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Human Ferritin Genes: Chromosomal Assignments and Polymorphisms

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SUMMARY

The ferritins are a family of proteins that function intracellularly to sequester iron that otherwise would be toxic to the cell. The molecules are comprised of 24 heavy and light subunits, the heavy:light ratio varying widely in a tissue-specific manner. We cloned DNA sequences for both the heavy (HL217-1) and light (HL227) subunits from a cDNA library derived from messages that are strongly regulated during in vitro–induced differentiation of a promyelocytic leukemia cell line, HL-60, into either neutrophils or macrophages. The heavy-subunit family (FTH) includes 15–20 genes and/or pseudogenes; the light-subunit family (FTL) includes at least three genes. We have confirmed and extended the chromosomal localization of the heavy-subunit "genes" to chromosomes 1–6, 8, 9, 11, 13, 14, 17, and X. We have also identified and characterized two genetic polymorphisms: FTH/*Bam*HI and FTH/*Taq*I. FTH/*Bam*HI localizes to chromosome 3, is biallelic, and has a heterozygosity frequency of .39, a minor allele frequency of .33, and a polymorphic information content (PIC) of .34. FTH/*Taq*I is measured by the presence or absence of a single 6-kb fragment that is absent (i.e., "homozygosity" being presumed) in ~63% of Caucasians (PIC = .27). We discuss the possibility that gene-family probes that hybridize to many discrete members of dispersed gene families could be used in conjunction with pulsed- or inverted-field gels to screen a large number of specific genomic regions for microdeletions.

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INTRODUCTION

As part of an effort to identify inherited DNA polymorphisms of genes that play an active role in hematopoietic differentiation, we screened cDNA clones from a library derived from mRNAs of the HL-60 promyelocytic leukemia cell line. The clones studied had been selected because they were either up-regulated or down-regulated during the induction of macrophage or neutrophil terminal differentiation in HL-60 cells (Davis et al. 1987). Of 16 regulated clones initially selected for characterization, most were members of large gene families (Chou et al. 1986; Davis et al. 1987). Sequence analyses showed that three clones coded for ferritin heavy subunits (FTH) or ferritin light subunits (FTL). Northern blots showed that these genes are strongly up-regulated when HL-60 cells are induced to terminally differentiate.

The human FTH gene family comprises ~15–20 genes, most of which are probably pseudogenes (Cragg et al. 1985; McGill et al. 1987). The human FTL gene family is smaller, including three genes that map to chromosomes 19q, 20q, and Xp (Lebo et al. 1985; McGill et al. 1987). A subclone of the FTH sequence was used to characterize *Bam*HI and *Taq*I DNA polymorphisms. A mouse-human cell-line panel has permitted us to make chromosomal assignments for monomorphic and polymorphic fragments obtained by hybridizing the FTH probe to genomic DNA digested with *Bam*HI, *Taq*I, or *Msp*I. We have also assigned the FTH/*Bam*HI polymorphism to chromosome 3. By contrast, no polymorphisms were found with the FTL probe when restriction enzymes *Eco*RI, *Bam*HI, *Msp*I, and *Taq*I were used.

MATERIAL AND METHODS

Genomic DNA

Initial screening of probes for genetic polymorphisms was performed on genomic DNAs from lymphoblastoid cell lines (LCLs) of eight unrelated donors representing four races (Caucasian, Amerindian, Oriental, and black). Genomic DNA from HL-60 cells was added to this screening panel, since the probes were originally derived from an HL-60 cDNA library (see fig. 1[a]). DNA was isolated by first lysing the cytoplasm with nuclear prep buffer (0.32 M sucrose, 10 mM Tris-HCl, pH 7.5, 5 mM $MgCl_2$, 1% Triton-X100) and then simultaneously lysing the nuclei and exposing the DNA to proteinase K digestion in Lindahl buffer (3% sarcosyl, 0.075 M NaCl, 0.024 M ethylenediaminetetraacetate, pH 8) (Lindahl et al. 1976). After overnight rotation at room temperature, the DNA was phenol/chloroform extracted and recovered by means of spooling from isopropanol. Additional studies were performed with genomic DNA from LCLs of members of large families supplied by the Center for the Study of Human Polymorphisms (CEPH), Paris. Each probe was screened for polymorphisms against genomic DNAs digested with each of four enzymes: *Eco*RI, *Bam*HI, *Msp*I, and *Taq*I.

