Am J Hum Genet 36:329–337, 1984

c-Ha-ras-1 Oncogene Lies between β-Globin and Insulin Loci on Human Chromosome 11p

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SUMMARY

DNA sequence polymorphisms have been used to determine the linear order and recombinational distances separating the Harvey ras 1 oncogene (c-Ha-ras-1), β-globin, insulin, and parathyroid hormone genes on the short arm of human chromosome 11. Our results indicate that c-Ha-ras-1 is closely linked to both the β-globin locus ($\hat{\theta}$ = .08 [8 centimorgans], lod score = 5.11) and the insulin locus ($\hat{\theta}$ = .04 [4 centimorgans], lod score = 3.31). Furthermore, the probable order of these loci on chromosome 11p is centromere–parathyroid hormone–β globin–c-Ha-ras-1–insulin.

INTRODUCTION

Several cellular transforming genes present in human and animal tumors have been identified by their ability to induce morphological transformation of tissue culture cells by DNA transfection. These transforming sequences are contained in tumors of spontaneous, chemical, or viral origin, and appear to be altered cellular homologs of the transforming genes of RNA tumor viruses [1–4]. The transforming gene isolated from the human bladder carcinoma cell lines EJ and T24 was shown to be an activated cellular homolog of the Harvey murine sarcoma virus ras gene (v-Ha-ras) [5–7]. Two distinct human cellular homologs of v-Ha-ras have been characterized (designated c-Ha-ras-1 and c-Ha-ras-2) [8]. The normal c-Ha-ras-1 gene encodes a guanine nucleotide-binding protein of molecular

Received August 5, 1983; revised October 25, 1983.

This work was supported by grants from the National Institutes of Health and the National Foundation to Haig H. Kazazian, Jr., and M. A. L; S. E. A. is the recipient of a New Investigator Research Award from the National Heart, Lung and Blood Institute, National Institutes of Health.

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weight 21,000, which differs from the transforming gene product of the T24 oncogene at the 12th amino acid [5–7]. c-Ha-ras-2 is presumed, on the basis of its structure, to be a pseudogene [8].

Somatic cell hybrids have previously been used to localize c-Ha-ras-1 to the short arm of human chromosome 11 (11p) [9, 10]. Among other genes assigned to 11p are the β-globin cluster [11], the insulin gene [12, 13], and the parathyroid hormone (PTH) gene [14]. Linkage has been previously established between the PTH and β-globin loci [15] and between the β-globin and insulin loci [15, 16], with genetic distances 7 and 11 centimorgans (cM), respectively. The linear order of the genes has been determined to be centromere–PTH–β-globin–insulin [15]. To provide a more precise localization of c-Ha-ras-1, we have determined the genetic distances between the c-Ha-ras-1, β-globin, insulin, and PTH genes and also their linear order using DNA polymorphisms adjacent to each gene.

METHODS

Subjects

Our subjects for linkage analysis were couples who had sought prenatal diagnosis for β-thalassemia or sickle-cell anemia, their offspring, and, in some cases, other relatives. In addition, linkage analysis was carried out on two large nuclear families.

Restriction Endonuclease Analysis

High molecular weight DNA was prepared from EDTA-anticoagulated blood of each individual [17]. Approximately 10 μg of DNA from each individual was digested overnight with the restriction enzyme of interest, using the reaction conditions suggested by the manufacturer. The resulting DNA fragments were separated by electrophoresis in 1.0% agarose gels, transferred to nitrocellulose, fixed, and hybridized to ^{32}P-labeled probes [18, 19]. All probes were radiolabeled with [^{32}P]dATP and [^{32}P]dCTP by the nick-translation function of *Escherichia coli* DNA polymerase I as described [20]. Washing of filters and autoradiography were performed as outlined [19]. The nitrocellulose filters were incubated with the following ^{32}P-labeled fragments: (1) a 6.6-kilobase (kb) Bam HI fragment containing the entire c-Ha-ras-1 gene and 5′- and 3′-flanking sequences provided by M. H. Wigler [21]; (2) genomic and cDNA fragments containing sequences of the γ, $\psi\beta_1$, and β-globin genes as well as sequences flanking the β-globin gene [22, 23]; (3) a 0.9-kb Pst I genomic DNA fragment derived from the recombinant plasmid pH1G900 containing human insulin gene sequences provided by A. Ullrich [24]; and (4) a 0.8-kb HpaII cDNA fragment derived from the recombinant plasmid pPTHm122 containing human PTH sequences provided by H. M. Kronenberg [25].

DNA Polymorphisms

The following DNA polymorphisms were studied for use as chromosomal markers: (1) Pst site 3′ to the PTH gene [15]; (2) Hind III sites in the γ-globin genes, Hinc II sites flanking the $\psi\beta_1$ gene, and Hinf I, Ava II, and Bam HI sites within and adjacent to the β-globin gene [22, 23, 26–29]; (3) the polymorphic insertions 5′ to the insulin gene [30–32]; and (4) the polymorphic insertions 3′ to the c-Ha-ras-1 gene [21, 33]. The 3′-flanking region of the c-Ha-ras-1 gene is extremely polymorphic in length due to fluctuations in the number of reiterations of a 28-bp consensus sequence 1.4 kb 3′ to the last exon of this gene [33]. The resulting DNA polymorphisms can be detected by a number of restriction endoncleases (e.g., Bam HI, Bgl II, Msp I) [21, 34]. We chose to use Msp I to perform

