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Extensive DNA Polymorphism at the Factor XIIIa (F13A) Locus and Linkage to HLA

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Summary

A 1,161-bp *Eco*RI fragment from the 5′ end of the cDNA coding for human factor XIIIa (gene symbol *F13A*) was used to identify RFLPs in human DNAs. Several different RFLPs were identified with 15 different restriction enzymes. Two RFLPs detected with the restriction enzyme *Bam*HI and one multiallelic RFLP detected with *Bcl*I were used for further studies. Linkage relationships between these three polymorphisms and the HLA complex were studied in DNA samples from the 40 Centre d'Etude du Polymorphisme Humain families. Combining all of the data to form highly informative haplotypes, we found linkage to HLA with a maximum lod score of 11.44 at a recombination fraction of .25 for males and .35 for females. These three RFLPs at the FXIIIa locus provide a highly informative marker for the short arm of chromosome 6 with an observed heterozygosity of 91%. Using this marker and the HLA locus, one can confirm or exclude the assignment of gene loci to most of chromosome 6p.

Introduction

Human coagulation factor XIII (FXIII) is the last proenzyme to become activated in the coagulation cascade (Lornad 1980). Plasma FXIII is a tetramer; it contains two noncatalytic b subunits and two catalytic a subunits. The activated a_2 dimer acts as an enzyme catalyzing the formation of cross-linked fibrin (Schwarz et al. 1973). Inherited deficiency of FXIII usually results from failure to produce active a subunits or from the production of functionally abnormal forms (Board et al. 1980; Castle et al. 1981). Board (1979) described polymorphism of plasma and platelet FXIIIa in several racial groups. Olaisen et al. (1983), using the protein polymorphism in plasma, discovered the linkage between FXIIIa and the major histocompatibility complex on chromosome 6. This was followed by several studies that confirmed the linkage between FXIIIa and the HLA complex (Board et al. 1984; Eiberg et al. 1984; Olaisen et al. 1985). Some smaller-sample studies failed to detect significant linkage, but they do not exclude distant linkage. (Graham et al. 1984; Keats and Elston 1985; Kompf et al. 1985; Nishigaki et al. 1986). To date, the maximum lod score ($\hat{Z}$) for FXIIIa and the HLA complex is $\hat{Z} = 15.7$ at a recombination fraction (θ) of .19 in males and $\hat{Z} = 0$ at θ of .5 in females (Lamm and Olaisen 1985). Since linkage closer than 15 cM has been excluded between FXIIIa and phosphoglucomutase 3 (PGM3), which is centromeric to HLA, it has been concluded that FXIIIa is telomeric to HLA.

Recently Takahashi et al. (1986) determined the complete amino acid sequence of human placental FXIIIa. Grundmann et al. (1986) used the reported peptide sequence to design oligonucleotide probes to screen a cDNA library prepared from human placenta. They isolated and sequenced a 1,704-bp cDNA coding for the placental FXIIIa subunit. Grundmann et al. provided us with this clone for the purpose of RFLP and linkage studies. Using a

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1,161-bp *Eco*RI fragment from the 5′ end of the FXIIIa cDNA as a probe, we have identified several RFLPs at the FXIIIa locus. The results of linkage studies using Centre d'Etude du Polymorphisme Humain (CEPH) DNA samples are presented to define further the genetic distance between FXIIIa and the HLA locus.

Material and Methods

Subjects

As a part of an ongoing study (Zoghbi et al., in press), six unrelated American black individuals were chosen as the source of DNA for detection of polymorphisms with a variety of restriction enzymes. For further characterization of the polymorphisms in Caucasians and for linkage studies, families from CEPH (Paris) were used. The CEPH families consist of 40 nuclear families, most with four grandparents and both parents available for study (Marx 1985).