Southern Blots

Most blots and radiolabeled probes were prepared according to our previously published protocol (Gatti et al. 1984). DNA was then loaded (5–10 μg/

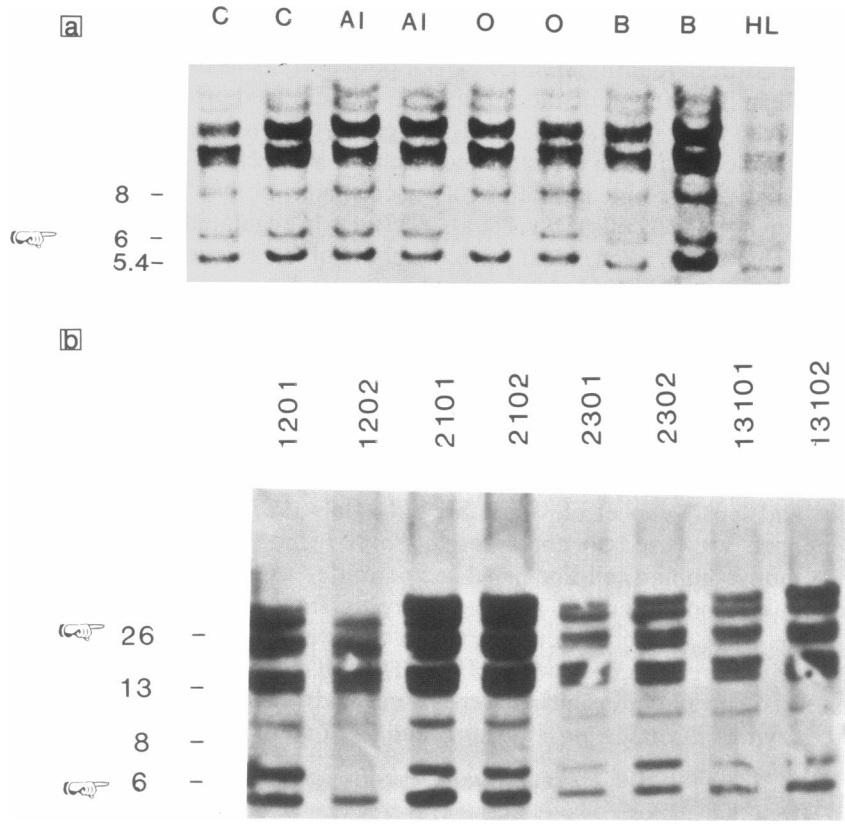

FIG. 1.—Autoradiograms: HL217-1/*Bam*HI. [a], DNA from nine racially divergent donors (C = Caucasian; AI = Amerindian; B = black; and O = Oriental). Note absence of 6-kb fragment in first O lane. [b], DNA from eight unrelated Caucasians. Note absence of 6-kb fragment in lane 1202.

lane). ZetaProbe™ membranes were used for blotting and were reused as many as 20 times. In later experiments, transfers were made under alkaline conditions, according to the method described by Reed and Mann (1985), although recent experience suggests that blots prepared in this way may not be reused as many times as blots transferred under high salt conditions.

Probes

cDNA clones HL217 and HL227, corresponding to the FTH and FTL genes, respectively, were isolated from a DMSO-induced HL-60 cell library (Chou et al. 1986; Davis et al. 1987). Together with 50 other clones, these clones were selected by means of differential hybridization that showed that the corresponding mRNAs were strongly regulated during HL-60 differentiation toward neutrophils (Davis et al. 1987). The FTH probe was HL217-1, a 550-bp *Pst*I subclone from the 3′ end of HL217 (783 bp) (Chou et al. 1986). The subclone was transferred into the M13 vector mp11. The 571-bp insert from pHL227 was

transferred into M13 vector mp11 to give mHL227, the probe used for the FTL gene.

Somatic-Cell Fusion Hybrid Panel

A panel of 18 cell hybrids was used for gene localization studies. Details describing the isolation and characterization of these hybrids have been published elsewhere (Mohandas et al. 1986). Karyotypes were determined at the time of DNA harvest. In the interpretation of Southern blots, a hybrid clone was considered positive for a given chromosome if ≥20% of cells analyzed contained that chromosome. In general, when a band was absent in a lane containing <20% DNA for the relevant chromosome, that relationship was scored as concordant. The interpretation of such marginal situations—i.e., those in which 5%–20% of the cells from which the DNA was prepared contain a particular chromosome—is one of the most difficult problems in such an analysis. The decision as to how such data will be treated must in part depend both on the intensity of the band in the parent-cell DNA and on an estimation of whether a band of correspondingly reduced intensity would be detectable over the background. Such marginal assignments depend on the sensitivity of hybridization to Southern blots; this can vary with the amount and radioactivity of labeled probe, the amount of covalently bound genomic DNA remaining on a multiple-use blot, the actual amount of DNA in a lane, the degree of homology between the probe and a particular fragment, hybridization and stringency wash conditions, and other factors; and these variables may cause occasional discordances. Assignments reported herein are based on the independent scorings of two investigators.

