資料1－4

Alarms ring over bird flu mutations.

（トリインフルエンザの変異に警鐘）抜粋

Butler D. Nature. 2006 Jan 19;439(7074):248-9.

The first mutation found, announced last week, involves a substitution in one sample of an amino acid at position 223 of the haemoagglutinin receptor protein. This protein allows the flu virus to bind to the receptors on the surface of its host's cells. It increases the virus's ability to bind to human receptors, and decreases its affinity for poultry receptors, making strains with this mutation better adapted to infecting humans.

赤血球凝集素（haemoagglutinin）受容体タンパクの 223 番目のアミノ酸配列に変異がある。このタンパクはインフルエンザウイルスが宿主細胞表面の受容体に結合するためのものである。この変異はウイルスがヒトの受容体に結合能力が増加し、家きんへの結合能力が減少する。

Finally, both samples from the Turkish teenagers show a substitution of glutamic acid with lycine, at position 627 of the polymerase protein, which the virus uses to replicate its genetic material.

トルコの10代の患者から、ウイルスのポリメラーゼタンパクの627番目のタンパクのグルタミンがリジンに変わってことがわかった。

The Turkey strains are the first in which the polymerase and receptor-binding mutations have been found together. They could make it easier for humans to catch the virus from poultry. But they might also favour human-to-human transmission. This is because the polymerase change helps the virus to survive in the cooler nasal regions of the respiratory tract, and the haemoagglutinin mutation encourages the virus to target receptors in the nose and throat, rather than lower down in the lungs The virus is thought to be more likely to spread through droplets coughed from the nose and throat than from infections lower down.

トルコの株は、ポリメラーゼと受容体結合タンパクの変異が初めて見つかった。この変異はヒトが家きんからのウイルスに感染しやすくなる。この変異は、ヒトからヒトへの感染を引き起こしやすいに違いない。ポリメラーゼの変異によってウイルスは冷たい鼻の部位で生存しやすくなる。そして、ウイルスは、赤血球凝集素に関わるタンパクの変異は深い肺の気道よりも、鼻や喉のレセプターに結合しやすくなる。咳をするときに、深い肺の気道からの飛沫よりも、鼻や気道からの飛沫の方がウイルスは拡散しやすくなる。

NEWS

Alarms ring over bird flu mutations

Scientists studying virus samples from the human outbreak of avian flu in Turkey have identified three mutations in the virus's sequence. They say that at least two of these look likely to make the virus better adapted to humans.

The Turkey outbreak is unusual, because of the large family clusters of cases; the fact that many of those infected have only mild symptoms; and the speed with which infections have arisen — twenty cases, including four deaths, in less than two weeks. So scientists are urgently trying to establish whether the virus is behaving differently in this outbreak from previous ones in Asia. In particular, international teams are investigating the possibility that the virus is moving between people.

"With such a large number of cases within such a short period of time, human-to-human transmission is something that we've had to consider," says Maria Cheng, a spokeswoman at World Health Organization (WHO) headquarters in Geneva.

As *Nature* went to press, samples from the first two teenagers in the country to die had been sequenced by a WHO collaborating centre at the National Institute of Medical Research (NIMR) in London.

The results so far are not comforting. The first mutation found, announced last week, involves a substitution in one sample of an amino acid at position 223 of the haemoagglutinin receptor protein. This protein allows the flu virus to bind to the receptors on the surface of its host's cells.

This mutation has been observed twice before — in a father and son in Hong Kong in 2003, and in one fatal case in Vietnam last year. It increases the virus's ability to bind to human receptors, and decreases its affinity for poultry receptors, making strains with this mutation better adapted to infecting humans.

The same sample also contained a mutation at position 153 of the haemoagglutinin protein, *Nature* has learned. Cheng says this information was not included in WHO statements, because "it is not clear what role this particular change plays".

Finally, both samples from the Turkish teenagers show a substitution of glutamic acid with lycine, at position 627 of the polymerase protein, which the virus uses to replicate its genetic material. This mutation has been seen in other flu sequences from Eurasian poultry over the past year. It was also present in the one person who died during an outbreak of H7N7 in the Netherlands in 2003, and in a few people in Vietnam and Thailand.

The recent outbreak of bird flu in Turkey has thrown up viruses with mutations that threaten humans. O. ORSAL/AP

"Human-to-human transmission is something that we have had to consider."

The polymerase mutation is one of the ten genetic changes that gave rise to the 1918 pandemic flu virus. Like the 223-haemoagglutinin mutation, it signals adaptation to humans, says Alan Hay, director of a WHO influenza laboratory at the NIMR. "There is this glutamic acid–lysine

flip," he explains. "Glutamic acid is associated with flu-virus replication in birds, and lycine is in primates."

The Turkey strains are the first in which the polymerase and receptor-binding mutations have been found together. They could make it easier for humans to catch the virus from poultry. But they might also favour human-to-human transmission. This is because the polymerase change helps the virus to survive in the cooler nasal regions of the respiratory tract, and the haemoagglutinin mutation encourages the virus to target receptors in the nose and throat, rather than lower down in the lungs. The virus is thought to be more likely to spread through droplets coughed from the nose and throat than from infections lower down.

Hay points out, however, that it is difficult to predict how the mutations will actually influence the virus's behaviour. He adds that just two changes are unlikely to create efficient human-to-human transmission on their own.

Establishing what effects these changes are having on the epidemiology of the current outbreak is a top priority for research teams working in Turkey. "We must learn more about the mild cases and be absolutely sure of whether these viruses are behaving differently from those we have seen elsewhere," says Hay. "It is early days in terms of what we know about the viruses causing these infections."

Researchers are sequencing more strains from the Turkey cases, to see whether they share the mutations and to check for further changes. Samples were expected to arrive in London on 18 January, after being held up for more than a week in Turkey because of the Eid ul-Adha holiday period. ■

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