Original Article

Possible Impact of Global Warming on the Evolution of Hemagglutinins from Influenza A Viruses*

YAN ShaoMin[1] and WU Guang[2,#]

1. National Engineering Research Center for Non-food Biorefinery, Guangxi Academy of Sciences, Nanning 530007, Guangxi, China; 2. Computational Mutation Project, DreamSciTech Consulting, Shenzhen 518054, Guangdong, China

Abstract

Objective To determine if global warming has an impact on the evolution of hemagglutinins from influenza A viruses, because both global warming and influenza pandemics/epidemics threaten the world.

Methods 4 706 hemagglutinins from influenza A viruses sampled from 1956 to 2009 were converted to a time-series to show their evolutionary process and compared with the global, northern hemisphere and southern hemisphere temperatures, to determine if their trends run in similar or opposite directions. Point-to-point comparisons between temperature and quantified hemagglutinins were performed for all species and for the major prevailing species.

Results The comparisons show that the trends for both hemagglutinin evolution and temperature change run in a similar direction.

Conclusion Global warming has a consistent and progressive impact on the hemagglutinin evolution of influenza A viruses.

Key words: Evolution; Global warming; Hemagglutinin; Influenza A virus; Mutation

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INTRODUCTION

The impact of global warming is a pressing problem related to studies in many research fields. Global warming affects various biological systems with the possibility of extinguishing many species[1]. At the same time, influenza A viruses continue to thrive and frequently threaten the world with the possibility of influenza pandemics and epidemics[2].

An important question thus arises: does global warming affect influenza A viruses? Because the phenomenon of global warming follows a time course, this question can be addressed in several ways: 1) if the cases of influenza either increase or decrease with global warming, then this may be difficult to assess, because anti-flu drugs would compromise our analysis; 2) if with global warming the virulence of influenza A virus becomes milder or more severe, then this could be investigated by arranging virulence along a time line; and 3) if global warming affects the evolution of influenza A virus, then this could be examined, because evolution also takes place along a time course.

However, the difficulty in estimating the effect of global warming on biological systems is that control tests cannot be run, because another earth uninfluenced by global warming is not available for comparison. However, we can analyze the evolution of influenza A virus, because the influenza A virus

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#Correspondence should be addressed to WU Guang. Tel: 86-771-2503930. Fax: 86-771-2503999. E-mail: hongguanglishibahao@yahoo.com

Biographical note of the first author: YAN ShaoMin, born in 1958, professor, majoring in computational mutation and quantitative pathological diagnosis.

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inhabits host cells in which the environment is stable in the short-term, but which would likely change with global warming.

With this in mind, we recently conducted several preliminary studies to analyze the potential impact of global warming on several protein families of influenza A viruses[3-5]. Influenza A viruses have ten different types of proteins and we now extend our analysis to another protein from the influenza A viruses. We have also incorporated newly available data from temperature and influenza databases.

Hemagglutinin is the major surface antigen of the influenza virus and is the most variable of the viral proteins. Neutralizing antibodies to hemagglutinin are elicited during virus infection and vaccination, making them the best protective immunity targets for vaccination strategies[6-9]. Because of its variability, hemagglutinin evolution should shed some light on the global warming questions listed above.

MATERIALS AND METHODS

Temperature Data

The global, northern and southern hemisphere temperature anomalies from 1850 to 2009, based on the period 1961–1990, were obtained from HadCRUT3 (variance adjusted combined land and marine temperature anomalies on a 5° by 5° latitude and longitude grid-box basis) on the website of the Climatic Research Unit, School of Environmental Sciences, University of East Anglia, UK[10-11]. The local temperatures from 1956 to 1998 based on 0.5° by 0.5° latitude and longitude grid-box basis cross globe were obtained from the website of the Oak Ridge National Laboratory[12].

Hemagglutinin Data

8 028 full-length hemagglutinin sequences of influenza A viruses sampled from 1956 to 2009 were obtained from the Influenza Virus Resources[13]. After excluding identical sequences[14], 4 706 hemagglutin ins were selected and used in this study.