RESULTS

1. *Chromosomal Assignments of Fragments of the FTH Gene Family*

Using a mouse-human somatic-cell hybrid panel and the FTH probe HL217-1, we attempted to assign to particular chromosomes the DNA fragments created by each of several restriction-enzyme digests. In this way, we hoped to (1) confirm and extend the mapping of the FTH gene family and (2) determine the location of polymorphic fragments that could then be used as genetic markers for those chromosomes. Figure 2 shows chromosomal assignments of fragments generated by digestions with *Bam*HI, *Msp*I, and *Taq*I, as well as the *Eco*RI-fragment assignments made by Drysdale and McGill and their coworkers (Cragg et al. 1985; McGill et al. 1987). Figure 1 also shows the relative sizes of mouse fragments that hybridized to our human FTH probe.

*Msp*I digests probed with HL217-1 revealed 17 fragments (labeled A–Q). Fourteen of these fragments were assigned to the following chromosomes: 1 (bands I and M), 3 (band O), 5 (bands K and L), 6 (bands B and D), 8 (band A), 9 (bands E and J), 11 (band F), 13 (band N), 14 (band G), and 17 (band Q). Figure 3 shows *Msp*I fragments A–Q under conditions that optimize both resolution and chromosomal assignments of *Msp*I fragments. Table 1 provides the data upon which the *Msp*I chromosomal assignments shown in figure 2 were

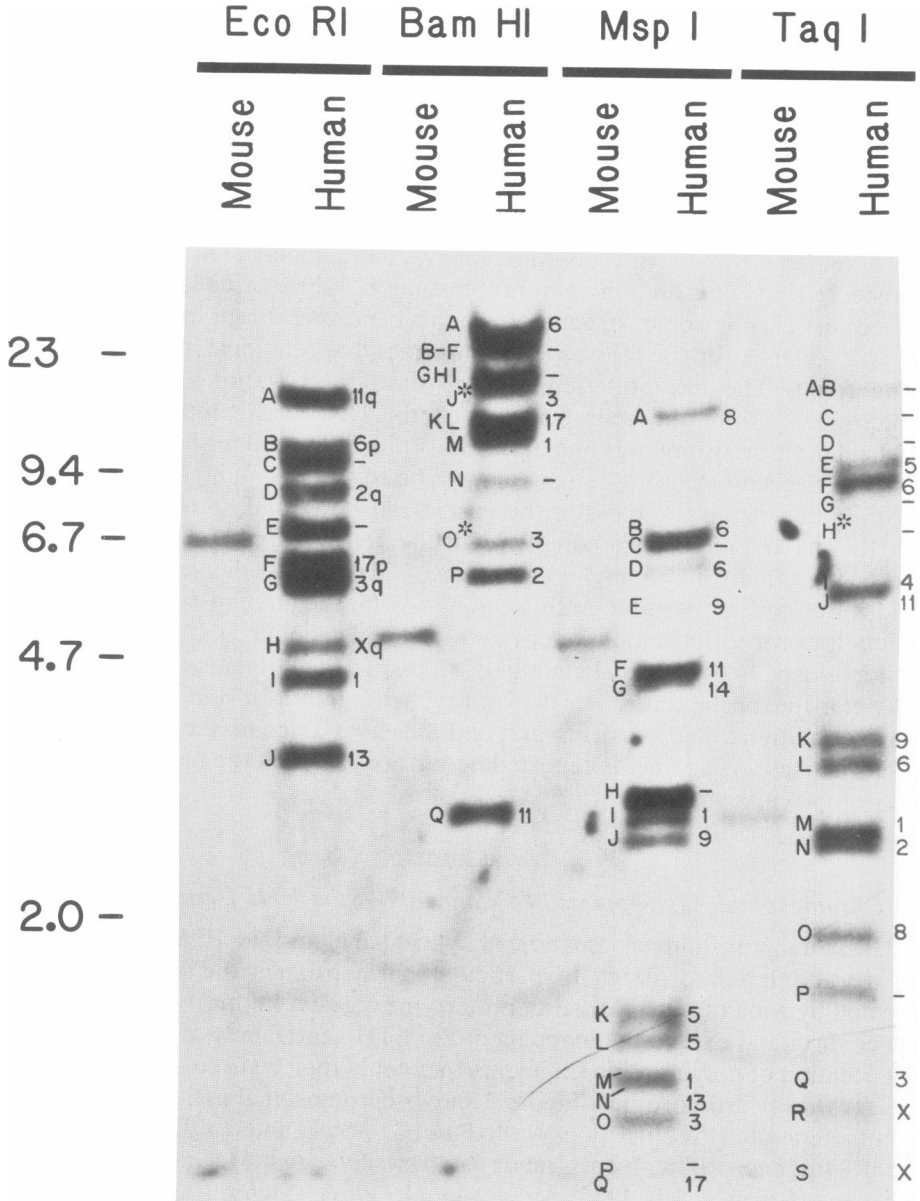

FIG. 2.—Autoradiogram showing chromosomal assignments of FTH fragments generated by digesting DNA with *Eco*RI, *Bam*HI, *Msp*I, or *Taq*I and hybridizing with probe HL217-1. To the left of each lane the bands are identified with consecutive letters; numbers to the right of each lane indicate the chromosomal assignments of each band. Mouse and human DNA were isolated from the parental cells (IMR91 and B82, respectively) used to generate somatic-cell hybrids (9). Asterisks indicate the positions of polymorphic fragments. Because of the large size range of fragments, electrophoresis of samples was done in a 1% agarose gel. High-molecular-weight bands were further resolved under other conditions (e.g., see figs. 4, 5, and 7).

