must be asked why the incidence of AIDS in the Ugandan population (and neighboring Zaire) has gone unnoticed for so long. It is possible that AIDS existed in African populations without being recognized as a separate disease entity. The virus may have originated in Africa in the past and exposure to the virus may be much more common than AIDS itself in some populations. As with many other infectious diseases, host responsiveness may vary between severe and subclinical. If recent reports of AIDS in central Africa suggesting that the disease is newly evolved and spreading are correct (*8*), then it is essential to determine which of the various host- and virus-related factors are responsible. For example, it is important to know whether the current spread of AIDS is due to a spread of HTLV-III from nonsusceptible to susceptible populations or to a molecular change in the virus. In this regard, our samples were taken from a sparsely populated subsistence-farming environment (*17*) where AIDS is not known to occur, while the recent spread in African AIDS appears to be in more densely populated urban environments and heterosexual populations (*25*). Clearly, epidemiologic and virologic studies are needed to examine changes in the occurrence of AIDS and AIDS-related diseases in healthy individuals (particularly children) in central Africa.

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24. Although HTLV-III–positive serum samples that cross-react with HTLV-I under the experimental conditions described here are occasionally seen, they have been sufficiently rare to suggest that they could have arisen from coinfection rather than cross-reactivity in the usual sense. The apparent difference between this and a previous report indicating serological cross-reactivity between HTLV-III and HTLV-I [M. Essex *et al.*, *Science* **220**, 859 (1983)] might arise from differences found in target antigens present in live cells versus antigens dissociated from purified virus particles and deposited on a solid surface. In any case, the data presented in the tables are representative of our experience and are clearly different from the relative titers and prevalence of HTLV-I and HTLV-III antibody reactivity in the Ugandan serum.
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Location of the c-*yes* Gene on the Human Chromosome and Its Expression in Various Tissues

Abstract. *Analysis of DNA from human embryo fibroblasts showed that ten Eco RI fragments were hybridizable with the Yamaguchi sarcoma virus oncogene (v-*yes*). Four of the Eco RI fragments were assigned to chromosome 18 and one to chromosome 6. There was evidence for multiple copies of* yes*-related genes in the human genome; however, only a single RNA species, 4.8 kilobases in length, was related to* yes *in various cells.*

At least 19 retrovirus genes have been identified as viral oncogenes (*1*) that were acquired from normal cellular sequences (cellular oncogenes) (*2*). Cellular oncogenes are highly conserved in vertebrates and lower organisms such as yeast (*2, 3*). The locations of several cellular oncogenes correspond to breakpoints involved in chromosome translocations and deletions found in various cancers. For example, the c-*myc* gene in Burkitt's lymphoma is involved in translocation between chromosome 8 and one of the chromosomes (2, 14, or 22) that carries an immunoglobulin gene (*4*).

An avian sarcoma virus, Y73, is defective in replication and the genome, 3.6 kilobases long, contains an oncogene (v-*yes*) in its central region (*5*). The product of the v-*yes* gene is associated with tyrosine-specific protein kinase activity (*6*) and its amino acid sequence shows a high degree of homology with that of the *src* gene product of Rous sarcoma virus (*5*). A cellular homolog of the v-*yes* gene, the c-*yes* sequence, was detected in the chicken genome and the human genome by Southern blot analysis (*7*).

Somatic cell hybrids were generated by the fusion of human embryo fibroblasts (HEF) with mouse cells (*8*). DNA's extracted from HEF, mouse cells, and 24 hybrid clones were digested with Eco RI and subjected to Southern blot analysis with a ^{32}P-labeled probe, 1.5 kbp (kilobase pairs) long, that contained about 85 percent of the v-*yes* gene (Fig. 1A). Ten Eco RI fragments specific to humans were identified, five of which (11.0, 8.7, 5.7, 5.0, and 1.9 kbp) were clearly distinguishable from the mouse c-*yes* fragments. These fragments, with the exception of the 11.0-kbp fragment, hybridized to the v-*yes* probe very efficiently. The 8.7- and 5.7-kbp Eco RI fragments were assignable to chromosome 18 (Fig. 2B and Table 1). Even though the 11.0-kbp and the 5.0-kbp frag-

ments migrated closely to one of the mouse Eco RI fragments, they could also be assigned to chromosome 18 on the basis of the appearance of the bands in Fig. 1B and in autoradiographs that had been exposed for different periods of time. These four Eco RI fragments were classified as c-*yes*-1 (Table 1). The only discrepancy was that karyotypic analysis and enzyme assay for peptidase A (*9*) (which would reveal the presence of the PEPA gene marker, located at 18q23-qter) failed to identify intact human chromosome 18 in clone 1a, while Southern blot analysis of the DNA isolated from this clone clearly showed the existence of c-*yes* sequences of human origin. Clone 1a must contain a fragment of