Isolation of DNA

For local DNA samples, 15 ml of blood was collected into a tube containing 10 mg EDTA. The blood was transferred to a 50-ml plastic tube and centrifuged for 15 min at 1,300 *g*. The plasma was aspirated, and 30 ml of cold lysis buffer (0.32 M sucrose, 10 mM Tris-Cl [pH 7.5], 5 mM $MgCl_2$, 1% [v/v] Triton X-100) was added with mixing. The specimen was incubated 30 min on ice, and nuclei were pelleted by centrifuging at 1,300 *g* for 15 min. The nuclear pellet was resuspended in 4.5 ml of a solution containing 10 mM Tris-Cl (pH 7.4), 10 mM NaCl, 10 mM Na_2EDTA, followed by addition of 250 μl of 20% SDS and 200 μl of 10 mg proteinase K/ml. The suspension was incubated for 16 h at 37 C. DNA was extracted twice with 5 ml of phenol:chloroform:isoamyl alcohol 25:24:1 (v/v) and once with chloroform:isoamyl alcohol 49:1 (v/v). The DNA was precipitated by the addition of 0.5 ml of 3 M sodium acetate (pH 4.8). DNA from the CEPH families was provided by the CEPH project and was prepared from lymphoblastoid cell lines according to published protocols.

Restriction-Endonuclease Digestion and Southern Blotting Analysis

Five micrograms of DNA was incubated for 6 h with 2–5 units of restriction endonuclease/μg of DNA according to conditions recommended by the suppliers. The digests were applied to 0.7% agarose gels and were electrophoresed at 2 V/cm for 16–20 h in TAE buffer (40 mM Tris acetate, 1 mM EDTA and glacial acetic acid to adjust the pH to 7.7). Gels were denatured in 0.5 M NaOH, 1.5 M NaCl and neutralized in 1 M Tris-Cl (pH 8.0), 1.5 M NaCl. The DNA was subsequently transferred overnight onto Nytran® (Schleicher and Schuell, Keene, NH) filters by using 10 × SSC (1 × SSC = 0.15 M sodium chloride, 0.015 sodium citrate [pH 7.0]). Filters were prehybridized for 6–16 h at 67 C in 6 × SSC, 1 × Denhardt's solution (1 × Denhardt's = 0.02% BSA, 0.02% polyvinylpyrrolidone, 0.02% Ficoll 400) and 0.25 mg denatured salmon-sperm DNA/ml. Hybridizations were done overnight at 67 C in 6 × SSC, 1 × Denhardt's, 0.25 mg salmon-sperm DNA/ml, 10% dextran sulfate and ^{32}P-labeled probes, using 5 ml/100 cm^2 of filter. Probes were labeled by means of the oligohexamer labeling method (Feinberg and Vogelstein 1983) to a specific activity of $5–10 \times 10^8$ cpm/μg and were added at 10^7 cpm/100 cm^2. Filters were washed at room temperature in 2 × SSC, 0.5% SDS for 15 min, followed by two changes of 0.1 × SSC, 0.5% SDS at 67 C for 2 h. Autotradiography was performed with an intensifying screen at −70 C for 48–72 h by using Kodak X-Omat™AR film.

Data Analysis

Allele frequencies were counted using 125 unrelated individuals—that is, grandparents or parents—from the CEPH families. All families were typed using both *Bam*HI and *Bcl*I. For linkage analysis, the families were broken into three groups. The first group included families in which combined *Bam*HI RFLPs alone yielded maximum information. In all these families *Bam*HI haplotypes for the two RFLPs were used. The second group included families in which the *Bcl*I polymorphism alone was the most informative, and the third group included families in which additional information was gained by constructing a complete haplotype for the *Bam*HI and *Bcl*I RFLPs. To accomodate the large number of possible haplotypes when the *Bam*HI and *Bcl*I were combined, individual chromosomes were coded as A, B, C, D, E, or F, according to the method proposed by Ott (1985). Haplotypes for HLA-(A-B-DQ-DR) haplotypes were encoded similarly. The HLA-(A-B) haplotypes were used in the three individuals with a crossover between HLA-(A-B) and HLA-DQ and/or HLA-DR.