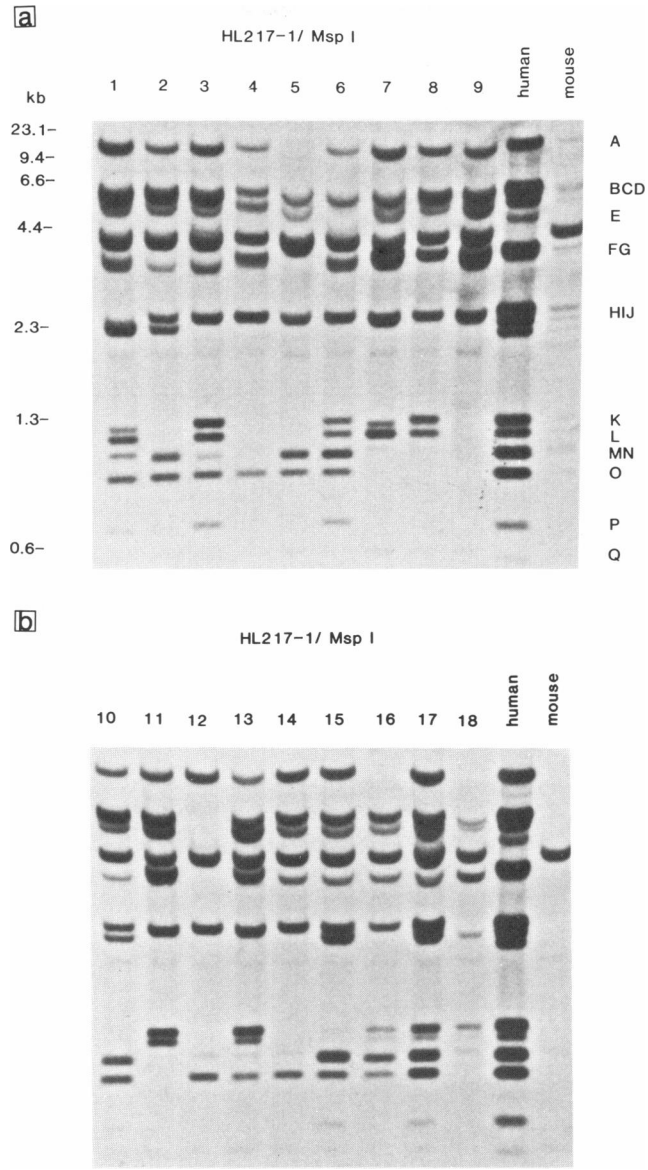

FIG. 3.—Autoradiograms: HL217-1/*Msp*I. DNA is from somatic-cell hybrids (9) and is arranged as follows: lane 1, 84-2; lane 2, 84-4; lane 3, 84-5; lane 4, 84-7; lane 5, 84-13; lane 6, 84-20; lane 7, 84-25; lane 8, 84-27; lane 9, 84-34; lane 10, 84-3; lane 11, 84-37; lane 12, 84-39; lane 13, 84-6; lane 14, 84-35; lane 15, 84-38; lane 16, 84-30; lane 17, 84-26; lane 18, 84-21; lane human, 1MR91; and lane mouse, B82. These data form the basis for table 1 and for the *Msp*I assignments in fig. 2.

TABLE 1

CHROMOSOMAL ASSIGNMENTS OF FTH GENES ON *MspI* FRAGMENTS WITH USE OF HYBRID-CELL PANEL AND PROBE mHL217-1

BAND (Size in kb)	CHROMOSOME	BAND STATUS				N	DISCORDANCE	χ^2	P
		Present[a]		Absent[a]					
		Chr. +	Chr. −	Chr. +	Chr. −				
A (17.0)	8	14	1	0	3	18	1	7.3	<.0025
	15	10	5	0	3	18	5	2.2	>.9
BC (5.9)[b]	6	15	1	0	2	18	1	5.5	<.025
	2	7	8	0	3	18	8	0.7	>.9
D (4.6)	6	15	0	0	3	18	0	11.5	<.001
E (4.5)	9	0	0	0	18	18	0	∞	<.001
F (3.7)	11	8	0	0	10	18	0	14.2	<.001
G (3.6)	14	14	0	0	4	18	0	16.9	<.001
H (2.6)[b]	3	12	3	0	3	18	3	4.0	<.05
	17	16	0	2	0	18	2	.8	<.3
I (2.5)	1	5	0	0	13	18	0	13.3	<.001
J (2.4)	9	0	0	0	18	18	0	∞	<.001
K (1.5)[b]	5	9	0	0	9	18	0	14.2	<.001
	2	4	2	3	9	18	5	1.4	>.9
	11	4	2	4	8	18	6	0.7	>.9
L (1.4)	5	9	0	0	9	18	0	14.2	<.001
M (1.1)[b]	1	5	0	0	13	18	0	13.3	<.001
N (1.0)[b]	13	8	0	0	10	18	0	14.2	<.001
O (0.9)	3	12	1	0	5	18	1	10.0	<.001
	18	10	3	1	4	18	4	2.8	<.1
P (0.7)	2	5	2	1	10	18	3	4.9	<.05
	19	6	1	2	9	18	3	5.4	<.025
Q (0.5)	17	18	0	0	0	18	0	∞	<.001

