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Research letters

Genomic characterisation of the severe acute respiratory syndrome coronavirus of Amoy Gardens outbreak in Hong Kong

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Severe acute respiratory syndrome (SARS) is a global health concern. In Hong Kong, two major outbreaks, one hospital based and the other in the Amoy Gardens apartments, were identified. The frequency of diarrhoea, admission to intensive care, and mortality differed significantly between the two outbreaks. We did genomic sequencing for viral isolates from five Amoy Gardens patients. The virus sequence was identical in four of these five patients. The sequence data from one hospital case and the four identical community cases had only three nucleotide differences. Alterations in the SARS coronavirus genome are unlikely to have caused the distinctive clinical features of the Amoy Gardens patients, and these results highlight the importance of non-viral genomic factors in this outbreak.

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Severe acute respiratory syndrome (SARS) is a global health concern. Hong Kong has been one of the greatest affected cities in the world. By May 15, 2003, the local case number had amounted to 1703, and a quarter of these cases were part of two major epidemiological outbreaks. The first took place at the Prince of Wales Hospital, Hong Kong, to which 156 SARS cases were admitted between March 11 and March 25, 2003.[1] The second major outbreak occurred in the community, where 321 residents of the Amoy Gardens had been infected by April 15, 2003.[2] The Amoy Gardens is a densely populated housing complex of ten 33-storey apartment blocks, with eight units per floor. The two outbreaks were characterised by the rapid spread of infection among individuals. Yet certain features in the disease spectrum differed between the outbreaks. The proportion of hospital patients reporting diarrhoea was 20% compared with 73% of Amoy Gardens patients.[1,3] The intensive-care unit admission rates were 23% and 32%, respectively, and the mortality rates were 4%[1] and 13%, respectively. Although several mechanisms might account for these differences, sequence variations in the viral genome have been postulated.[3] To investigate this possibility, we compared the viral genomic sequences obtained from representative cases of both outbreaks.

The two outbreaks were probably epidemiologically linked. The Prince of Wales Hospital outbreak was traceable to an inpatient who was among the first cluster of SARS cases in Hong Kong linked to a local hotel.[1] The suspected Amoy Gardens index case was a man who attended the Prince of Wales Hospital regularly for haemodialysis (patient 1).[2] He attended three haemodialysis sessions during the stay of the hospital-outbreak reference patient, and on the same hospital floor. 3 days after a haemodialysis session on March 12, 2003, patient 1 complained of fever, cough, and myalgia. Subsequently, on March 19, 2003, he lodged overnight with his brother, who lived in the Amoy Gardens complex. Patient 1 developed diarrhoea, and SARS coronavirus (SARS-CoV) infection was confirmed by RT-PCR. The number of Amoy Gardens residents diagnosed as having SARS rose strikingly after his stay, peaking on March 24.[2] 41% of cases were from the same block in which patient 1 stayed, many from the same or the adjacent unit. These two units shared a common ventilation light-well and a vertically linked faulty sewage system that were implicated as the environmental factors contributing to the outbreak.[2]

To identify the SARS-coronavirus sequence characteristic of the Amoy Gardens outbreak, we obtained clinical samples from patient 1 and from two other residents infected with SARS (patients 2 and 3) randomly selected from the unit where patient 1 had stayed or from the adjacent unit. These two patients had serological and virological evidence of SARS-CoV infection. Patients 2 and 3 presented initially with fever, myalgia, and malaise, and developed diarrhoea from days 3 and 4, respectively, after symptom onset. Patient 2 recovered, but patient 3 required intensive-care treatment and died. We did full genome sequencing for SARS-CoV on RT-PCR products of uncultured clinical materials: serum from patient 1 (isolate CUHK-AG01, GenBank accession number AY345986); nasopharyngeal aspirate from patient 2 (CUHK-AG02, AY345987); and stools from patient 3 (CUHK-AG03, AY345988; details are available at http://image.thelancet.com/extras/03let8014webappendix.pdf). We compared sequence data of the three viral isolates with the

	Open reading frame*	Tor2 (AY274119)	Urbani (AY278741)	Mother of inpatient Su-10 (AY282752)	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Nucleotide positions*									
3852	orf1a	T serine	T serine	T serine	C serine	C serine	C serine	C serine	C serine
11 493	orf1a	C tyrosine	C tyrosine	C tyrosine	T tyrosine	T tyrosine	T tyrosine	T tyrosine	T tyrosine
17 166	orf1b	A isoleucine	A isoleucine	A isoleucine	A isoleucine	A isoleucine	G valine†	A isoleucine	A isoleucine
28 102	orf11	A asparagine	A asparagine	A asparagine	A asparagine	A asparagine	C threonine†	A asparagine	A asparagine
28 696	Nucleocapsid protein	G glycine	G glycine	T cysteine†	G glycine	G glycine	G glycine	G glycine	G glycine

Tor2 and Urbani sequences listed for reference among Amoy Gardens and Prince of Wales Hospital isolates. Information in parentheses=GenBank accession numbers.*Nucleotide positions and organisation of open reading frames based on Tor2 sequence (reference 5). †Altered aminoacid.

