тираж 300. Заказ 4.