[a] "Chr. +" denotes the presence of a particular chromosome in a hybrid cell; and "Chr. −" denotes the absence of that chromosome in a hybrid cell.

[b] These fragments occasionally resolve into two bands of very similar size. This could distort the chromosomal assignment unless both fragments are on the same chromosome, e.g., the data for band H are compatible with the hypothesis that two 2.6-kb fragments assign to chromosomes 3 *and* 11 (data not shown). Consequently, no assignment has been made for this band in fig. 2.

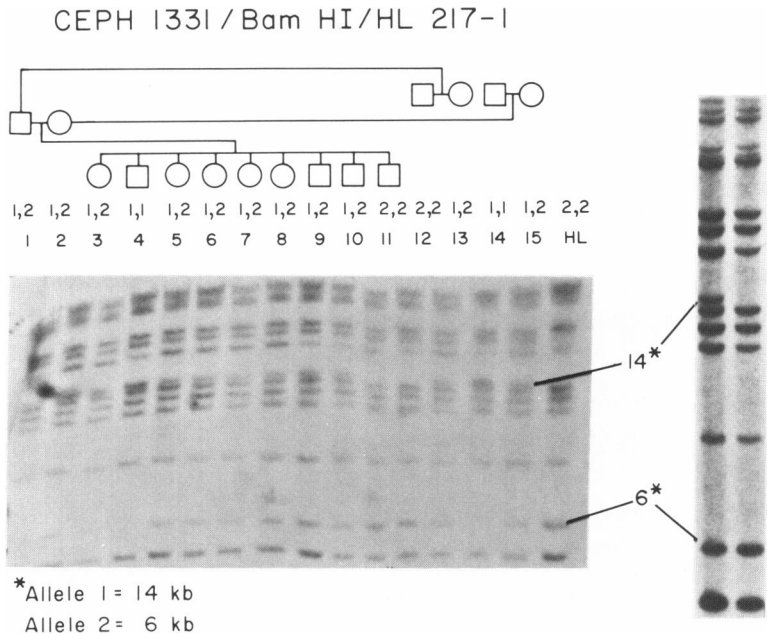

FIG. 4.—Autoradiogram: HL217-1/*Bam*HI. Separation of *Bam*HI-digested DNA from a Caucasian family (CEPH 1331) by means of 0.6% gel; relationships are shown. Genotypes are expressed as allele 1 (band J [14-kb] fragment present) and/or allele 2 (band O [6-kb] fragment present). HL = HL-60 DNA.

based. *P*-values were considered for all chromosomes. The *P*-values for all potential chromosomal assignments not shown in table 1 were >.9. When any discordance was observed, the chromosomes giving the two most significant *P*-values for that fragment were included in the table, even though some of these alternatives seemed to be clearly excluded by the high *P*-values (e.g., bands A, C, and O). Bands C, H, and P could not be assigned.

In experiments similar to those described above, *Bam*HI digests hybridized to HL217-1 revealed 17 fragments (labeled A–Q in fig. 2). Eight of these fragments were assigned to the following chromosomes: 1 (band M), 2 (band P), 3 (bands O and J), 6 (band A), 11 (band Q), and 17 (bands K and L). The 6.0-kb fragment (band O) is polymorphic and is allelic with a 14-kb fragment (band J, indicated by the asterisks in fig. 2); the latter cannot be distinguished in the 1% agarose gel shown in figure 2 but is resolved in figure 4. The tight clustering of high-molecular-weight bands made it difficult to localize *Bam*HI fragments B–I to specific chromosomes.