Hemagglutinin Evolution

Because it is impossible to create an earth without global warming to compare the effects of global warming on hemagglutinin evolution, we studied this problem in the same way that we analyzed global warming, by observing the hemagglutinins along a time course. Thus, we analyzed hemagglutinin evolution driven by mutations.

Mutations are documented as changes in amino acids represented by letters. Therefore it is possible to represent the hemagglutinin evolution using letters along a time course. However, this approach is complicated, because we would have to use four variables; the hemagglutinin length, the mutation position, the original amino acid, and the mutated amino acid, along the time course. In this study hemagglutinin evolution is represented by the primary structure alone. Secondary structure could also be used as a measure to represent hemagglutinin evolution, as other approaches use human weight, height, and other parameters as measures to represent human evolution.

Because temperature is a number presented along the time course, we decided to use a number to represent hemagglutinin evolution and selected amino-acid pair predictability as the measure of choice. Because pure chance is often considered to lie at the heart of nature[15], this measure is based on a random mechanism and has been used successfully in many of our previous studies[16-26].

For a hemagglutinin sequence, we counted the first and second amino acids as an amino-acid pair, the second and third amino acids as another pair, and so on, to the next to terminal and the terminal amino acids as the last pair. Then, we determined whether the permutation could predict the appearance of each amino-acid pair. Finally we calculated the percentage of how many amino-acid pairs were predictable or unpredictable.

For example, ABX58294 human hemagglutinin, strain A/Kentucky/UR06-0259/2007(H1N1), has 565 amino acids, of which 45 are asparagine (N), 37 are valine (V), and 43 are glycine (G). The permutation could accurately predict the frequency of appearance of the NV amino-acid pair. Theoretically, it should appear three times (45/565×37/564×564=2.9 496) and in this hemagglutinin sequence the NV pair does appear three times, confirming that the frequency of appearance of the NV pair was predicted correctly. Similarly, the permutations predict the frequency of appearance of the NG amino-acid pair to be three (45/565×43/564×564=3.4 248); however, it actually appears nine times in the ABX58294 sequence, indicating the unpredictability of the NG pair.

In this way, we classified all the amino-acid pairs in this hemagglutinin as predictable (37.83%) or

unpredictable (62.17%), and then used either 37.83 or 62.17 as a scalar datum to represent this hemagglutinin.

Because mutations produce many different hemagglutinin sequences, different sequences will have a different predictable and unpredictable percentage of amino-acid pairs. For example, although ABX58558 human hemagglutinin, strain A/Tennessee/UR06-0076/2007(H1N1), has only one amino acid (at position 290) that is different from ABX58294 hemagglutinin, the predictable and unpredictable amino acid pairs were 38.43% and 61.57%, respectively, different from ABX58294 hemagglutinin.

Using this method, we transformed the 4 706 hemagglutinin sequences from a series of different letters into 4 706 numbers representing the predictable/unpredictable portions of the amino-acid pairs. Because the year when a hemagglutinin was sampled is well recorded, we could plot the 4 706 predictable/unpredictable portions of amino-acid pairs on to the time line and study the evolutionary trend along the time course compared with the changes in global temperature.

RESULTS

Using our representation of hemagglutinin evolution along the time course, we were able to determine the possible impact of global warming on hemagglutinin evolution. We used a simple and effective method to determine the trends for both global temperature and hemagglutinin evolution: 1) if global warming consistently affects hemagglutinin evolution, then both trends would run in similar or in opposite directions, and 2) if global warming has no impact on hemagglutinin evolution then the trend in hemagglutinin evolution would be horizontal and stable while the global temperature progressively increased. We then used these two possible outcomes to either reject or accept our hypothesis. To the best of our knowledge, there is no statistical test that can be used to compare the significance between two continuous lines.

Global Trend

The hemagglutinin database includes samples from around the world and is, therefore, very suitable to study the global trends for both hemagglutinin evolution and temperature change. As seen in Figure 1, both trends ran progressively in similar directions, indicating that global warming consistently affects hemagglutinin evolution. The unpredictable portion representing hemagglutinin evolution is plotted in Figure 1. As expected, the predictable portion, when plotted, runs in the opposite direction to the global warming trend (data not shown). These results support the hypothesis that global warming has an impact on hemagglutinin evolution of influenza A virus. Both the regressed lines (dotted lines in Figure 1) that are the elaboration of these data clearly show a similar trend.

