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Association Between HLA Gene Polymorphism and the Genetic Susceptibility of SARS Infection

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1. Introduction

Theoretically, any infectious disease with an infection source, transmission route, and susceptible population is able to infect any population. However, studies of human development history, especially those of infectious disease history, have clearly shown that ethnic and regional differences in susceptibility to some infectious diseases actually exist, even if their infection sources and transmission routes are the same. In terms of the 40 types of new infectious diseases that have occurred worldwide in the past 40 years, the epidemiology of some infectious diseases (including severe acute respiratory syndrome (SARS)) has been dominated by regional/territorial or ethnic oriented infections. Examples, along with the year of first occurrence, include: Ebola hemorrhagic fever caused by Ebola virus (1977), Legionnaires' disease caused by *Legionella pneumophila* (1977), hemorrhagic fever with renal syndrome caused by hantavirus (1977), T cell lymphoma leukemia caused by human T-lymphotropic virus type I (1980), hemorrhagic colitis caused by *E. coli* O157:H7 (1982), hairy cell leukemia caused by human T-lymphotropic virus type II (1982), and the British BSE (bovine spongiform encephalopathy) that created worldwide shock. Along with the effects of infection sources and transmission routes, the contributions of racial or genetic factors to these regional/territorial diseases are still under discussion. Clearly, these infectious diseases occurred more frequently and with greater severity in certain regions and ethnicities. The SARS outbreak in 2002-2003 spread mainly in Asia, especially in China; the most susceptible populations were mainland and overseas Chinese. These observations lead us to consider the important theoretical and practical topic of the relationship between SARS genetic predisposition and individual clinical onset. However, the sudden disappearance of SARS also left us with many revelations.

2. The correlation of disease genetic predisposition and MHC gene polymorphism

It is well known that the investigation of genetic predisposition is an important topic in modern medicine. It helps to clarify not only the fundamental reasons for patients' individual differences but also the pathogenesis of many diseases. Better understanding of genetic predisposition can provide prevention and treatment strategies for the corresponding diseases, an especially important consideration for individualized disease prevention and treatment. Modern medical studies have shown that disease is a specific life process formed by interactions of environmental factors (external) and the human body (internal). Genetic factors are the major basis of an organism's reactivity, including defensive immunity, the functional states of the nervous and endocrine systems, nutritional status, psychological factors, age, gender, etc. Among these numerous factors, genetic factors predominate because, besides external factors, immune responses and neuropsychological and endocrine functions are constrained by genetic factors. Even nutrition status is not based only on the quality and quantity of the exogenous nutrient supply. It is also influenced by digestion, absorption, and utilization functions controlled by genetic factors. Gender and age (an organism's reactive characteristics at different ages) are even more determined by genetic factors. Therefore, organism reactivities determined by genetic factors have been collectively called genetic predisposition. Numerous studies have demonstrated that many severe diseases, such as cancer, atherosclerosis, coronary heart disease, diabetes, schizophrenia, and high blood pressure, have significant genetic predispositions. In addition, some infectious diseases caused by bacteria and viruses have significant individual genetic predispositions. The human immune and genetic system most closely related to genetic predisposition to disease is the major histocompatibility complex (MHC).

Human MHC is also named as human leucocyte antigens (HLA) system, which codes for the most polymorphic antigen system that is known. The correlation of HLA and human diseases has been studied for nearly 40 years. The rapid development of advanced technologies in modern molecular biology and their wide applications to HLA studies have effectively promoted studies of HLA mechanisms and their associations with disease, leading to significantly increased accuracy of disease association analysis. Many alleles have been identified as being primarily associated with certain aspects of diseases. For example, in autoimmune diseases, Hodgkin's disease and HLA-A1 have relative risk (RR) of 32. 0; congenital adrenal hyperplasia and HLA-B47 have relative risk of 15. 4; ankylosing arthritis and HLA-B27 have relative risk of 87. 4; Reiter's syndrome and HLA-B27 have relative risk of 37. 0; acute anterior uveitis and HLA-B27 have relative risk of 10. 4; psoriasis and HLA-Cw6 have relative risk of 13. 3, etc. In infectious diseases, Hepatitis B virus associated glomerulonephritis and HLA-DQB1*03 have relative risk of 12. 90; infection and development of AIDS are highly correlated with HLA-A29, HLA-B35, and B57; infection and development of flu are closely correlated with HLA-A2 antigen; hepatitis B is separately correlated with HLA-B13, B8, DR7, DR13; and infection and development of hepatitis C are closely correlated with HLA-DRB1*0402, DRB1*12 and DQB1*0301. Therefore, correlation studies of HLA and different diseases can

help the identification and classification of diseases. The studies could also be treated as auxiliary diagnostic tools. While conducting such studies, researches could further clarify the relationships between diseases and genetic inheritance, provide genetic consulting services to specific families, detect HLA-linked disease genes, and, most importantly, provide early predictions and preventions of these diseases.