*Taq*I digests probed with HL217-1 revealed 19 bands (labeled A–S in fig. 2). Eleven of these fragments were assigned to the following chromosomes: 1 (band M), 2 (band N), 3 (band Q), 4 (band I), 5 (band E), 6 (bands F and L), 8 (band O), 9 (band K), 11 (band J), and X (bands R and S). A polymorphic 6.0-kb *Taq*I fragment (band H, fig. 5) was not present in the human parental cells used

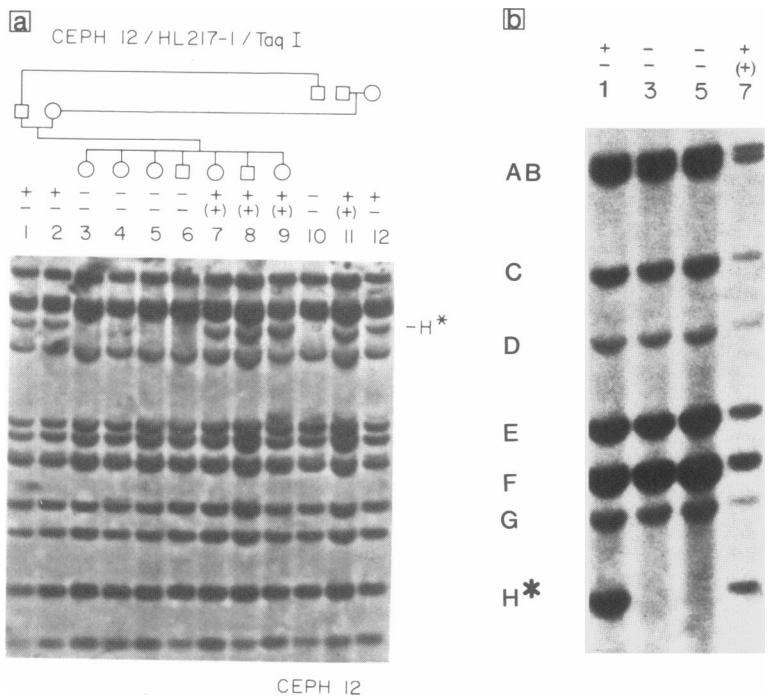

FIG. 5.—Autoradiograms: HL217-1/*TaqI*. [a], DNA from a Caucasian family (CEPH 12); relationships are shown. Genotyping was not possible for all members (absence of fragment H presumes −/− homozygosity); the stronger relative intensity of band H in lanes 7–9 and 11 is compatible with homozygosity for the presence of band H (+/+). [b], DNA from individuals 1, 3, 5, and 7 of fig. 5*a* was retested under conditions optimizing resolution of higher-molecular-weight fragments. A reciprocal fragment could not be identified in individuals who lacked band H. Also note doublet (band AB) in lane 4. Genotypes for the FTH/*TaqI* polymorphism are shown at top.

for preparing cell hybrids and, consequently, could not be mapped in these experiments. (Its position is indicated by an asterisk in fig. 2.)

2. *FTH*/Bam*HI*/*14;6-kb Polymorphism*

Figure 1*a* demonstrates polymorphism of a 6-kb *Bam*HI fragment in genomic DNA from nine racially divergent individuals probed with HL217-1. Figure 1*b* demonstrates the same 6-kb polymorphism in Caucasian individuals and also shows potential polymorphism of an ~30-kb fragment (i.e., lane 1202). When higher-molecular-weight fragments were further separated using a 0.6% agarose gel, a 14-kb fragment (band J, fig. 4) was identified that was reciprocal with the 6-kb fragment. These alleles segregated in accordance with Mendelian inheritance. The polymorphism was tested in 63 unrelated Caucasians. Allelic frequencies were .33 and .67 for the 14-kb (band J) allele and the 6-kb (band O) alleles, respectively. Genotype frequencies were .13 for 14-kb homozygosity, .48 for 6-kb homozygosity, and 0.39 for heterozygosity. The polymorphic information content (PIC) index was .34.