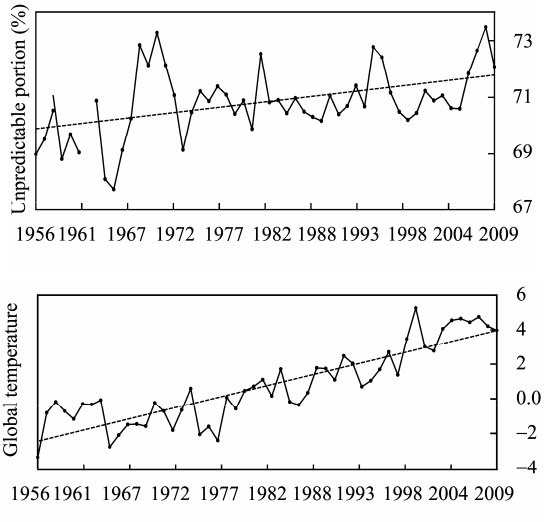

Figure 1. Global temperature anomaly (°C) and hemagglutinin evolution from 1956 to 2009. The dotted lines are the regressed lines, and the points for unpredictable portion are the mean of all hemagglutinins in a given year. Discontinuity of the curve is because of the lack of data in the given year.

The global temperatures are divided into northern and southern hemisphere temperatures and the area of ocean is far larger in the southern hemisphere, whereas influenza prevailed more in the northern hemisphere. Therefore, to determine if the trends still held, we grouped the hemagglutinins based on where they were found. Of the 4 607 hemagglutinins, 4 280 were sampled in the northern hemisphere and 327 were sampled in the southern hemisphere.

As seen in Figure 2, the general trend in which the unpredictable portion increased along the time course as the temperature rose still holds, especially in the northern hemisphere. Although it could be argued that this result is to be expected, because Figure 2 is a subset of the data from Figure 1, it does, however, rule out the possibility of significant differences caused by possible outliers from the data in Figure 1.

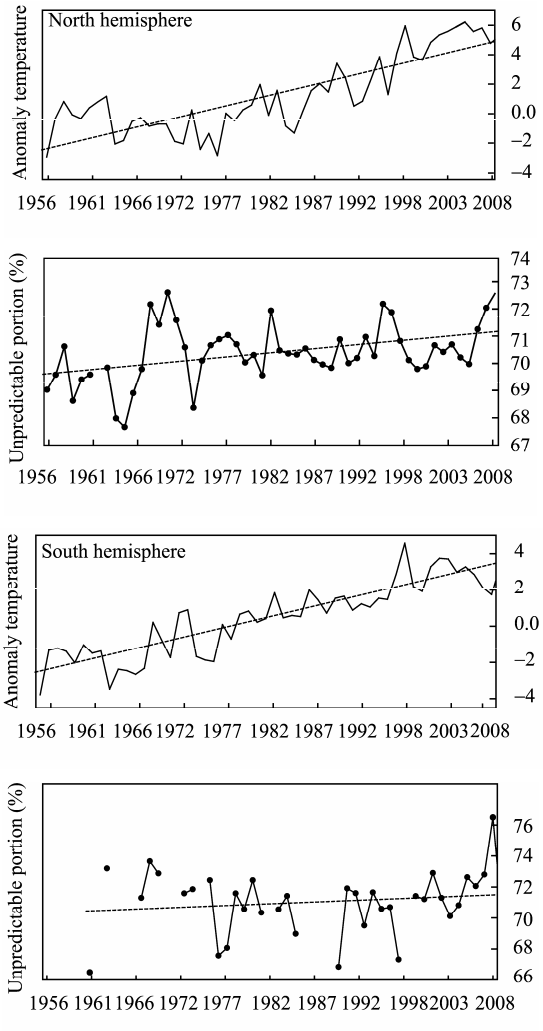

Figure 2. Temperature anomaly (°C) and hemagglutinin evolution from 1956 to 2009 grouped according to northern (n = 4 280) and southern (n = 327) hemispheres. The dotted lines are the regressed lines.

