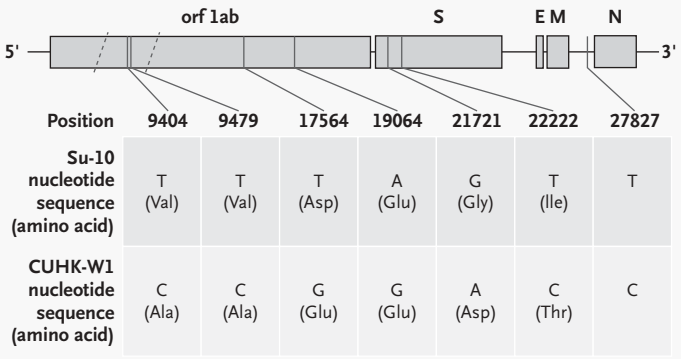
CORRESPONDENCE

Coronavirus Genomic-Sequence Variations and the Epidemiology of the Severe Acute Respiratory Syndrome

TO THE EDITOR: Our teaching hospital was the site of a major outbreak of the severe acute respiratory syndrome (SARS).[1] We sequenced viral isolates cultured from clinical specimens from seven patients with SARS in this outbreak. The viral isolates were from passage 1 of the SARS coronavirus cultured in Vero cells.[2] We obtained the complete genomic sequence of the virus cultured from the mother of the index patient in this hospital outbreak (isolate Su-10, GenBank accession number AY282752).[1] The mother's symptoms had begun on March 5, 2003; she died on April 13, 2003. We also sequenced the spike glycoprotein gene from viral isolates cultured from six contacts of the index patient, and all these sequences were identical to that of isolate Su-10.

To investigate whether there were other strains of the SARS coronavirus in Hong Kong at the time of this outbreak, we sequenced the spike glycoprotein gene from isolates of passage 1 virus cultured from four other patients with SARS who had had no contact with the index patient. Sequence variations were observed at two nucleotides (positions 21721 and 22222) (Fig. 1) in one isolate (isolate CUHK-W1) and at one nucleotide in two other isolates. Since culturing would be expected to introduce mutations, we compared these sequences with other SARS coronavirus sequences in GenBank. The two nucleotide changes observed in the spike glycoprotein gene of CUHK-W1 could also be observed in several other isolates (GenBank accession numbers AY278489, AY278488, and AY278487), so these were unlikely to be culture-derived artifacts. CUHK-W1 was cultured from a patient who had traveled to Shenzhen, Guangdong Province, China, six days before the onset of his symptoms on March 15, 2003. We therefore sequenced this isolate completely (GenBank accession number AY278554). Of the 10 observed nucleotide differences between Su-10 and CUHK-W1, 7 were also observed in at least one other isolate in GenBank (Fig. 1).



Position	9404	9479	17564	19064	21721	22222	27827
Su-10 nucleotide sequence (amino acid)	T (Val)	T (Val)	T (Asp)	A (Glu)	G (Gly)	T (Ile)	T
CUHK-W1 nucleotide sequence (amino acid)	C (Ala)	C (Ala)	G (Glu)	G (Glu)	A (Asp)	C (Thr)	C

Figure 1. Comparison of the Sequences of Two Strains of SARS Coronavirus Isolated from Patients in Hong Kong at the Beginning of the Epidemic.

This schematic representation of the genomic organization of the severe acute respiratory syndrome (SARS) coronavirus shows only selected open reading frames (orf), including orf 1ab (including the polymerase), S (spike glycoprotein), E (envelope protein), M (membrane protein), and N (nucleocapsid protein). Sequence variations at seven positions between the two viral strains (Su-10 and CUHK-W1) are indicated. The nucleotide positions are numbered according to the sequence published by the Centers for Disease Control and Prevention (CDC-Urbani isolate; GenBank accession number AY278741).[3]

THIS WEEK'S LETTERS

Our data show that since the first reports of SARS in November 2002 in Guangdong Province,[4] at least two strains of SARS coronavirus have emerged. It is epidemiologically significant that even by mid-March 2003, these two strains of the SARS coronavirus had already been found in patients in Hong Kong. This observation means that there was more than one source of infection present at the beginning of the SARS epidemic in Hong Kong. Therefore, even if there had been no outbreak at the Metropole Hotel,[5] SARS would probably have broken out eventually in Hong Kong. These results emphasize the need for vigilance in order to prevent the resurgence of this disease. The results also show the usefulness of spike glycoprotein sequences as a molecular epidemiologic tool.

Stephen K.W. Tsui, Ph.D.
Stephen S.C. Chim, Ph.D.
Y.M. Dennis Lo, D.M.
Chinese University of Hong Kong
Shatin, New Territories, Hong Kong
loym@cuhk.edu.hk
for the Chinese University of Hong Kong (CUHK) Molecular SARS Research Group

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Protection of Research Subjects

TO THE EDITOR: Regarding the study by the Acute Respiratory Distress Syndrome (ARDS) Network, discussed by Steinbrook (April 3 issue),[1] some may wonder whether the institutional review boards (IRBs) had enough information to evaluate the risks of this study properly. As a member of an IRB that reviewed this protocol, I want to assure readers that there was indeed a very diligent review. The local consent form carefully and properly represented the risks involved in the study. There was ongoing review of adverse events, which were assiduously reported by the investigators. The public overall and the research subjects in particular were protected as much as possible by the investigators and by their local IRBs. Despite the criticisms of this study, the process of conducting proper research involving human subjects did work here.

Jeffrey L. Kaufman, M.D.
Vascular Services of Western New England
Springfield, MA 01107
kaufman@massmed.org

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TO THE EDITOR: In his Sounding Board article on research involving cognitively impaired adults, Dr. Karlawish (April 3 issue)[1] argues for limits on the risks that proxies are allowed to accept on behalf of cognitively impaired subjects. In the case of experimental therapeutic interventions, he asserts that the risk associated with the procedure must be justified by its potential benefits. Although this standard is reasonable, its application requires difficult, value-laden decisions.

The fact that patients must be enrolled in studies without their direct consent necessitates an extraordinary certainty in the determination of allowable risk. Rather than leaving the medical investigator and IRB alone to shoulder the burden of making this determination, we recommend that a process of community consultation be required for all trials enrolling cognitively impaired subjects. Such a process is already mandated in the guidelines of the Food and Drug Administration (FDA) and the Department of Health and Human Services that govern emergency research conducted without informed consent.[2-4]

Community consultation serves to enlighten investigators and IRBs about the values that should inform the analysis of the risks and benefits of a proposed trial. Furthermore, this process helps to reduce the perception that vulnerable persons may be abused by the medical establishment.[5]

Brian T. Bateman
Philip M. Meyers, M.D.
H. Christian Schumacher, M.D.
Columbia University
New York, NY 10032
btb2002@columbia.edu

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