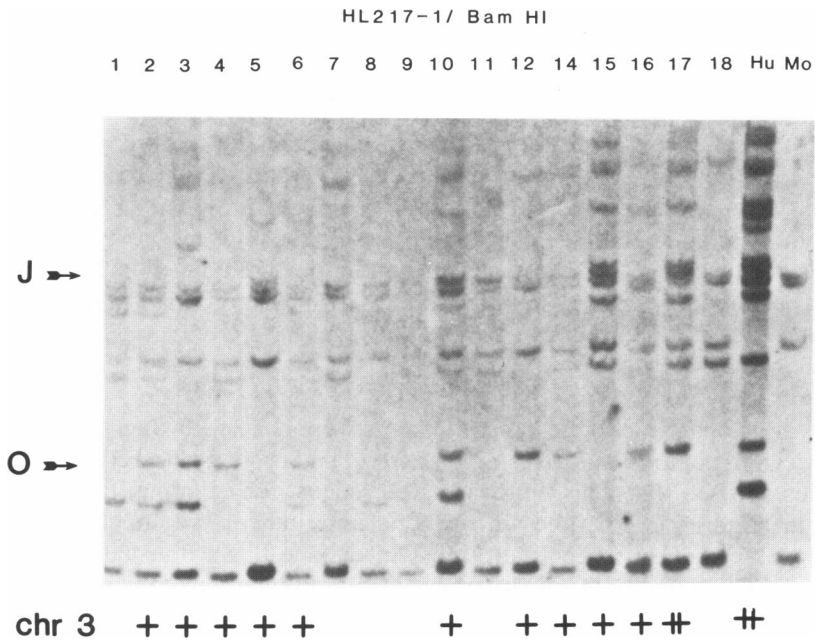

FIG. 6.—Autoradiogram: HL217-1/*Bam*HI. DNA from the same mouse-man hybrid-cell panel described in fig. 3 (lane numbers are comparable). *Bottom*, + = Haploid for chromosome 3; and + + = diploid for chromosome 3. Pointers indicate position of polymorphic bands at 14 kb (J) and 6 kb (O). Note presence of both bands J and O in hybrid 84-36 (lane 17), which is diploid for chromosome 3. Hybrids 84-13 (lane 5) and 84-38 (lane 15) are haploid for the haplotype carrying the 14-kb fragment. Lanes 2–4, 6, 10, 12–14, and 16 represent hybrids that are haploid for the haplotype carrying the 6-kb fragment.

To confirm the chromosomal assignment of this biallelic marker, it was necessary to demonstrate that both polymorphic fragments could be assigned to chromosome 3 (fig. 6). Under conditions that optimized the resolution of high-molecular-weight fragments, fragment J (14 kb) was visualized in the human parental cell line and in hybrids 5, 15, and 17. Fragment O (6 kb) was observed in the human parental cell line and in hybrids 2–4, 6, 10, 12, 14, 16, and 17. Independently, karyotyping of each hybrid-cell line revealed that all hybrids were haploid for chromosome 3—except for hybrid 17 (84-36), which was diploid like the parental cell line. Thus, it appears that (1) the FTH/*Bam*HI/14;6-kb polymorphism demonstrates the heterozygosity of both the parental cell line and hybrid 17, (2) hybrids 5 and 15 are hemizygous for the haplotype carrying fragment J (14 kb), and (3) all other hybrids in the panel are hemizygous for the haplotype carrying fragment O (6 kb).

3. *FTH*/Taq*I*/*6-kb Polymorphism*

Figure 5[a] demonstrates the FTH/*Taq*I/6-kb polymorphism and its Mendelian segregation, again with use of the HL217-1 probe. We have not been able to identify a reciprocal band for the polymorphic 6-kb fragment on gels that op-

timize the resolution of either high- or low-molecular-weight fragments (fig. 5[b]). The 6-kb fragment (band H) is absent in 63.5% of 63 unrelated Caucasian individuals. If 63.5% is assumed to represent q^2, then $q = .8$ and $p = .2$. If genotypes were identifiable on the basis of the intensity of the 6-kb fragment, the PIC for this marker would be .27 and the frequency of heterozygosity would be .32. However, we have not found this approach to be very reliable (e.g., see fig. 5[b]); thus, the operational PIC will be somewhat lower than .27. The chromosomal assignment of this marker was not possible using the hybrid-cell-line panel, because the 6-kb fragment is absent in the parental cell line. We hope to map this polymorphism by applying linkage analysis to CEPH families such as the one shown in figure 5[a].

4. *Digests That Did Not Yield Polymorphisms*

Several apparent polymorphic fragments were observed when genomic DNA of unrelated persons was digested with *Msp*I and probed with HL217-1. Family studies showed that major intensity differences, for example, failed to segregate in patterns compatible with genetic inheritance. We concluded that the FTH polymorphisms seen were most likely due to an unusual resistance of some CCGG sites to *Msp*I digestion, despite precautions taken to ensure the completeness of restriction digests, such as monitoring with "daughter digests."

No polymorphisms were noted when *Eco*RI digests of nine persons representing four races were probed with HL217-1. Similarly, no polymorphisms were noted with the FTL probe when the same set of DNAs was digested with *Eco*RI, *Bam*HI, *Msp*I, or *Taq*I.

DISCUSSION

The FTH/*Bam*HI/14;6-kb polymorphism that we have described localizes to chromosome 3. On the basis of an assignment made by McGill et al. (1987) by means of in situ hybridization of an FTH gene on chromosome 3q21 (FTHL4, according to Human Gene Mapping 8), it is likely that this new FTH/*Bam*HI polymorphism will correspondingly localize to chromosome 3q. This is of special interest because the genes for transferrin and transferrin receptor have been localized to 3q21-q26.1 and 3q26.2-qter (van de Rijn et al. 1983; Yang et al. 1984), respectively, and these also involve iron metabolism. Linkage-analysis studies in progress will further test the significance of this association. Screening of parents from CEPH families indicates that 22 of 37 families are potentially informative. To use the HL217(FTH)/*Bam*HI/14;6-kb genetic marker, it is necessary to optimize separation of high-molecular-weight fragments.

