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Trends in Global Warming and Evolution of Neuraminidases from Influenza A Virus since 1918*

近百年来全球气候变暖的倾向和甲型流感病毒神经氨酸酶进化的倾向

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Abstract Using the amino-acid pair predictability to quantify 3874 neuraminidases of influenza A viruses, we analyzed their evolutionary trend and compared with the change in global temperature since 1918. The results showed the clearly similar trends in both the neuraminidase evolution and the global temperature change, and also these trends held on in several neuraminidase subtypes and different species. Our analysis was the first step for understanding the impact of global warming on the evolution of influenza A virus.

Key words global warming, amino-acid pair predictability, evolution, neuraminidase, influenza A virus, mutation

摘要:用氨基酸对的可预测性量化3874个甲型流感病毒神经氨酸酶,分析其进化趋势,并与近百年来全球气温变化趋势进行比较。结果显示,神经氨酸酶的进化和全球气温的变化有明显的相似趋势,而且这种趋势在一些神经氨酸酶的亚型和不同种属中依然存在。该分析结果是了解全球变暖影响甲型流感病毒进化的第一步。

关键词:全球变暖 氨基酸对可预测性 进化 神经氨酸酶 甲型流感病毒 变异
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The global warming is an important factor deeply affecting the life of humans and other species[1]. On the other hand, the influenza threatens the world with epidemics/pandemics, which in the past resulted in the death of millions of people[2~4]. An interesting question raised here is if the global warming could have impact on the evolution of influenza A virus, because history has evidenced the extinction of many species due to the dramatic climate changes[5~8]. Very recently, we have conducted several concept-initiated studies on the possible impact of global warming on the proteins from influenza A viruses[9~11], where we found the similar trends between global warming and the evolution of several protein families. However, there are ten types of proteins in influenza A virus, thus it is important to analyze if other proteins from influenza A viruses would have the similar trends as we found[9~11].

In this study, we are particularly interested in the neuraminidases from influenza A viruses, not only because our previous studies focused on three internal proteins of influenza A viruses, say, polymerase acidic protein[9], polymerase basic protein 2[10] and matrix protein 2[11], while the neuraminidase is a surface

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protein, but also because the neuraminidase has a critical enzymatic activity and has been a suitable target for designing agents against influenza A virus[12~14]. Therefore, understanding the mechanisms of neuraminidase evolution has a significant impact on humans to prevent influenza. Hence, it is important to see if the trend of neuraminidase evolution is similar to that of global warming, which is designed as the aim of this study.

1 Materials and methods

1.1 Temperature data

The global, north and south hemispheric temperature anomalies from 1850 to 2007, whose anomaly is based on the period 1961~1990, were obtained from HadCRUT3v[15,16]. The local temperature from 1918 to 1998 based on 0.5° by 0.5° latitude and longitude grid-box basis cross globe was obtained from New et al[17].

1.2 Neuraminidase data

A total of 4782 full-length neuraminidase sequences of influenza A viruses sampled from 1918 to 2008 was obtained from the influenza virus resources[18]. After excluded identical sequences, 3874 neuraminidases were used in this study.

1.3 Transferring neuraminidases into scalar data

Because the global warming is defined as the increase of temperature along the time course, we need the way to present influenza A virus neuraminidases along the time course in order to see their trends. However, it is impossible to present the neuraminidases in their current forms, which use 20 letters to represent amino acids, thus it is necessary to change the neuraminidases into numbers, which can be presented along the time course as the temperature does. We use the amino-acid pair predictability to do this job[19~21].

For example, the AAO46226 neuraminidase sampled from human influenza A virus is composed of 469 amino acids, of which there are 47 serines "S" and 40 isoleucines "I". If the permutation can predict the appearance of amino-acid pair SI: it must appear four times ($47/469 \times 40/468 \times 468 = 4.0085$), which actually is true, so the appearance of SI is predictable. By contrast, there are 32 asparagines "N" in this neuraminidase. If the permutation can predict the appearance of SN: it must appear three times ($47/469 \times 32/468 \times 468 = 3.2068$), but it appears seven times, so the pair SN is unpredictable. In this way, we classify all amino-acid pairs as either predictable or unpredictable, which are 32.91% and 67.09% in AAO46226 neuraminidase.