3. The correlation of SARS genetic predisposition and HLA gene polymorphism

SARS virus is a recently discovered infectious pathogen that can cause severe human diseases, and, to date, we know little about it. Knowledge of its occurrence and development pattern remains limited, and studies of its pathogenesis, treatment, and prevention strategies remain limited. Considering that SARS displays significant regional/territorial and ethnic and individual specificity, and that the SARS-associated antigen epitopes are almost all related to HLA antigen recognition, as inferred by known SARS gene and protein sequences, we hypothesize that there is a close correlation between the occurrence of a SARS epidemic and the HLA system.

3.1. Speculations regarding susceptible genes based on SARS coronavirus (SARS-CoV) structure

Previous studies demonstrated that although SARS-CoV and other known coronaviruses have less than 40%-50% homology in amino acid sequence, their structures and functions are similar to those of other known coronaviruses. The antisera of transmissible gastro-enteritis virus (TGEV), murine hepatitis virus (MHV), Feline infectious peritonitis virus (FIPV), and 229E human coronavirus can inhibit the growth of cultured SARS viruses. In the known OC43 and 229E coronavirus strains, HLA-A3.1 was shown by some studies to be the receptor of OC43 and aminopeptidase N (APN), also known as metalloproteinases or CD13, and the co-receptor of human coronavirus 229E and cats/pigs coronavirus. A recent study using molecular 3D structure simulation showed that CD13 also interacted with the S protein of SARS virus. Carcinoembryonic antigen (CEA) is the S protein receptor of human/rats coronavirus. The invasion, infection, and disease caused by OC43 must be accompanied by the presence and expression of HLA-A3.1. The invasion, infection, and disease caused by coronavirus 229E must be accompanied by the presence and expression of aminopeptidase N. On the other hand, carcinoembryonic antigen may be the required co-receptor for many coronavirus infections. Theoretically, HLA-A3.1 is the susceptible gene of SARS coronavirus, and individuals without this susceptible gene are not easily affected or have resistance to the disease.

3.2. Population genetics studies of HLA gene polymorphism and SARS genetic predisposition

SARS is a highly contagious disease with high disease incidence and mortality rate. The limited diffusion mode based on East and Southeast Asian countries has indicated the existence of

susceptible genes in these populations. This has been corroborated in numerous clinical case-control studies, but some other studies yielded opposite results. In the 2 months immediately following the last outbreak of SARS in Taiwan, Taiwan scholars recruited 658 employees from hospitals who had just experienced their initial or the most severe SARS infections to help the investigation of related infectious and genetic factors of SARS-CoV. They used an enzyme immunoassay to test the infections of SARS-CoV and then employed western blot analysis, antibody neutralization, and commercial SARS tests for verification. Risk evaluations were prepared through questionnaires and sequence-specific oligonucleotide probe analysis of the human leukocyte antigen (HLA) allele. The study showed that 3% (20/658) of the participants were positive. A female nurse with a subclinical case was identified. Identified risk factors of SARS-CoV infection included working in the same building, such as hospital emergency rooms and infection wards, direct nursing for SARS patients, and carrying the HLA-Cw*0801 allele. The SARS-CoV infection ratio of homozygous and heterozygous Cw*0801 carriers was 4.4:1 (95% confidence interval, 1.5-12.9; $P=0.007$). However, in September 2006, 3 years after the SARS outbreak in Taiwan, 130 diagnosed SARS patients were studied to evaluate the correlation of their SARS antibody levels and HLA types. Western blot analysis illustrated that 6.9% of the participants still had anti-spike and antinuclear antibodies. HLA-SARS case-control studies revealed that HLA-Cw*1502 and DRB1*0301 genes might be the resistance factors of SARS infection ($P<0.05$).