Chromosomal assignments of *Eco*RI fragments of FTH were made by Drysdale and McGill and co-workers (Cragg et al. 1985; Hentze et al. 1986; McGill et al. 1987). These assignments are shown in figure 2 for comparison with our assignments. By and large, the fragment assignments with different enzymes correspond well. However, whereas earlier reports suggested that the FTH gene family contained at least nine genes (Cragg et al. 1985; Chou et al.

1986; McGill et al. 1987), the data that we report here, which attempt to optimize sensitivity and resolution of large fragments for four different restriction enzymes, suggest that as many as 15–20 genes and/or pseudogenes exist. Thus, it was inevitable that we would make chromosomal assignments in addition to those made in earlier reports.

The major FTH gene maps to chromosome 11q13 (Hentze et al. 1986). Most other fragments may represent pseudogenes. Our data indicate that the gene at 11q13 is cleaved by *Bam*HI, *Taq*I, and *Msp*I to yield fragments of 3 kb, 5.5 kb, and 4.7 kb, respectively. Each of these fragments gives a strong hybridization signal. We—and others—have failed to confirm an earlier assignment of an FTH gene to chromosome 19 (Caskey et al. 1983), an assignment that, in retrospect, probably resulted from immunological cross-reactivity with the product of the ferritin light-chain gene, which *does* localize to chromosome 19q13 (McGill et al. 1987).

Using *Eco*RI digests of DNA from somatic-cell hybrid-cell lines, Cragg et al. (1985) assigned FTH genes to the following eight human chromosomes: 1–3, 6, 11, 14, 20, and X. Using the same restriction enzyme, McGill et al. (1987) confirmed the assignments to chromosomes 1–3, 6, 11, and X and added assignments to chromosomes 13 and 17; they could not confirm the earlier assignments to chromosomes 14 and 20. In addition, using in situ hybridization, they assigned FTH genes to 1p22-31, 1q32-42, 2q32-33, 3q21-23, 6p12-21.3, 11q13, 13q12, and Xq26-28. They could not confirm the Cragg et al. assignments to chromosomes 14 and 20, nor could they support their own assignment of a 6.2-kb/*Eco*RI fragment to chromosome 17 by means of in situ hybridization. Our data derive from somatic-cell DNA digested with *Bam*HI, *Msp*I, or *Taq*I and confirm the Cragg et al. and McGill et al. assignments to chromosomes 1–3, 6, 11, and X, as well as the assignments to chromosomes 13, 14, and 17. In agreement with McGill et al., we find no evidence for an FTH gene on chromosome 20. In addition, we have resolved additional bands; and, on the basis of fragment assignments with at least two restriction enzymes, the data also localize FTH genes to chromosomes 5, 8, and 9. *Taq*I digests further suggest that yet another FTH gene exists on chromosome 4 (band I, fig. 2). This would bring the total number of localized FTH genes (including two assignments on chromosome 1) to 14, i.e., chromosomes 1–6, 8, 9, 11, 13, 14, 17, and X.

Localizations by means of either somatic-cell mapping or in situ hybridization have technical limitations and are likely to leave some genes unassigned when such a large gene family is being mapped; for example, using only one enzyme digest may underestimate the number of chromosomal sites involved. Several reasons might account for this. First, smaller fragments may run off the mapping gels and prevent mapping of those fragments. Second, fragments of similar size may obscure one another and create contradictory localization data, since the two indistinguishable bands may map to different chromosomes. Third, enzyme-cleavage sites may create fragments that no longer hybridize to the probe with sufficient intensity to be visualized. Fourth, probes from different laboratories may correspond to different genes or parts of genes and may visualize some different fragments.

With the FTH-gene-family polymorphisms, we have not yet accomplished our original goal of developing probes that might be useful for identifying allelic variants of genes expressed during hematopoietic differentiation. The polymorphisms that we describe in the present report involve fragments other than the active gene on chromosome 11p and most likely correspond to nonfunctional genes. On the other hand, cDNA probes of large gene families may be useful in other ways, such as in screening large amounts of genomic DNA on different chromosomes. We estimate that the HL217-1 probe visualizes ~50 kb of DNA when conventional gels and restriction enzymes are used. If, in contrast, such a probe were used in combination with pulsed- or inverted-field gel techniques for following DNA fragments averaging 100–500 kb in size, perhaps as much as 2,000–10,000 kb of DNA could be visualized on a single blot. This might prove useful for monitoring chromosomal deletions and microdeletions; for example, given the prognostic association of serum ferritin with neuroblastoma (Hann et al. 1985), the HL217-1 (FTH) probe might be appropriate for following neuroblastoma-related deletions on chromosome 1p (Gilbert et al. 1984) while also following the inheritance of the *Bam*HI polymorphism on chromosome-3q haplotypes. Furthermore, cDNA probes belonging to large gene families can be used by investigators seeking to recover fragments in the chromosomal regions where corresponding bands have been localized.

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