On the other hand, another neuraminidase (accession number AAO46227) has only one amino acid different from AAO46226 neuraminidase at position 290. However, their predictable and unpredictable portions are 33.33% and 66.67%, which are different from AAO46226 neuraminidase.

In this manner, we have different numbers to represent different neuraminidases for all 3874 neuraminidase. As each neuraminidase has its sampling year, we have two sets of data, one is global temperature and the other is the neuraminidases in numbers, thus we can plot both along the time course. In this study, we use the unpredictable portion to plot the data over time, which in fact is the evolution of neuraminidases.

2 Results and discussion

At first we compare the general trend in both global warming and neuraminidase evolution. Fig. 1 shows that the regressed lines have a clearly similar trend with respect to either temperature or neuraminidases, indicating that the unpredictable portion of neuraminidase increases as global temperature rises although the slopes for both regressions are different. There may be at least two explanations for different slopes, (i) the global temperature anomaly is based on the period 1961–1990[15,16], while we did not make such calibration for neuraminidases because this period would take about half of sampled neuraminidases, which would lead to bias in dataset; and (ii) the sampled neuraminidases are not balanced due to various historical and environmental restrictions, and the unbalanced data would lead the regression to have different slopes.

The global temperature has been divided into the temperatures in north and south hemispheres as there is more area of ocean in south hemisphere[17]. Therefore we can group the neuraminidases accordingly to see if the global trends still hold on in such a circumstance. As seen in middle and lower parts of Fig. 1, the general trend that the unpredictable portion increases along the time course as the temperature rises still holds on firmly. Clearly, the trend pattern of neuraminidase evolution in global scale mainly came from the neuraminidase evolution in north hemisphere.

The predictable portion represents the amino-acid pairs to be constructed with largest probability, i.e.,

nature would spend the least time and energy to construct a predictable amino-acid pair. On the other hand, nature would deliberately spend more time and energy to construct an unpredictable amino-acid pair with small probability, whose structure would be more complex[19-21]. From this viewpoint, the global warming is likely to lead the neuraminidase to deliberately spend more time and energy to against the changed environment, say, the influenza A virus adapts the global warming by means of creating more complex structure of neuraminidase to maintain its function.

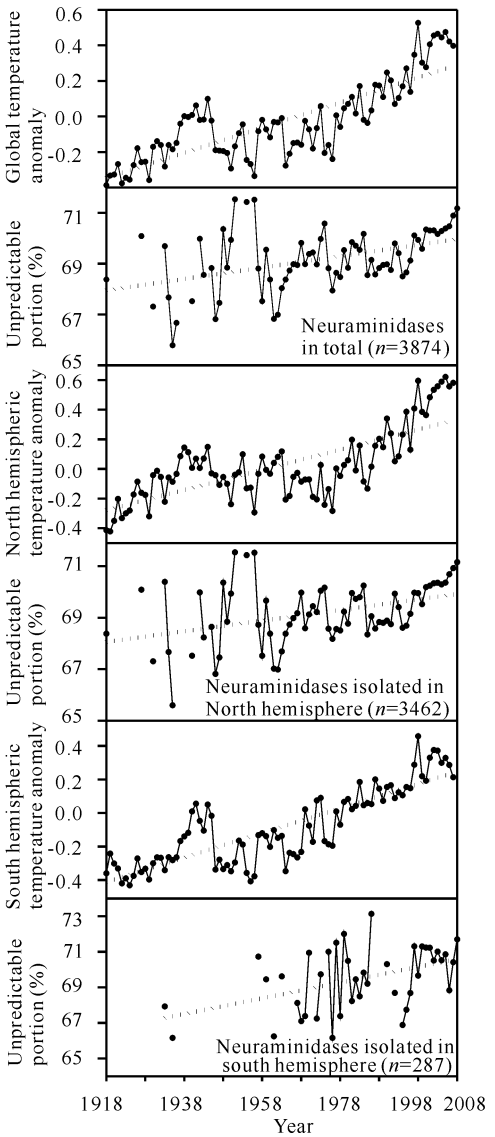

Fig. 1 Global, north and south hemisphereic temperature anomaly (℃) and neuraminidase evolution.

