

COMMENTARY

on article by

Seese, N.K., Venditti, C.P., Chorney, K.A., Gerhard, G.S., Ma, J., Hudson, T.J., Phatak, P.D., Chorney, M.J. Localization of the Hemochromatosis Disease Gene: Linkage Disequilibrium Analysis Using an American Patient Collection. Blood Cells, Molecules, and Diseases (1996) 22(3) Feb 15: 36-46.

Most physicians seem unaware of the fact that hereditary hemochromatosis is an exceedingly common disorder among people of European origin. They are astonished to learn that about 3 per 1000 population are affected and that about 10% are heterozygotes for the gene that causes this autosomal recessive disorder. The disease is difficult to diagnose and easy to treat; thus, finding the gene is medically very important. The fact that the hemochromatosis gene is linked to the HLA complex has been known since 1975(1). Nonetheless, the goal of identifying the disease-producing gene has remained elusive. There are two reasons for this. First of all, it has not been possible to localize the gene to small region. Secondly, there is no in vitro system that can be used to tell us when the proper gene has been found.

The paper by Seese, Venditti, et al makes an important contribution in helping to resolve the first of these difficulties by narrowing the region to be studied. The classical approach to localizing a gene is the study of families. In the case of the hemochromatosis gene it appears to us that it is the type of linkage disequilibrium studies that Seese, Venditti et al. have carried out that are likely to be the most helpful. Family studies are unsuitable for localization of genes to small regions. If the crossover frequency is 1% (thought to represent an average distance of 1,000,000 bases), a very large number of informative matings are required. Another difficulty, not commonly appreciated, is that the diagnosis of hemochromatosis is not simple, and misclassifications will invariably creep into any large body of data. In family studies such errors can profoundly affect the putative distance between the gene of interest and a marker; the

effect of errors of diagnosis is not nearly so great when linkage disequilibrium is used to localize a gene.

We have studied genetic markers of 71 American hemochromatosis patients and 99 controls for some of the same markers reported by Seese, Venditti et al with very similar results. The diagnostic criteria used to select our patients were not as stringent as those used by Seese, Venditti et al, but, as pointed out above, misdiagnosis of a small percentage of cases should not greatly affect the results, and, indeed, our findings are very similar to theirs. The table provides a comparison.

Marker	Study	Frequency in HFE	Frequency in control	P _{excess}
D6S265-1	1	0.39	0.13	0.30
	2	0.36	0.13	0.26
*D6S258-6	1	-	-	-
	2	0.69	0.47	0.41
D6S306-3	1	0.82	0.59	0.56
	2	0.70	0.55	0.34
*D6S1001-3	1	-	-	-
	2	0.77	0.60	0.42
D6S105-5	1	0.54	0.28	0.36
	2	0.50	0.15	0.41
D6S464-3	1	0.81	0.60	0.53
	2	0.78	0.58	0.47
D6S1260-4	1	0.76	0.42	0.59
	2	0.70	0.52	0.38

*allele # according to (2)

1 = Seese, Venditti et al.

2 = our data

There is one minor difference between the data of Seese, Venditti et al and our finding, and this is in the order of markers. They report the order from centromere to telomere as D6S105, D6S306, D6S464. We, and others (2), believe the order to be D6S306, D6S105, D6S464. From Southern blots of two YACs containing these three markers we have found D6S105 and D6S464 to be associated with the same *NotI* and *MluI* fragments which do not contain D6S306 (3). Based on the data that Seese, Venditti et al have reported and illustrated in their figure 3, the area

from D6S105 to D6S1558 would seem to represent the best fishing grounds for the hemochromatosis gene. We have reported on one attractive candidate from this general region, viz LD5-1(3) and are studying other candidate genes as well. But there is one concern. In the Italian population a greater degree of linkage disequilibrium is found in the region of HLA-A (4,5), far centromeric to the region delineated by Seese, Venditti et al. This could be an artifact caused by the happenstance that several different hemochromatosis alleles in the population share a common HLA-A haplotype. But perhaps the gene is there and the marked disequilibrium in the more telomeric region is the artifact. The last chapter in this story will not be written until long after the hemochromatosis gene is cloned.

Ernest Beutler
Carol West

The Scripps Research Institute
Department of Molecular and Experimental Medicine
La Jolla, CA

REFERENCES

1. Simon M, Pawlotsky Y, Bourel M, Fauchet R, Genetet B. Hémochromatose idiopathique: Maladie associée à l'antigène tissulaire. *Nouv Presse Med* 4:1432,1975.
2. Raha-Chowdhury R, Bowen DJ, Stone C, et al. New polymorphic microsatellite markers place the haemochromatosis gene telomeric to D6S105. *Hum Mol Genet* 4:1869-1874, 1995.
3. Beutler E, Gelbart T, West C, Kuhl W, Lee P. A strategy for cloning the hereditary hemochromatosis gene. *Blood Cells Mol Dis* 21:207-216, 1995.
4. Totaro A, Grifa A, Roetto A, et al. New polymorphisms and markers in the HLA class I region: relevance to hereditary hemochromatosis (HFE). *Hum Genet* 95:429-434, 1995.
5. Camaschella C, Roetto A, Sbaiz L, et al. Molecular studies of genetic hemochromatosis. *Blood* 86(Suppl 1):474a, 1995.