

paraganglioma syndrome 1; in the extent of multifocal tumors in the group with MEN-2, the group with von Hippel–Lindau disease, and the group with paraganglioma syndrome 1; and in the extent of extraadrenal tumors in the group with MEN-2, the group with von Hippel–Lindau disease, the group with paraganglioma syndrome 1, and the group with paraganglioma syndrome 4.

Patients with neurofibromatosis type 1 had a relatively high (but not significant) prevalence of malignant disease (12 percent), second only to that among patients with paraganglioma syndrome 4 who had a germ-line mutation in the *SDHB* gene (24 percent). Taken together, 33 percent of all symptomatic patients with pheochromocytoma in the registry carried germ-line mutations in one of the five genes, including *NF1*.

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Birke Bausch, M.D.
Wiktor Borozdin, Ph.D.
Hartmut P.H. Neumann, M.D.

University of Freiburg
79106 Freiburg, Germany
neumann@med1.ukl.uni-freiburg.de

for the European-American Pheochromocytoma Study Group

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Fatal Infection with Influenza A (H5N1) Virus in China

TO THE EDITOR: A 24-year-old man had pneumonia and respiratory distress in November 2003 and died four days after being hospitalized. Because the clinical manifestations were consistent with those of the severe acute respiratory syndrome (SARS) and occurred when sporadic cases of SARS were described in southern China,¹ serum and lung tissue from the patient, as well as fluid aspirated from his chest, were examined for SARS coronavirus with the use of indirect fluorescence antibody tests and the reverse-transcriptase polymerase chain reaction (RT-PCR). All tests were negative for SARS.

A virus was isolated from the lung tissue in Vero-cell cultures and was characteristic of influenza A virus on electron microscopy. A serum sample collected on day 8 of the patient's illness was positive for IgM antibody against the isolated virus. Fragments of both the influenza A virus matrix gene (*M*) and the H5-subtype hemagglutinin gene (*HA*) were amplified from the infected Vero cells with the use of RT-PCR assay.^{2,3} The nucleotide sequences of the fragments were identical to those amplified from the stored specimens of the patient's serum, chest fluid, and lung tissue.

The genomic sequence of the virus (A/Beijing/01/2003) was determined, and its eight segments were genetically related most closely to corresponding sequences of influenza A (H5N1) viruses that had been isolated from chickens in various regions of China in 2004. The segments of the polymerase basic protein 1 gene (*PB*) and the non-structural gene (*NS*) were most closely related to those from Guangdong Province (in southeastern China), with 99 percent identity. The segments of the polymerase basic protein 2 gene (*PB2*) and *HA* gene were closest to those from Jilin Province (in northeastern China), with 99 percent and 97 percent identity, respectively. The segments of the neuraminidase gene (*NA*), nucleoprotein gene (*NP*), and *M* gene were closest to those from Hubei Province (in mideastern China), with 98 percent, 98 percent, and 99 percent identity, respectively, and the polymerase acidic protein gene (*PA*) segment was closest to that from Japan, with 99 percent identity.

These findings suggest that influenza A/Beijing/01/2003 may be a mixed virus. Phylogenetic analyses of the *HA* and *NA* genes of the representative influenza A (H5N1) strains have revealed that the viruses isolated from patients in Thailand

and Vietnam in 2004 and 2005 belong to the same clade, and those obtained from patients in Hong Kong in 1997 and 1998 are from another clade (Fig. 1 in the Supplementary Appendix, available with the full text of this letter at www.nejm.org). A sample of virus obtained from a patient in Hong Kong in 2003 seems to represent a transitional genotype, of which the HA gene sequence was close to the cluster from southeastern Asia (Fig. 1A in the Supplementary Appendix), whereas the NA gene sequence was close to that of the cluster from Hong Kong in 1997 and 1998 (Fig. 1B in the Supplementary Appendix). Phylogenetic analyses of the HA or NA gene indicated that the influenza A/Beijing/01/2003 strain was genetically distant from viruses previously isolated from humans, although it appears to have originated from a lineage similar to the influenza A/goose/Guangdong/1/96 (Gs/GD) lineage.⁴

These findings have important implications for selecting viruses for the development of vaccines to prevent infection in humans. The genetic distance between the isolate reported and the strain currently proposed for vaccine development (A/Vietnam/1203/2004)⁵ implies that viruses from different regions may need to be considered in the development of an effective vaccine against influenza A virus.

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Qing-Yu Zhu, M.D.

State Key Laboratory of Pathogens and Biosecurity
Beijing 100071, China

E-De Qin, M.D.

Beijing Institute of Microbiology and Epidemiology
Beijing 100071, China

Wei Wang, M.D.

309th Hospital of the People's Liberation Army
Beijing 100091, China

Jun Yu, Ph.D.

Beijing Genomics Institute
Beijing 101300, China

Bo-Hua Liu, Ph.D.

State Key Laboratory of Pathogens and Biosecurity
Beijing 100071, China

Yi Hu, Ph.D.

Beijing Institute of Microbiology and Epidemiology
Beijing 100071, China

Jian-Fei Hu, Ph.D.

Beijing Genomics Institute
Beijing 101300, China

Wu-Chun Cao, M.D., Ph.D.

State Key Laboratory of Pathogens and Biosecurity
Beijing 100071, China
caowc@nic.bmi.ac.cn

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