Another study in the Taiwan population also proved the correlation between HLA and SARS. The researchers used PCR-sequence specific oligonucleotides probe (SSOP) to study the genotyping of HLA type I and type II alleles. The study population included 37 suspected SARS cases (28 fever patients were excluded from SARS) and 101 non-infected medical staff who might have been exposed to SARS-CoV. Another control group contained 190 healthy, non-related Taiwanese people. Initially, during the analysis of SARS infected patients and the high-risk medical staff, the researchers found that HLA-B*4601 (OR = 2.08, $P = 0.04$, $P_c = n.s.$) and HLA-B*5401 (OR = 5.44, $P = 0.02$, $P_c = n.s.$) might be the most probable factors assisting SARS-CoV infection. When comparing the "severe patient" group (selected from the SARS patient group) and the high-risk medical staff group, the researchers found that the severity of SARS was significantly correlated with HLA-B*4601 ($P=0.0008$ or $P_c=0.0279$). Until recently, no SARS patient had been found among local Taiwanese whose genes were different from ordinary Taiwanese. They carry no HLA-B*4601 gene but have HLA-B*1301 at a high frequency. However, the increased HLA-B*4601 allele frequency found in the suspected SARS patient group was significantly higher in severe patient group. These results support the hypothesis that the HLA-B*4601 gene in Asian populations is correlated with the severity of SARS infection.

Another study also showed that SARS infection was correlated with Chinese HLA. This study determined a strong correlation between SARS development and HLA-B*0703 (OR, 4.08; 95% CI, 2.03-8.18; $P=0.00072$ [Bonferroni corrected P value, $P_c<0.0022$]) and DRB1*0301 (OR, 0.06; 95%, 0.01-0.47; $P = 0.00008$ [Bonferroni corrected, $P_c<0.0042$]), through the human leukocyte antigen (HLA) A, B, DR, or DQ allele type analysis of 90 serologically diagnosed Chinese SARS patients. Compared with the expected value (0.4%) in ordinary people, the joint

inheritance rate of B*0703 and B60 (9.6%; 95% CI, 4.6% - 19%) showed a significant increase in the SARS patient group ($P = 3 \times 10^{-9}$).

Evidences of the SARS-HLA correlation has also been found in other Asian populations. In Vietnam 44 out of 62 SARS patients participated in a study. The control groups were 103 individuals who had contact with SARS patients and 50 individuals who had not. Compared with the control groups, HLA-DRB1*12 occurred more often in the SARS patient group (corrected $P = 0.042$). HLA-DRB1*1202, the dominate gene in Vietnamese, showed the strongest correlation with SARS in the dominant model (corrected $P = 0.0065$ and 0.0052 , depending on the size of the control group).

However, some studies resulted in the opposite conclusions. Xiong P, *et al.* conducted correlation studies of HLA gene polymorphism and SARS in Cantonese after their initial infection by SARS, but did not find a correlation. The study included 95 SARS rehabilitation patients and 403 genetically unrelated healthy people (control group). HLA -A, B, and DRB1 allele analysis was conducted by sequence-specific primer polymerase chain reactions. The severity of disease was evaluated by assisted ventilation and lymphopenia based on their history of pulmonary infiltrates. Although the frequencies of A23, A34, B60, and DRB1*12 alleles were slightly higher in SARS group and the frequency of A33, -B58, and -B61 alleles in SARS group were all lower than those in control group, the P values indicated no statistical significance. Similarly, the correlation between HLA alleles and disease severity was not found. Therefore, the main organization of MHC variation appears not to have significant correlation with Cantonese SARS predisposition or severity.

4. The revelations SARS brought to people

Early in Feb. 2005 on an annual meeting of Association for the Advancement of Science (AAAS), an American microbiologist Kathryn Holmes, who had long been engaged in coronavirus researches, pointed out that it was not impossible to have another outbreak of severe acute respiratory syndrome (SARS) in the world like the one 2 years ago. The SARS-CoV used to spread in populations might only exist in laboratory samples. Her words shocked the world. It has been 10 years since the SARS pandemic. Many scholars conducted broad and indepth studies but have not achieved breakthroughs with respect to the origin of SARS CoV. On the contrary, the new influenza A virus (H1N1) that spread worldwide in April 2009 was studied thoroughly during the first 2 months of its spreading. It has 8 types of genes coming from 4 pedigrees and is very similar to the North American popular triple ligand swine H1N1 virus. Different from other viruses, there has been no SARS patient other than lab infections after the widespread infections in January 2004. SARS-CoV does not exist in nature or people now. Hence the natural SARS epidemic history has some extraordinary abnormalities. What are the reasons? The most important reason could be that there is no direct ancestor of SARS-CoV in nature. It had an "unusual evolution". It is very likely that it was "unnaturally" introduced to populations, so it did not follow the normal epidemic transmission rules.