For linkage analysis, a version of LIPED (Ott 1985), recompiled to accept 21 phenotypes/locus, double precision, running on IBM PC/AT with an 80287

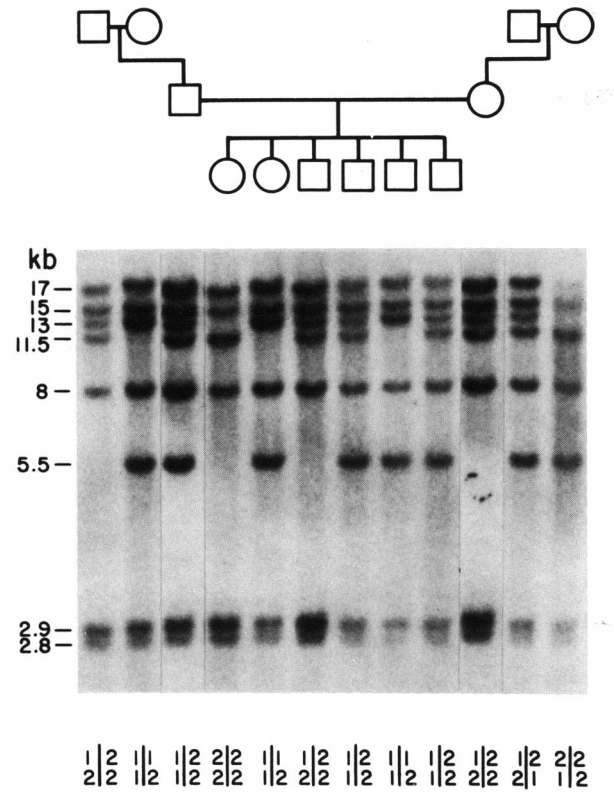

Figure 1 The two RFLPs detected with *Bam*HI and the FXIIIa cDNA probe. The genotypes of individuals are shown directly below their symbols in the pedigree. RFLP A is identified by the 13- and 11.5-kb fragments; and RFLP B is identified by the 5.5-, 2.9-, and 2.8-kb fragments.

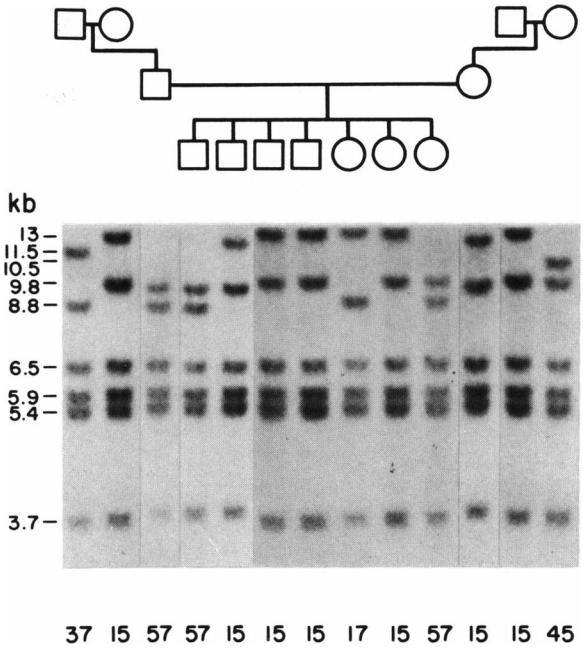

Figure 2 RFLPs detected with *Bcl*I and the FXIIIa cDNA probe. Lanes 3–5 and 11, counting from the left, were run on a separate gel with a slightly shorter running time, so fragments are not exactly aligned. Genotypes at the bottom of the figure provide correct interpretations.

math coprocessor, was used. Lod scores were calculated at 1-cM intervals to determine the maximum values separately for female θ (θ_f) values equal to male θ (θ_m) values and for θ_f values different from θ_m values. Several CEPH families share grandparents, specifically families 102 and 104, 1344 and 1375, and 13291–13294. These were combined for LIPED analysis.