The dotted lines and points are regressed lines and the mean of all neuraminidases in a given year.

At the current level of documentation, we can see some synchronization between global temperature and neuraminidase evolution although we cannot exclude that there may be the lag-time between them.

Another way to further look at this issue is to analyze the point-to-point trend between temperature and neuraminidase, that is, we take the temperature measured at each geographical latitude and longitude of place where a neuraminidase was sampled at the same year to make the comparison.

For example, the 1918 H1N1 neuraminidase was sampled at Brevig Mission (accession number AAF77036), whose latitude and longitude are 65.34 and 166.49 west according to Get Lat Lon[22]. So we can find that the average yearly temperature was 6.26℃ in 1918 according to the 0.5° by 0.5° latitude and longitude grid-box basis cross globe obtained from New et al[17].

In this way, we can determine 1196 point-to-point comparison between the temperatures and unpredictable portions of neuraminidases. The regression in Fig. 2 demonstrates the similar trends between temperature and unpredictable portion of neuraminidase.

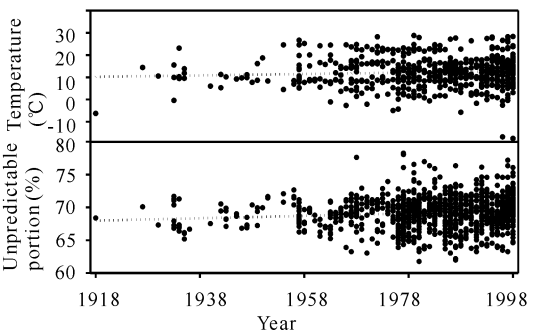

Fig. 2 Point-to-point temperature versus neuraminidase (n = 1196).

Each point represents a local temperature (℃) at the given year (upper panel), corresponding to the place where a neuraminidase was sampled (lower panel). The dotted lines are regressed lines.

This again supports the explanation that the neuraminidases are becoming less randomly constructed as the temperature increases.

Along the similar thoughts and approaches, we also compare the evolutionary trend in different subtypes and species of neuraminidases with respect to the global temperature. Fig. 3 displays the evolutionary trend in various neuraminidase subtypes along the time course with respect to global temperature. From this figure, we can see that each subtype seemingly has its own trend, which should be dealt case by case with respect to the global temperature trend.

In general, two features can be drawn from Fig. 3, that is, (i) the neuraminidase construction becomes less random in N1, N2 and N5 subtypes, but

more random in other subtypes as the temperature increases over time, so the global warming has different impact on different subtypes of neuraminidases; and (ii) N1 and N2 weigh heavily on the total trend of neuraminidase evolution because far more samples were collected. Another explanation for the difference among subtypes may be due to the fact that different subtypes of neuraminidase evolution reflect their different resistance to neuraminidase inhibitors[23, 24].