SARS-CoV has an unordinary phylogeny. It has a fast and obvious “reverse evolution.” “Reverse evolution” is defined as “regaining the ancestor’s state” and is an evolution component that commonly exists in the biosphere, including microbial communities. In the long course of natural evolution, “reverse evolution” might be largely supplemental and it might coordinate “forward evolution”, acting as the twists and turns of mainstream evolution. However, the “reverse evolution” of SARS-CoV appears earlier and more powerfully, and it has more presence and lasts longer. In the early state of its epidemic, it had already lost the genes related to host adaptability (characteristic 29-ntORF8 gene) and presented “reverse evolution” of key amino acids on the virulence and transmission-related receptor’s binding site. The SARS-CoV outbreak in 2003-2004 in Guangzhou was phylogenetically closer to earlier viruses in the 2002-2003 epidemics than the later viruses. Under natural conditions, it is not possible that the adaptive evolution of Bt-SLCoV could have developed to the human level through carnivores in such a short time. Therefore, the only possible explanation is that SARS-CoV was produced through “unusual evolution (UE),” via processes such as like GM technology.

There have already been some debates about the technical maturity of transforming animal virus to human virus (for example, GM technology). However, it would be indisputable now, as in May and June 2012, a top international journal published 2 papers, which shocked the international natural science field in 2011 and clarified this problem by facts. However, according to some international information sources, in 2000 or earlier some scientists were studying or had already mastered these technologies at those early dates.

Therefore, Xu D *et al.* reasoned that there was no storage host of SARS-CoV in nature and it was made by “unnatural ways (GM technology)” from Bt-SLCoV, which means we had already entered a new era where a “novel artificial virus” could cause a global epidemic. We can further explain the unnatural origin of SARS from its apparently abnormally epidemiological and clinical characteristics: 1) in the early and middle stages of the epidemic, all Cantonese patients were from the west and the south of Guangzhou while there was not even 1 patient from the north or the east; 2) During December 2003 to January 2004, 4 cases in Guangzhou had only mild symptoms and no sustainability due to the reverse evolution of SARS-CoV in the population. However, during March and April 2004, the outbreak from a laboratory (9 cases and 1 death) was super transmissible, which was the same as in the 2002-2003 epidemic, without reverse evolution; and 3) As a specific infection source, infected civets were found only in 2 animal markets in Guangzhou and Shenzhen and could have been used for unnatural introduction. Therefore, we are facing unprecedented threats today, and we must deal with them together.

5. Conclusions

The investigation of the SARS in-out flow epidemic transmission network in mainland China shows that Beijing and Guangdong were the places where the exported cases and self-transmission cases were the most severe. Guangzhou was the origin of the transmission of

SARS and the main import source of the early-stage regional cases of infection in most areas, but it did not cause significant radiation of transmission to its neighboring regions. Nevertheless, the in-out flow between Beijing and its neighboring regions did not start until the middle to late stages of the epidemic transmission. The transmission, however, was able to radiate significantly across regions. There have been no other cases reported among people and among animals except for laboratory infections and 4 mild infections reported in Guangzhou in December 2003 and January 2004. This is different from the trend of typical epidemic transmissions, and it is different from the correlation between the HLA gene polymorphism and SARS, as demonstrated by many studies. The HLA alleles that are closely related to the infection of SARS, such as B*4601, B*5401, Cw0801, and DRB1*0301, as found among populations from Taiwan, Hong Kong, and mainland China, are types of HLA alleles that are relatively common in the Chinese population. Why were only people in limited regions infected? Further, why did the transmission disappear rapidly?

The study of Xu D *et al.* appeared to provide a good explanation to the paradox between the HLA gene polymorphism and the genetic predisposition to SARS. Because of the unusual virus phylogeny of SARS-CoV, with rapid and evident “reverse evolution,” it is likely that SARS CoV was produced through an unnatural mechanism (such as gene modification techniques). The SARS CoV from the outbreak in Guangzhou during 2003-2004 was phylogenetically closer to earlier viruses in the 2002-2003 epidemics than the later viruses, which led to its rapid decrease in virulence. Therefore, the correlation would be expected to disappear because of the reverse genetics of SARS-CoV, regardless of whether the susceptible gene existed in the Chinese population. Of course, these conclusions can be supported and the nature of this mysterious disease can be explained only with the support of a large number of valid and convincing investigational results.

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