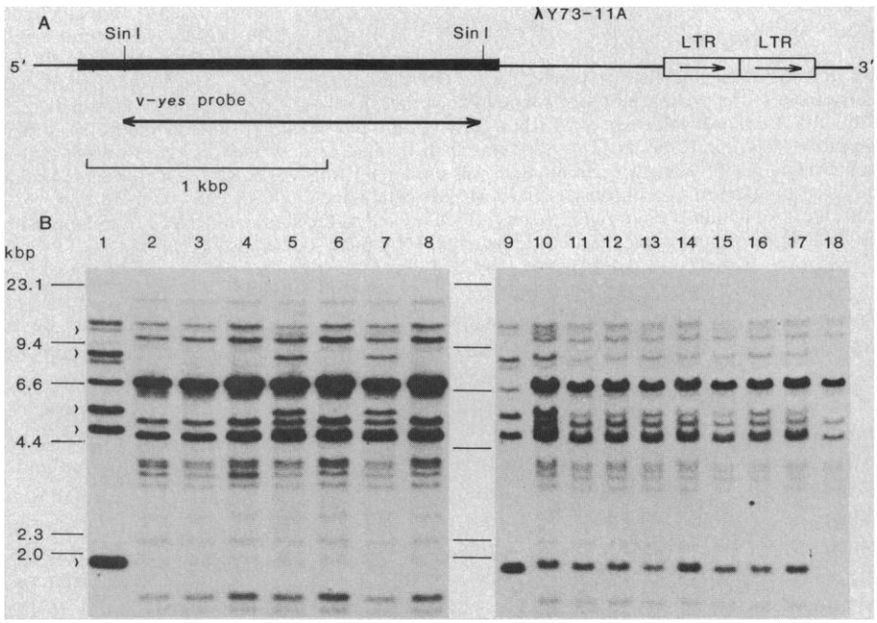

Fig. 1. Identification of human c-*yes* in DNA of human-mouse somatic cell hybrids. (A) Schematic illustration of the DNA fragment used as v-*yes* probe in hybridization analyses. λY73-11A is a DNA clone of the Y73 genome (*5*). The 1.5-kbp Sin I fragment that was cloned into pBR322 at the Sal I site was used as the probe. LTR, long terminal repeat. (B) Hybridization of v-*yes* probe to DNA from human-mouse hybrid cells. High molecular weight genomic DNA was isolated as described (*18*). Eco RI–digested cellular DNA (15 μg) was fractionated by electrophoresis on agarose gels (0.9 percent) and then subjected to Southern blot analysis (*7*) using the ^{32}P-labeled v-*yes* probe. Hybridization was carried out in a solution of formamide (30 percent), 4× SSC, 50 m*M* Hepes-OH (*p*H 7.0), 10× Denhardt solution, yeast RNA(10 μg/ml), and denatured salmon sperm DNA(20 μg/ml) at 42°C for about 15 hours. The filter was then washed with a solution of 2× SSC and 0.1 percent sodium dodecyl sulfate (SDS) at room temperature and then with a solution of 0.44× SSC and 0.1 percent SDS at 50°C. Lanes 1 and 9, DNA's from human embryo fibroblasts HE2144 and HE2301, respectively; lanes 8 and 18, DNA's from mouse FM3A and B82 cells, respectively; lanes 2 to 7 and lanes 10 to 17, DNA's from hybrid clones—H/B 1-1, H/B 1-4, H/B 1B1, H/B 3-2, H/B 4C2, H/B 5-1 and H/B la, H/F Al, H/F A2, H/F II-5, H/F II-6, H/F II-7, H/F III-1, H/F Bm, respectively.