Point-to-Point Comparison

At global level, we used only the mean values that were the averages of thousands of samples of temperatures and hemagglutinins to test our hypothesis. Clearly, it is also important to scrutinize our hypothesis at a more local level, to look at the trends of temperature and hemagglutinin evolution in particular geographical regions. To do this, we used the latitude and longitude points along the time course. For example, ABQ01355 human hemagglutinin was sampled in Albany, where the latitude and longitude is 42.65° and 73.76° west according to Get Lat Lon[28]. We found that its average yearly temperature in 1960 was 8.38 °C according to the 0.5° by 0.5° latitude and longitude grid-box basis cross globe obtained from the website of the Oak Ridge National Laboratory [12].

Figure 3 is a plot of the point-to-point comparison, which was constructed as follows: 1) take, for example, ABQ01355 hemagglutinin that was documented in 1960 in Albany; and 2) plot its unpredictable portion (69.7%) in the lower panel and the average yearly temperature of Albany (8.38 °C) in the upper panel (see arrow in Figure 3). In this way, all 1 340 hemagglutinins that were documented the sampling place were associated with their local temperature for the point-to-point comparison.

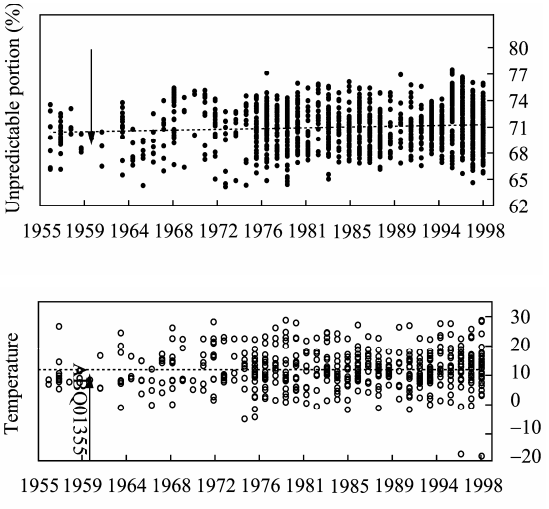

Figure 3. Point-to-point comparison of local temperature (°C) with hemagglutinin sampled from 1956 to 1998 (n = 1 340). Each point represents a local temperature in the given year (upper panel), corresponding to the place where a hemagglutinin was sampled (lower panel). The dotted lines are the regressed lines.

The temperature data with the 0.5° by 0.5° latitude and longitude grid-box were available until only 1999[12], limiting the point-to-point comparison in Figure 3. However, as demonstrated by the regressed lines, the trends can still be seen for both temperature change and hemagglutinin evolution as they both run parallel in a similar direction.

Point-to-Point Comparison for Species

To confirm the results obtained above, we further stratified the datasets to compare the trends of temperature and hemagglutinins sampled from different species. Figure 4 (a similar plot to Figure 3) is a plot of the point-to-point comparison of local

temperature and the species-wise unpredictable portion of the hemagglutinins. A consequence of the stratification of the dataset is the smaller sample size, which would be more susceptible to outliers. However, the trends that we have observed are still detectable in avian and human. Ideally, such point-to-point comparisons should be conducted in 4-dimensional space with latitude, longitude, time, and temperature as the four axes. However, the 4-dimensional presentation is beyond our ability.