The extent of linkage disequilibrium between the three RFLP loci was determined in two steps. First, the significance of the difference between the observed and expected pairwise haplotypes was established using the conventional χ^2 test. To assure expected values of sufficient size, the four least frequent alleles detected with *Bcl*I were pooled. Second, the square root of the χ^2 metric proposed by Morton and Wu (1988) was used to establish actual disequilibrium values. In the two-by-two case this method is identical to the delta measure proposed by Chakravarti et al. (1984). Confidence intervals were determined using the Z transformation (Chakravarti et al. 1984).

Results

Polymorphisms and Allele Frequencies

Twenty-seven restriction endonucleases were examined for RFLPs by using DNA from six unrelated American black individuals and the 1,161-bp *Eco*RI fragment of cDNA from FXIIIa. Two-allele polymorphisms were detected with *Eco*RV, *Fnu*4HI, *Hin*dIII, *Sph*I, and *Taq*I. The enzymes *Apa*I, *Bam*HI, *Bcl*I, *Bgl*I, *Eco*RI, *Msp*I, *Pvu*II, *Sca*I, *Sst*I, and *Stu*I detected polymorphisms that had more than two alleles. For many pairs of RFLPs there were individuals who were heterozygous with one but not with the other, a result implying that many of these RFLPs varied relatively independently. No polymorphism was detected with *Ava*II, *Ban*I, *Ban*II, *Bgl*II, *Dra*I, *Hin*cII, *Kpn*I, *Mbo*I, *Pss*I, *Pst*I, *Rsa*I, and *Xba*I.

The *Bam*HI and *Bcl*I polymorphisms were selected for further study on the basis of the extent of polymorphism and the ease of scoring, and these were characterized using DNAs from the CEPH families. Figures 1 and 2 show examples of Southern blot anal-

Table 1

***Bam*HI and *Bcl*I RFLPs and Allele Frequencies**

Restriction Enzyme (No. of Chromosomes)	Invariant Fragment (kb)		Variant Fragment			PIC	Heterozygosity Observed[a] (%)
			Allele	Kb	Frequency		
*Bam*HI (250)	17[b], 15, 8	RFLP A	1	13.0	.78	.284	34
			2	11.5	.22		
		RFLP B	3	5.5	.27	.317	41
			4	2.9, 2.8	.73		
*Bcl*I (224)	6.5, 5.9, 5.4, 3.7, 2.5		1	13	.049		
			2	12	.004		
			3	11.5	.040		
			4	10.5	.004	.653	64
			5	9.8	.277		
			6	9.0	.027		
			7	8.8	.447		
			8	8.4	.148		
			9	6.5	.004		

[a] Calculated using 122 independent individuals for *Bam*HI and 95 independent individuals for *Bcl*I.
[b] The 17-kb *Bam*HI fragment was observed to vary rarely with a 19-kb allele; 5% of 120 independent individuals were heterozygous.

ysis using these enzymes. Table 1 shows the sizes of constant and variable restriction fragments detected with the FXIIIa cDNA probe when *Bam*HI and *Bcl*I were used. Data on allele frequencies calculated using (*a*) 250 independent chromosomes and *Bam*HI and (*b*) 224 independent chromosomes and *Bcl*I are also provided. Haplotype frequencies for the pair of *Bam*HI RFLPs (A and B) and for all three RFLPs taken together are given in table 2. PIC was calculated according to the method of Botstein et al. (1980). PIC values for the different alleles and haplotypes are shown in tables 1 and 2, respectively.

The observed heterozygosity for 122 unrelated members of the CEPH families was 63% with the *Bam*HI haplotypes alone (two RFLPs), 64% with *Bcl*I alone, and 91% with the combined *Bam*HI and *Bcl*I haplotypes. The percent heterozygosity for 10 unrelated American blacks was 70% for the *Bam*HI haplotypes alone, 80% for *Bcl*I alone, and 90% with *Bam*HI and *Bcl*I combined.