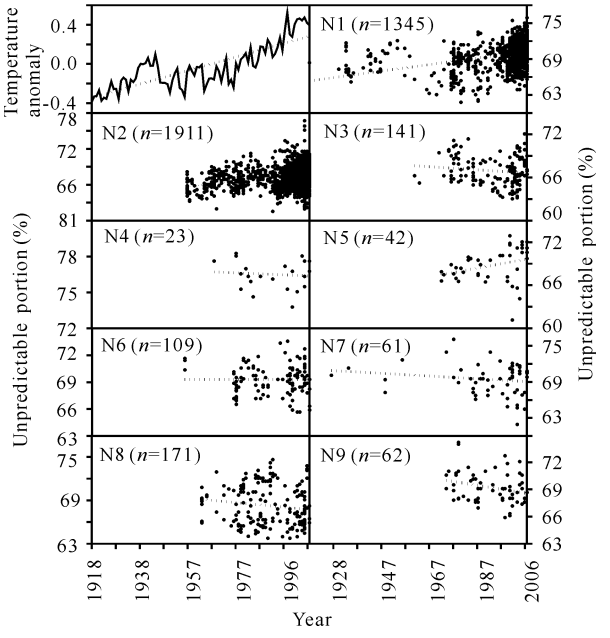

Fig. 3 Global temperature anomaly (℃) and neuraminidases in different subtypes.

Fig. 4 displays the neuraminidase evolution in several species with reference to global warming. The trend that it is similar to the global temperature can be found in all these species, from which the samples are obtained. However, the trend in avian is less clear than in other species, which is very suggestive because the other species are generally localized whereas the avian cannot be considered as a localized species, whose migration has drawn a great attention in virus spread[25-28].

Influenza A viruses live in their host cells, which are excellent microenvironment with respect to environmental temperature. In recent years, a structural difference with respect to temperature has been revealed in metabolic networks, implying that metabolic networks transit with temperature[29].

Our results demonstrate the similar trends in both temperature change and neuraminidase evolution, indicating that the global warming has the impact on the neuraminidase evolution, for which our explanations are (i) currently the only well-known and profound factor existed for last 100 years is global warming, and we cannot find out other factors having such a long effect in such a global scale; and (ii) we would not expect to have an explicit and direct relationship between global warming and neuraminidase evolution as host cell plays a certain role between them. In fact, many relationships related to evolution are implicit and indirect.

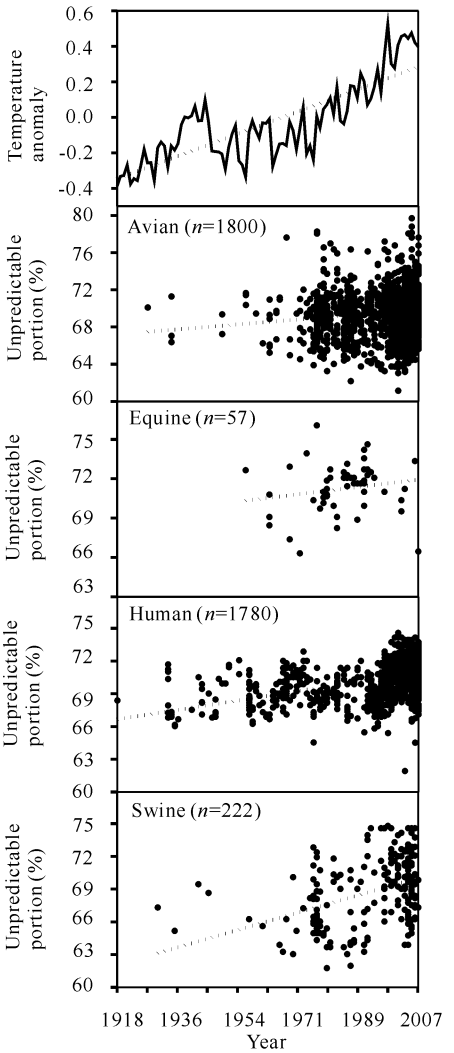

Fig. 4 Global temperature anomaly (℃) and neuraminidases sampled from different species.

It is also hard to apply a statistical test to this type of analysis, simply because we cannot create another Earth without global warming with active influenza A virus for statistical comparison. However, this type of study is the first step for our understanding of the impact of global warming on the evolution of influenza A virus.

3 Conclusions

In this proof-of-concept study, we compare the trends in the global warming and in the evolution of neuraminidases from influenza A viruses. The results are consistent with our previous studies, show the clear trends in both the evolution of neuraminidase family and the global temperature change, and these trends hold on still in several neuraminidase subtypes and different species. Our analyses are the first step for understanding the impact of global warming on the evolution of influenza A virus.

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