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LETTER

Congenital bilateral absence of the vas deferens and recombination at *CFTR*

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Pompei *et al*[1] report a paucity of variation on V470 haplotypes at the *CFTR* locus relative to M470 haplotypes on unselected chromosomes from the general population. A conservative estimate of the region of 'extended haplotype homozygosity' that they report would extend from I148T (29 kb 5′ of V470) to S1235R (68 kb 3′ of V470). The authors suggest that this pattern could be explained by a recent increase of the V470 variant to high frequency, either by natural selection for V470 itself or for another, linked variant in *cis*. In this scenario, V470 haplotypes are depauperate for sequence variation because they have had little time to accumulate variation due to mutation or by recombination with M470 haplotypes.

Variation at the polymorphic repeats in intron 8 is of particular interest. Pompei *et al* found $(tg)_{12}$ occurred on 16/76 (0.211) M470 haplotypes but only 8/218 (0.037) V470 haplotypes. Similarly, t_5 occurred on 4/76 (0.053) M470 haplotypes but only 2/218 (0.009) V470 haplotypes. This pattern of variation contrasts markedly with the haplotypes reported from men with congenital bilateral absence of the vas deferens (CBAVD). In a recent paper,[2] 11 of 13 men with CBAVD possessed a $(tg)_{12}t_5$V470 haplotype, and two possessed a $(tg)_{11}t_5$V470 haplotype, confirming the observation of Cuppens *et al*[3] that $(tg)_{12}t_5$V470 is the most common t_5-bearing haplotype in men with CBAVD.

These data raise the possibility that men with CBAVD have a high frequency of chromosomes that have undergone recent recombination between t_5 in intron 8 and V470 in exon 9, and suggest an interaction in the disease process between variants on either side of the putative crossovers. The simplest interpretation would be that these variants are $(tg)_{12}t_5$ and V470 themselves. The former would result in low proportion of transcripts containing exon 9 and the latter in a translated gene product with reduced chloride channel activity.[3] The selective elimination of recombinant haplotypes would contribute to maintaining the different patterns of genetic variation seen on M470 and V470 haplotypes.

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Reply to Professor Haig

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D Haig offers the interesting suggestion that selective elimination of a recombinant CFTR gene TG12-T5-V470 haplotype would contribute to maintaining the different patterns of genetic variation seen on the M470 and the V470 haplotypes. He correctly indicates an increased frequency of the haplotype in CBAVD, and one might add in CF-like lung disease[1] and nonclassic CF[2] as well.

The effect of the selective elimination would be rather low though, as the haplotype would be eliminated only if: (1) it occurs in a male, and (2) it is compounded with a CF mutation (0.02). Therefore, the efficiency of transmission of this haplotype would be less than that of the other haplotypes, but just by 1%.

He suggests that a recombination process might have occurred between T5 and V470 on the CFTR gene: we would like to indicate that also a replication slippage mechanism might be involved in a change of nucleotide repeat number to generate the haplotype.

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