χ^2 Values and disequilibrium values for the three pairs of loci are shown in table 3. The observed types are significantly different from the expected types in each case. However, for *Bam*HI A versus *Bam*HI B and *Bam*HI A versus *Bcl*I, the actual disequilibrium values are small and the 99% confidence intervals overlap zero. By contrast, the deviation from expectation for the *Bam*HI B versus *Bcl*I haplotypes is highly significant; the confidence interval for the disequilibrium value does not overlap zero, but the actual disequilibrium is substantially less than complete.

Linkage Analysis

No recombinations were detected between the *Bam*HI and *Bcl*I RFLPS in more than 100 informative meioses. Linkage analysis was performed on 32 CEPH families for which HLA data were available. The lod scores calculated using LIPED are reported in table 4 according to the convention for presenting data proposed by Conneally et al. (1985). Strong evidence for linkage of FXIIIa to the HLA locus was found with a ($\hat{Z}$) of 11.44 at a θ_m of .25 and a θ_f of .35. The 95% confidence interval (± 1 lod) was θ_m = .19–.32 and θ_f = .27–.44. $\hat{Z}$ was found to be 10.64 at a θ of .29 when θ_m and θ_f were equal, with a 95% confidence interval of $\theta_m = \theta_f$ = .24–.34.

Marginal lod scores calculated for females and males separately are also shown in table 4. These values are summed with previously published data, and the combined lod scores are presented. On the basis of the summed data, the most likely θ_f = .3–.4 when the θ_m is fixed at .5. Conversely, the maximum θ_m = .15–.25 when the θ_f is fixed at .5. These values are consistent with the most likely θ values for females and males considered jointly on the basis of our data.

The χ^2 test of homogeneity proposed by Ott (1985) was used to test the significance of the difference between the lod scores at $\theta_m = \theta_f$ and $\theta_m \neq \theta_f$. The result was $\chi^2_{[1]} = 3.68$, $.10 > P > .05$.

Table 2

***Bam*HI and *Bcl*I Haplotypes**

Restriction Enzyme(s)	Haplotypes		No. of Chromosomes	PIC	Heterozygosity Observed[a] (%)
	Observed	Frequency			
*Bam*HI	1-3	.184	250	.538	63
	1-4	.600			
	2-3	.084			
	2-4	.132			
*Bam*HI-*Bcl*I	1-3-1	.050	220	.854	91
	1-3-2	.005			
	1-3-3	.041			
	1-3-4	.005			
	1-3-5	.005			
	1-3-7	.064			
	1-3-8	.014			
	1-4-5	.218			
	1-4-6	.027			
	1-4-7	.222			
	1-4-8	.104			
	1-4-9	.005			
	2-3-7	.072			
	2-3-8	.023			
	2-4-5	.050			
	2-4-7	.086			
	2-4-8	.009			

[a] Calculated using 122 individuals for *Bam*HI haplotypes and 110 individuals for *Bam*HI-*Bcl*I haplotypes.

Discussion

This study established that the gene locus for FXIIIa is highly polymorphic at the DNA level and is therefore an extremely useful genetic marker on the short arm of chromosome 6. Many RFLPs were detected with different restriction enzymes. There was minimal linkage disequilibrium between many of the RFLPs, so that analysis with multiple enzymes and construction of haplotypes was very useful. The combined use of this marker and markers within the HLA complex will significantly facilitate genetic mapping of chromosome 6p. FXIIIa would appear to be one of the most informative structural loci available for linkage studies in humans. Some other similarly informative loci include the HLA complex (Botstein et al. 1980), the α-globin gene cluster (Higgs et al. 1986), and clones with a variable number of tandem repeats (Nakamura et al. 1987). Using only two restriction enzymes, we observed 91% heterozygosity. If one incorporates the several additional RFLPs detected by this probe, then heterozygosity could increase, rendering the FXIIIa locus one of the 5% most polymorphic loci identified to date.