Table 1. Segregation of *yes*-1 and *yes*-2 genes with human chromosomes in mouse × human cell hybrids. The human chromosome content was determined by the method for differential staining of human and mouse chromosomes (*22*). The gene *yes*-1 represents the four Eco RI fragments (11.0, 8.7, 5.7, and 5.0 kbp) and the gene *yes*-2 represents the 1.9-kbp Eco RI fragment. H/F and H/B represent hybrid clones between human HE2144 and mouse FM3A and between human HE2301 and mouse B82 cells, respectively.

Hybrid	Chromosome																								Hybridization to:	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	X	Y	*yes*-1	*yes*-2
H/F 1a	−	−	+	+	−	+	−	+	−	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+
II-5	−	+	+	+	+	+	+	−	−	+	−	+	−	+	+	+	+	−	−	+	+	+	+	−	+	+
III-1	−	−	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Al	−	−	+	+	+	+	−	+	−	−	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+
A2	+	−	−	+	+	+	+	−	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+
II-6	−	+	−	+	+	+	−	+	−	−	+	−	−	+	+	−	+	+	−	+	+	+	+	+	+	+
II-7	−	−	−	+	−	+	+	+	−	−	+	−	+	+	+	−	+	+	−	+	+	+	−	−	+	+
Bm	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
H/B 1-1	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−
1-3	−	−	−	+	−	+	−	−	−	−	−	−	−	+	−	−	+	−	−	−	−	−	−	−	−	+
1B1	+	−	+	−	−	−	+	−	−	−	−	−	+	+	−	−	+	−	+	+	−	−	−	−	−	−
1B1-5	−	−	−	−	−	−	+	−	−	−	−	−	+	−	+	−	−	−	−	−	−	−	−	−	−	−
1B1-26	−	−	−	−	−	−	−	−	−	−	−	−	+	−	+	−	−	−	−	−	−	−	−	−	−	−
1-4	+	−	−	+	−	−	+	+	−	+	+	−	+	+	−	−	+	−	+	+	+	+	+	−	−	−
3-2	−	−	−	−	−	−	+	−	−	−	−	−	+	+	−	−	+	+	−	−	−	−	−	−	+	−
3-3	−	+	−	+	+	−	−	−	−	−	−	−	−	−	+	−	+	−	+	−	+	−	−	−	−	−
4C2	−	−	−	+	−	−	−	−	−	−	−	−	−	+	−	−	+	−	−	+	+	−	−	−	−	−
5-1	−	−	+	+	+	−	+	+	−	−	−	−	−	−	−	+	+	+	−	+	+	−	−	−	+	−
5D1	−	−	−	+	+	−	+	−	−	−	−	−	−	−	−	−	+	+	−	+	+	−	−	−	+	−
7-1	−	−	+	−	+	−	−	−	−	+	+	−	+	+	−	−	+	−	−	−	+	−	−	−	−	−
7-1-B6	−	−	−	−	−	−	−	−	−	−	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−
7-2	−	−	+	−	+	−	−	−	−	−	−	+	+	+	−	−	+	−	−	+	+	−	−	−	−	−
7D5	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	+	−	−	−	−	−	−	−	−	−
7-1-A2	−	−	+	−	−	−	−	−	−	−	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−
Percent discordance																										
***yes*-1**	46	38	38	21	25	17	25	21	46	38	25	33	67	42	25	25	38	4	42	21	25	17	21	25		
***yes*-2**	38	29	38	21	33	0	42	21	38	29	17	25	67	33	17	25	46	21	33	29	33	8	13	17		