Sequence comparison of SARS-CoV isolates of hospital and community outbreaks restricted to nucleotide positions with sequence differences between community and hospital isolates

sequence previously obtained from the infected mother of the index case of the Prince of Wales Hospital outbreak (isolate Su-10, GenBank accession number AY282752; table). The table shows that only three nucleotide differences (at positions 3852, 11 493, and 28 696) were noted between patient 1 and the Su-10 sequence, which provides molecular evidence that patient 1 probably acquired the infection from the hospital. Two of these nucleotide changes did not result in aminoacid substitutions. The remaining one (at position 28 696) resulted in a change from cysteine to glycine, but this substitution is unlikely to be related to the distinctive clinical features of the Amoy Gardens outbreak because a glycine at this position is seen for many other SARS-CoV isolates, including the Tor2 and Urbani isolates (table).[4,5]

The viral genomic sequence for patient 2 was identical to that of patient 1, whereas that for patient 3 differed at two nucleotides (positions 17 166 and 28 102; table). To further elucidate the importance and prevalence of these latter changes, we sequenced the five nucleotide positions referred to in the table for viral isolates obtained from naso-pharyngeal aspirates from two additional Amoy Gardens patients (patients 4 and 5; table). Patient 4 had mild diarrhoea and did not require admission to intensive care. Patient 5 had no diarrhoea. Each of these additional viral isolates showed a sequence identical to those from patients 1 and 2, which suggests that the nucleotide alterations at positions 17 166 and 28 102 in the viral isolate from patient 3 were a special case.

The viral isolates obtained from the Amoy Gardens outbreak were typified by that of patient 1. Our findings further support the likelihood of patient 1 being the index of the outbreak. The unique nucleotide differences that distinguish this viral isolate represent the molecular fingerprint of the Amoy Gardens viral isolate. The recurrent demonstration of the presence of this isolate among studied Amoy Gardens patients lends further support to the proposed environmental route of transmission implicated in the outbreak. Sequence variation in the SARS-CoV genome is not responsible for the distinct clinical features of the Amoy Gardens outbreak. Thus, further work should be focused on investigating the possible role of other unique features on this outbreak in explaining the clinical characteristics of this cohort. Our findings highlight the usefulness of molecular investigations in supplementing investigations in clinical and environmental epidemiology.

Contributors

S S C Chim and S K W Tsui contributed equally to this article. S S C Chim, S K W Tsui, K C A Chan, T C C Au, Y K Tong, and E K O Ng did genomic sequencing of viral isolates. E C W Hung and R W K Chiu assessed the correlation between clinical and molecular data. P K S Chan and J S Tam did the virus isolation work. J J Y Sung, C M Chu, and K Y Yuen collected the clinical data. K P Fung, M M Y Waye, and C Y Lee reviewed the sequencing results. Y M D Lo planned the study and interpreted the data.

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Conflict of interest statement

None declared.

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Food-aid cereals to reduce neurolathyrism related to grass-pea preparations during famine

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Neurolathyrism is a spastic paraparesis that can be caused by excessive consumption of the drought-resistant grass pea *(Lathyrus sativus)*. Devastating neurolathyrism epidemics have occurred during major famine crises in various parts of the world. We investigated in a case-control study the effects of food aid on risk of paralysis. Risk increased with consumption of boiled grass pea (adjusted odds ratio 2·78, 95% CI 1·09–7·13 with cereals; 5·22, 2·01–13·55 without cereal) and raw unripe green grass pea (1·96, 1·16–3·31; p=0·011), but not with the fermented pancake, unleavened bread, and gravy preparations. In a correlational study there was an inverse relation between the number of new cases and the amount of food-aid cereals distributed per person. During famine, cereals and nutritional information should reach people before they have grass pea as the only food.

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Neurolathyrism is a neurodegenerative and irreversible spastic paraparesis that can be crippling and lead to complete dependency. This disorder can be caused by excessive consumption of the drought-resistant pulse grass pea (*Lathyrus sativus*). Grass pea contains the glutamate analogue neurotoxin β-N-oxalyl-L-α,β-diaminopropionic acid (β-ODAP), which is thought to cause neuronal damage through excitation of the AMPA-activated receptors.[1] All major famines and chronic food shortages in Ethiopia from the mid-1970s onwards have been accompanied by reports of