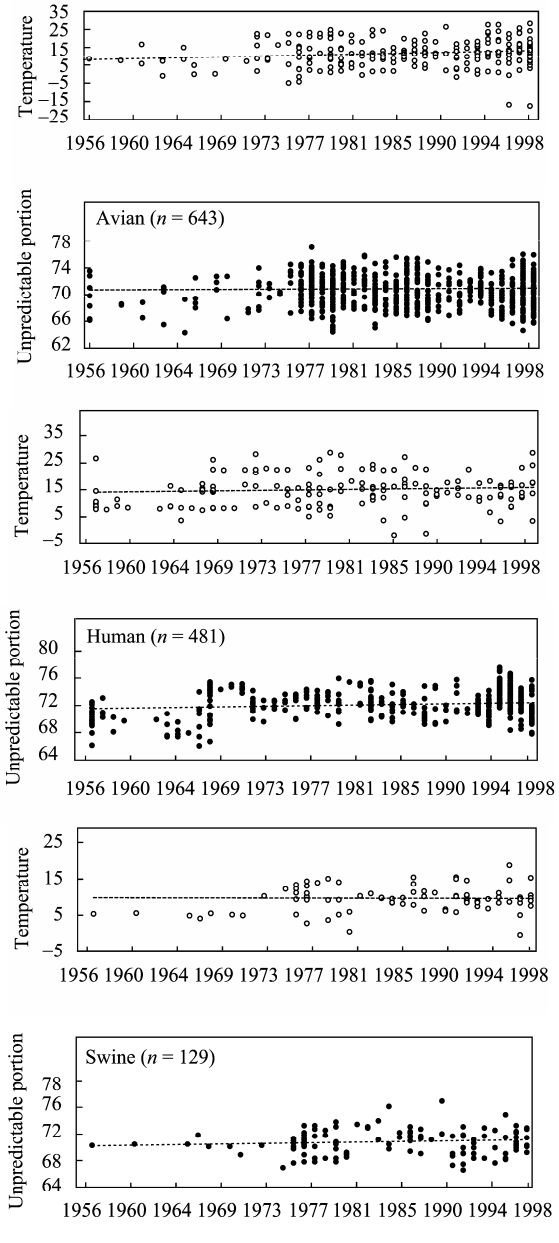

Figure. 4. Point-to-point comparison of local temperature (°C) and hemagglutinins sampl ed from avian, human and swine species.

DISCUSSION

In this study, we have examined the trends for both temperature change and hemagglutinin evolution from the global level to the local level, and to the hemagglutinins in selected species from all hemagglutinins available in the databases. The first question that we asked was, can a measure of randomness, in this case the predictable/ unpredictable portion of amino-acid pairs, in the hemagglutinins along the time course represent the evolution of hemagglutinin? The answer is yes, because pure chance can be considered to lie at the very heart of nature[15] and we have used this method successfully in many other studies[16-26]. More importantly, randomness (entropy) is clearly related to evolution either by the second law of thermodynamics[29] or by the dissipative structure[30].

It is well-known that influenza viruses display a remarkable genetic flexibility based on their high mutation rate under different selection pressures. Thus, while influenza vaccination provides hosts with protection from influenza infections, vaccination promotes mutations in the influenza virus to adapt to the new environment.

We earlier estimated the year-to-year mutation rate in proteins from influenza A virus using the fast Fourier transform[23]. The hemagglutinin evolution presented here is not directly linked to changes in the evolutionary rate of the virus genes, because global warming was recorded as temperatures at different years, whereas evolutionary rate is the mutations per year at different years. This would have given us to units that were not comparable.

The increase in the unpredictable portion of amino-acid pairs with time suggests that influenza A virus does its best to adapt to increases in the environmental temperature[31]. This is so because nature's parsimony demands that the least time and energy is used to construct non-functional parts of protein (the predictable portion of amino-acid pairs) and more time and energy is used to construct functional parts of protein (the unpredictable portion of amino-acid pairs)[27].

The second question raised here was: if global warming has an impact on hemagglutinin evolution, then to what degree is the impact exercised? The answer can be addressed in this way: when looked at as a whole, because the regressed line of hemagglutinin evolution is almost parallel to the regressed line of the global temperature along the time course, it seems likely that global warming

affects hemagglutinin evolution. However, case-by-case, global warming may have a different impact. The hemagglutinins hosted in avian and in other species will be subjected to different environmental influences, because, for example, birds can emigrate and are not affected by anti-flu drugs[32], whereas humans are generally localized and immunized. Climate change almost certainly alters bird migration, influencing the avian influenza virus transmission cycle and directly affecting virus survival outside the host[33-34]. Thus, the influence of global warming on the influenza A virus must go through multiple steps.

At this stage in our study, systematic trends are more important than the trends in individual cases, because numerous random and uncertain factors are masked. We aim to understand how the principal average trends arise before attempting to explain the individual cases that depart from them[35].

The results from this study are consistent with those from similar studies on other proteins[3-5] and extend them to include more data and a new level of discussion, which highlights the possible impact of global warming on the evolution of influenza A virus.

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