

# UPDATE

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## GENETIC STRUCTURE OF AIDS VIRUS NOW MAPPED

National Cancer Institute (NCI) scientists in collaboration with researchers at Harvard Medical School and Dana-Farber Cancer Institute in Boston, E.I. duPont de Nemours in Wilmington, Delaware, and Centocor in Philadelphia have mapped the entire genetic structure (genome) of HTLV-III, the virus strongly implicated in the development of Acquired Immune Deficiency Syndrome (AIDS). This map, or nucleotide sequence, will help researchers understand how this virus functions and facilitate development of substances for the detection, prevention, and treatment of AIDS. The researchers will report their findings in the January 24, 1985, issue of Nature.

This report represents an important milestone in AIDS research. Any part of the viral genome can now be reproduced. The protein or nucleic acid products of the genes can be synthesized for tests and possible applications. This knowledge is already being used to develop methods for detection of the virus in blood samples, but it may be some time before means or methods are available for prevention and treatment.

HTLV-III belongs to a family of retroviruses known as human T-cell leukemia-lymphotropic viruses (HTLV) that have now been identified in human tissues. Besides HTLV-III (the AIDS virus) other members of this family are HTLV-I, strongly associated with an adult form of leukemia-lymphoma that is unusual in the United States but fairly common in southwest Japan, the Caribbean basin, parts of Africa, and South and Central America; and HTLV-II,

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isolated from a patient with a leukemia called hairy cell leukemia, but the virus has not yet been linked to the cause of this disease. Both HTLV-I and -II were originally isolated in the laboratory of Dr. Robert C. Gallo, Jr., at NCI.

Comparison of the information contained in the HTLV-III virus with earlier reports of the human leukemia viruses shows that although there are similarities between the AIDS virus and the other HTLV viruses, the AIDS virus is indeed different in several important respects. The researchers conclude that the AIDS virus did not arise by a small change in known viruses that are already present in the population, but rather is a new virus now affecting certain members of the U.S. population.

NCI's Dr. Flossie Wong-Staal said, "Although we recognize several key features of the virus structure from studies of related viruses, other features of the virus are new and unique to this virus. We speculate that some of these unusual features may be involved with mechanisms of disease." More specifically, the AIDS virus shares several features common to all viruses of this class, called retroviruses. These viruses contain RNA genetic material and a set of proteins that surrounds this material that protect the RNA (core proteins). The virus also contains an enzyme (polymerase) that converts the RNA to DNA as part of its life cycle. In addition, the HTLV virus, like other viruses of this general class, is surrounded by a structure called the envelope. The envelope protein is especially important, as it determines what cells can be infected by the virus. Moreover, it is the body's reaction to this protein that provides the first line of defense against virus infection.

The organization and structure of the core proteins and polymerase genes are generally the same as those of other retroviruses. However, when looked

at in more detail, these proteins more closely resemble the structure of the other HTLVs than that of other groups of viruses associated with disease of non-human species such as mice, chicken and Gibbon apes. However, the organization of the key envelope genes is unprecedented in other types of viruses, even in the other human T-cell leukemia viruses.

Dr. Lee Ratner, senior author of the paper and a scientist in Dr. Gallo's laboratory, said, "It--the envelope gene--is not where we expected it to be. Not only that, the envelope protein gene is much bigger than similar genes of other viruses. The envelope proteins generally contain two parts, a part that is outside the virus and the part inside. For the AIDS virus both the inner and outer parts are much bigger than in other viruses."

The AIDS virus also resembles HTLV-I and HTLV-II in the presence of a gene called lor. This gene is thought to be important not only for the growth of the virus itself, but also for determining the effects of virus infection on the target cells. Although the AIDS virus probably has the lor gene, the organization of this gene is quite different from that of the other human leukemia viruses.

Dr. William Haseltine of the Harvard Medical School said, "The lor gene of the AIDS virus overlaps the envelope gene. One genetic region of the AIDS virus has two distinct functions in this virus, i.e., it encodes both the envelope and lor proteins. This is a major difference from the human leukemia viruses (HTLV-I and II) in which envelope and lor are separate genes."

Both the leukemia viruses and the AIDS virus infect exactly the same kind of immune cells. However, the AIDS virus kills these cells causing failure of the immune system, whereas the human leukemia viruses cause these cells to grow out of control. One researcher speculated that it is the difference in the organization of these genes that may be, at least in part, responsible for

the different effects of the virus in the same type of cell. Detailed analysis of how the gene products work could be important in the design of new therapeutic approaches for treatment of AIDS infections.

In addition to known genes, there are at least two regions of the AIDS virus that have no direct counterpart in any other retrovirus studied. These are called sov and 3' orf. Sov may be the remnant of a former envelope gene, according to the Nature report, and 3' orf may not be a gene at all, since only one of the two AIDS strains studied here contains such a potential coding region. These and other questions await further analysis that is now made possible by the elucidation of the complete structure of the virus.

The work was initiated in the laboratory of Dr. Robert C. Gallo and Dr. Flossie Wong-Staal at NCI. This laboratory also provided the key reagents for the work, i.e., the molecular recombinant DNA clones of the AIDS virus. The work was done in collaboration with four other groups: a group at Harvard Medical School and Dana-Farber Cancer Institute, in the laboratory of Dr. William Haseltine; a group at E.I. duPont de Nemours under the direction of Dr. Mark Pearson; another laboratory at NCI under the direction of Dr. Takis Papas; and at Centocor under the direction of Dr. Nancy Chang.

Dr. Peter Fischinger, NCI Associate Director, said, "This is one of the finest examples I have seen of cooperation among government, university and industry research groups to obtain an important and timely research result. Five different groups teamed up on this problem. Information was pooled. The importance of the information for future directions in AIDS research made it necessary that we obtain the information as soon as possible. This has been a real team effort. Everyone contributed to the final answer. It would not have been possible to obtain all the information, the complete sequence of both viruses, in such a short period of time otherwise. This information is

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now available to the entire community of AIDS researchers, and we hope that it will speed the progress in understanding and preventing disease."

In other related studies it has been found that the AIDS virus, like the other human leukemia viruses, alters cells by affecting the mechanism by which genes are transcribed, a phenomenon called trans-acting transcriptional regulation--the TAT phenomenon.

The researchers suggest that the common structural features of the human leukemia viruses (e.g., the presence of the l<sub>or</sub> gene) and the common functional features (TAT phenomenon), set these viruses apart from other previously described retroviruses. According to Dr. Mark Pearson of E.I. duPont de Nemours: "These viruses appear to represent a new type of virus. Other members of this new virus family may be involved in other chronic diseases. We are just beginning to understand these agents and their role in human disease."

Authors of the Nature paper, "Complete nucleotide sequence of the AIDS virus, HTLV-III," are: Lee Ratner\*, William Haseltine†, Roberto Patarca†, Kenneth J. Livak‡, Bruno Starcich\*, Steven F. Josephs\*, Ellen R. Doran‡, J. Antoni Rafalski‡, Erik A. Whitehorn‡, Kirk Baumeister‡, Lucinda Ivanoff‡, Stephen R. Petteway, Jr.‡, Mark L. Pearson‡, James A. Lautenberger§, Takis S. Papas§, John Ghrayeb††, Nancy T. Chang††, Robert C. Gallo\*, and Flossie Wong-Staal\*.

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