

linked was used, and this also cosegregated, as indeed it could not fail to do since the same family was analysed and because previously informative meioses were not excluded.

This type of preliminary trawl followed by detailed study has recently been recommended by Lander⁵, who writes:

In the future, we envisage that linkage studies will initially employ a standard battery of perhaps 100–200 highly informative RFLPs distributed throughout the genome. Any interval showing suggestive evidence of linkage will then be studied with a higher density of RFLPs. This will extract the full information from the pedigrees, and will increase the LOD score.

This procedure will certainly increase the lod score, but it would be more accurate to state that it will also extract full mis-information, and there is no way in which information and mis-information can be separated unless different families are used.

Lander summarizes the problem lucidly by stating that "if the trait is, in fact, more complicated than assumed, linkage will not be detected. A negative result in a complete genome search will at least prove that the disease is more complex than had been assumed". While amentia and dementia are good grist for the mill now available for the shotgun geneticist, it would be useful to know who the assumers are for simplicity in the psychoses.

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Analogous alternative splicing

STR—The two molecular forms of the A chain of platelet-derived growth factor (PDGF), which arise by alternative modes of mRNA splicing, differ in length by a 15-residue C-terminal extension rich in basic amino acids which is derived from a separate sixth exon¹³. The differently spliced mRNAs have so far been found in

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|--------------------------|-----|-----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---------|---|---|---|---|---|---|--------------|---|---|---|---------|
| hPDGF-A | | 194 | G | R | P | R | E | S | G | K | K | R | K | R | L | K | P | T | end 211 | | | | | | | | | | | |
| xPDGF-A | 198 | G | F | F | T | S | P | A | L | V | L | T | G | R | T | R | E | T | G | K | K | Q | K | R | K | L | K | P | T | end 226 |
| hVEGF/VPF | | 116 | K | S | V | R | G | K | G | K | G | Q | K | R | K | K | K | S | R | Y | K | S | W | S | V | cont. to 169 | | | | |
| conserved basic residues | | | | | * | * | | | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * |

Amino acid sequence homology in the regions of human PDGF-A, *Xenopus* PDGF-A and human VEGF/VPF encoded by the sixth exon. The longer versions of both human and *Xenopus* PDGF end with this region while the molecule of VEGF/VPF continues for a further 50 residues.

all cell lines and tissues expressing PDGF (ref. 4), although the shorter form invariably predominates. The recognition that two forms persist even in the amphibian *Xenopus laevis* shows that the process of alternative splicing, involving an exon corresponding to human exon 6, is well-conserved in evolution⁵.

Recent reports of the cloning of an endothelial cell mitogen called vascular endothelial growth factor (VEGF)⁶ or vascular permeability factor (VPF)⁷, whose structure is distantly related to those of the A and B chains of PDGF, make it clear that alternative modes of splicing, involving a sequence similar to that of the sixth exon of human PDGF-A, also takes place with this mRNA, and at an analogous position. The figure shows an alignment of the amino acid sequences of the various growth factors encoded by the differently spliced mRNAs. Interestingly, the degree of sequence identity between human PDGF and VEGF/VPF is greater in this region than in any other part of the molecules.

Although the biological function of the basic motif encoded by the sixth exon of the genes for the two molecules is not known, the basic domains of the A and B

chains of PDGF might serve as nuclear targeting sequences if the N-terminal signal sequences for secretion were deleted^{8,9}. But it is difficult to imagine a function for the PDGF chains in the nucleus as well as a normal route by means of which the molecules would escape secretion. Instead, it is possible that the

basic motif common to the longer variants of PDGF-A and VEGF/VPF is an address for an extracellular target, perhaps one involved in regulating the accessibility of the polypeptides or in directing it to a specific interstitial structure.

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Origins of T-cell leukaemia virus

STR—The causal retrovirus of adult T-cell leukaemia (ATL), termed HTLV-1, is also responsible for HTLV-1-associated myelopathy (HAM) and tropical spastic paraparesis (TSP). So much is clear from investigations in Martinique, Colombia and Jamaica and, more recently, in Japan. But the origin of the carriers of HTLV-1, and the route by which they reached South America, remain obscure.

Gallo's suggestion¹ that the origin of HTLV-1 was in Africa, and that it reached Japan and the Americas by the slave trade, has been vigorously disputed^{2–4}. According to Hinuma, one of the co-discoverers of the virus, HTLV-1 may first have infected human beings some thousands of years ago, when the infection would not have been fatal because people did not live long enough to develop ATL⁵.

It is significant that there is a high frequency of HTLV-1 carriers among the Ainu people of Hokkaido, who are commonly regarded as the descendants of the native population living mostly in northern Japan in the pre-agricultural Jomon period more than 2,500 years ago⁶. Evidence of a high frequency of HTLV-1 carriers among the aborigines of Papua New Guinea and in several Melanesian islands suggests a route between Asia and South America, yet the main endemic focus of infection in Colombia is a group of blacks of African origin living on the South Pacific coast, which would support an African origin of the virus.

On the other hand, cases of TSP positive for HTLV-1 have been found in Chile. (5 of 34 patients were of mixed white and araucano descent.) We have also found three South American Indian women of the Páez group sick with TSP and carrying HTLV-1 in an isolated region of the Colombian Andes at more than 2,000 m above sea-level. These, and the similar cases reported from the high valleys of the Peruvian Andes, make it difficult to accept an exclusive African origin for South American HTLV-1. We think it more likely that migration from Asia carried the virus to this continent.

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