Table 3

Disequilibrium Values

Locus 1–Locus 2	Test of Difference			No. of Chromosomes	Disequilibrium Value	
	χ^2	df	*P*		Value	99% Interval
*Bam*HI A–*Bam*HI B	5.13	1	.02	250	+.14	−.02 to +.30
*Bam*HI A–*Bcl*I	19.56	5	.001	222	+.13	−.04 to +.30
*Bam*HI B–*Bcl*I	72.93	5	≪.001	222	+.26	+.09 to +.41

Table 4

Lod-Score Values for Factor XIIIa and HLA

	θ								95% Confidence		
	.001	0.05	0.10	0.20	0.30	.40	$\hat{Z}$	θ_m	θ_f	Interval	Source
$\theta_m = \theta_f$	< −100	−37.91	−11.92	6.82	10.63	7.25	10.64	.29	.29	.24–.34	Present study
θ_m = .25,[a] θ_f = ...	< −100	−16.89	−3.26	7.57	11.08	11.15	11.44	.25	.35	.27–.44	Present study
θ_f = .35,[a] θ_m = ...	−83.69	−6.94	3.89	10.82	10.96	7.60	11.44	.25	.35	.19–.32	Present study
Marginal scores (θ_m = .5):											
θ_f = ...	< −100	−25.28	−11.83	−1.29	1.98	1.88	2.25	.50	.34	.26–.44	Present study
θ_f = ...		−48.34	−25.77	−8.31	−2.05	−.07	0	.50	.50		Lamm and Olaisen 1985
Total		−73.62	−37.60	−9.60	−.07	1.81	2.25				Present study and Lamm and Olaisen 1985
Marginal scores (θ_f = .5)											
θ_m = ...		−8.64	2.09	8.87	8.86	5.41	9.40	.25	.50	.19–.31	Present study
θ_m = ...		4.73	13.65	15.65	12.15	5.48	15.68	.19	.50		Lamm and Olaisen 1985
Total		−3.91	15.74	24.52	21.01	10.89	25.08				Present study and Lamm and Olaisen 1985

[a] θ Values when the global maximum lod score is found on the basis of data from the present study.

This puts two of the most informative loci in the genome, the HLA complex and FXIIIa, within detectable linkage distance of each other. This will allow for very precise measurement of linkage in this area and provides two "anchor" loci for the short arm of chromosome 6. Because the two markers are ~25–35 cM apart and because the length of 6p is estimated at 55 cM, one can confirm or exclude the assignment of a gene locus to most of 6p, depending on the results of linkage analysis using these two loci alone. We are currently studying a large American black kindred with the HLA-linked form of spinocerebellar ataxia (SCA1). The use of this probe should resolve definitively if SCA1 is centromeric or telomeric to HLA. Similarly, the probe should be useful for studies of disorders such as long QT interval (LQT; MIM 19250); atrial septal defect, secundum type (ASD2; MIM 10880), Paget disease of bone (PDB; MIM 16725) (MIM = *Mendelian Inheritance in Man* [McKusick 1986]). These disorders are either linked to or associated with HLA.

The use of the CEPH families for the linkage studies provided a powerful tool for precise determination of the genetic distance between FXIIIa and HLA. Nishigaki et al. (1986) have questioned linkage of FXIIIa to HLA on the basis of their data. Our $\hat{Z}$ of 11.44 is very persuasive evidence for linkage between FXIIIa and the major histocompatibility complex. Through the use of these families, we were able to calculate lod scores by using male recombination distances different from female recombination distances as well as by using recombination fractions equal in males and females. In addition, the use of these families allowed us to perform analysis of linkage disequilibrium. Linkage disequilibrium values for two pairs of RFLP loci, *Bam*HI A versus *Bam*HI B and *Bam*HI A versus *Bcl*I, are marginally significant but not substantial. Disequilibrium between *Bam*HI B and *Bcl*I is substantial and highly significant but is much less than 1.0 (complete disequilibrium). In spite of these significant disequilibrium values, though, there is little loss of polymorphic information in constructing haplotypes. This is demonstrated by the high frequency of observed heterozygosity and by the large number of different haplotypes found in the CEPH families. Independent data also suggest that many haplotypes are found in American blacks, with levels of heterozygosity comparable with those found in Caucasians.

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