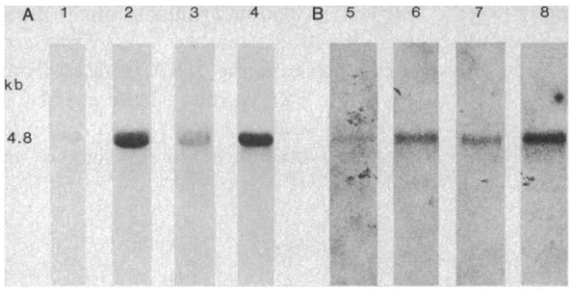

Fig. 2. Transcripts from c-*yes* in human tissues and cell lines. Total cellular RNA was extracted using the guanidinium-thiocyanate-cesium chloride method (*19*) and polyadenylated RNA was selected. Polyadenylated RNA (5 μg) was subjected to electrophoresis on a 1 percent agarose gel containing 2.2*M* formaldehyde (*20*). RNA's were transferred directly to a nitrocellulose filter and hybridized to the ^{32}P-labeled v-*yes* DNA as described (*21*). The hybridization was carried out in the presence of formamide (40 percent), 4× SSC, 50 m*M* sodium phosphate (*p*H 7.0), 10× Denhardt solution, yeast RNA (250 μg/ml), and denatured salmon sperm DNA (500 μg/ml) at 42°C for 16 hours. The filter was then washed as described in Fig. 1 except that a solution of 0.2× SSC and 0.1 percent SDS was used in the final wash. RNA's were isolated from cultured human embryo fibroblasts (lane 1), KB cells (lane 2), K562 cells (lane 3), and A431 cells (lane 4); a human embryo (12 weeks old) was used as the source of RNA's from lung (lane 5), liver (lane 6), and kidney (lane 7). Placental RNA (lane 8) was also analyzed.

chromosome 18, since there was no significant correlation between hybridization to c-*yes* fragments and the presence of the other chromosomes that clone 1a carries.

Table 1 also shows that the 1.9-kbp Eco RI fragment (c-*yes*-2) was located on chromosome 6. To examine the possibility that one of the loci identified above represents a processed c-*yes* gene, we hybridized human cellular DNA to three DNA probes that included the 5′-terminal, the middle, or the 3′-terminal portion of the 1.8-kbp v-*yes* sequence. Only the 1.9-kbp Eco RI fragment reacted strongly with all the probes, an indication that the sequence located in chromosome 6 may represent a processed c-*yes* gene (*10*). Translocation between chromosomes 6 and 14 is associated with ovarian papillary adenocarcinoma and the translocation between chromosomes 14 and 18 is associated with follicular small cleaved, follicular mixed, and follicular large cell lymphomas (*11*). Precise localization of the c-*yes* gene and further analysis of the translocations are needed to show whether expression of the c-*yes* gene is related to these diseases.

Of the other five Eco RI fragments (25.0, 12.0, 9.4, 8.2, and 7.0 kbp) of human origin, the v-*yes* probe hybridization signals were too weak for the 25.0- and 8.2-kbp fragments to be analyzed in hybrid clones and the other three fragments were not distinguishable from the mouse c-*yes* fragments. Therefore, we could not determine the chromosomal locations of these sequences. The weakly hybridizing fragments such as the 25-kbp fragment might represent another cellular oncogene that belongs to the *src* gene family, since the conditions of hybridization used could have allowed cross hybridization.

At least three of the human c-*yes* gene copies had both introns and exons and one c-*yes* gene copy appears to be a pseudogene (*10*). The restriction maps of these copies differed, although they hybridized to the same limited portion of the v-*yes* gene (*10*). Possibly one copy of the human c-*yes* gene contains duplicated or triplicated exons that hybridize to a limited portion of the probe, as in the case of the c-K-*ras* gene, which contains two homologous exons (*12*). Alternatively, some of the clones isolated might contain part of another functional gene that is partially homologous to the v-*yes* gene. This gene could be the c-*fgr* gene, since the amino acid sequences of the v-*yes* gene product and the v-*fgr* protein of feline sarcoma virus are highly homologous (*13*).

The transcripts of the human c-*yes* gene were also characterized. Polyadenylated RNA's from cultured cells and human embryo tissues were purified and hybridized to v-*yes* probes. A single transcript (4.8 kb) was detected in all preparations which suggests that there is only one functional c-*yes* gene. We cannot, however, exclude the possibility that the length of transcripts from several copies of the c-*yes* genes might be the same. The c-*yes* gene is actively transcribed in tumor cell lines (Fig. 2A), especially in A431 cells which produce a high level of the receptor for epidermal growth factor (EGF) (*14*). Transcription of c-*yes* in cultured embryo fibroblasts is less active than in tumor cell lines and very few transcripts were observed in IM9, which was derived from human B lymphocytes and is known to produce a high number of insulin receptors (*15*). Densitometric analysis revealed that the copy number of c-*yes* transcripts in A431 cells is five times that in embryo fibroblasts.

It has been suggested that the v-*erb* B oncogene, a member of the *src* gene family (*16*), originated from cellular sequences that encode the avian EGF receptor (*17*). The fact that the *yes* gene is a member of the *src* gene family suggests that the *yes* gene product may also function in the receptor-activated pathway leading to cell proliferation.

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