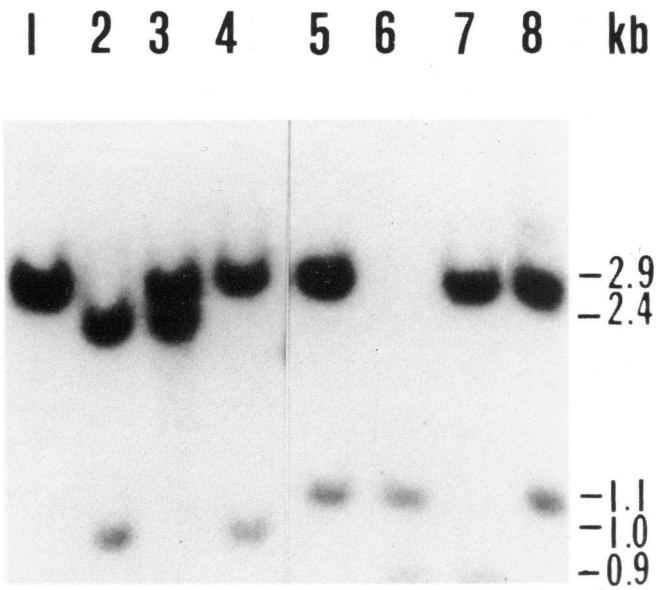

FIG. 1.—Mendelian inheritance of Msp I polymorphic c-Ha-ras-1 fragments in two informative nuclear families. *Lanes 1–4* are family A: father, mother, F1-1, and F1-2, respectively. *Lanes 5–8* are family B: father, mother, F1-1, and F1-2, respectively.

the linkage analysis because of the ease with which the resulting fragments can be resolved on agarose gels (see fig. 1).

Linkage Analysis

The linkage analysis was performed using the method of maximum likelihood [35] and the computer program LIPED [36], which calculates, for each pedigree, the lod scores at various recombination fractions θ. The lod for each recombination fraction represents the log of the odds in favor of linkage vs. nonlinkage. Information from several pedigrees may be combined by summing lod scores at each value, and the best estimate of the recombination fraction is obtained at the θ value where the lod score is a maximum. By using quadratic interpolation, the estimated maximum likelihood of θ ($\hat{\theta}$) and its corresponding lod score ($\hat{z}$) may be obtained. A lod score of 3 (odds of 1,000:1 in favor of linkage) is generally considered strong evidence for linkage, while a lod score of -2 (100:1 against linkage) is considered strong evidence against linkage [35].

Multipoint analysis, using the method of maximum likelihood developed by Meyers et al. [37, 38], was performed to determine the most likely order of the four loci. Specifically, the maximum likelihood estimates of the recombination fractions between each pair of loci and the corresponding likelihood for each of the possible orders are calculated simultaneously from the two-point data (all families informative for any two of the loci), the three-point data, and the four-point data. The linear order of the four loci was determined from the data in table 1 and from four families with informative recombinants (families nos. 10, 14, 17, and 18 of table 2).

RESULTS

To perform the linkage analysis between c-Ha-ras-1, β-globin, insulin, and PTH loci, we employed DNA sequence polymorphisms adjacent to each locus.

TABLE 1

SUMMED LOD SCORES FOR c-Ha-ras-1, β-GLOBIN, INSULIN, AND PTH

LOCI	θ									$\hat{\theta}$	$\hat{z}$	95% CONFIDENCE LIMITS
	0	.05	.10	.15	.20	.25	.30	.35	.40			
β-globin–c-Ha-ras-1	−20.90	4.93	5.02	4.60	3.99	3.27	2.43	1.63	0.89	0.08	5.11	.06–.11
Insulin–c-Ha-ras-1	−2.93	3.25	2.99	2.60	2.18	1.74	1.30	0.87	0.49	0.04	3.31	.02–.07
β-globin–insulin [15] ...	...	3.02	3.48	3.32	2.90	2.36	1.76	1.17	0.63	0.11	3.57	.08–.13
PTH–c-Ha-ras-1	...	−0.19	0.68	0.83	0.97	0.88	0.68	0.47	0.26	0.19	0.99	.14–.25
β-globin-PTH [15]	...	4.45	4.52	4.12	3.51	2.81	2.08	1.37	0.73	0.07	4.63	.05–.10

NOTE: The lod scores for chosen recombination fractions for each pair of loci are shown, as well as the maximum estimate of the recombination fraction ($\hat{\theta}$) and its corresponding lod score ($\hat{z}$).

TABLE 2

DNA POLYMORPHISMS FLANKING THE PTH, INSULIN, β-GLOBIN, AND c-Ha-ras-1 LOCI OF MEMBERS OF FOUR FAMILIES INFORMATIVE FOR ALL FOUR LOCI, AND A FAMILY WITH A RECOMBINATION BETWEEN β-GLOBIN AND c-Ha-ras-1 LOCI (FAMILY NO. 17)

Family no.	Loci	F		M		F_1-1		F_1-2		F_1-3		F_1-4	
7	PTH	−	−	+	−	+	−	+	−	−	−	...	
	β-Globin	A	T_1	B	T_2	B	A	B	T_1	T_1	T_2	...	
	c-Ha-ras-1	b	a	a	c	a	b	a	a	a	c	...	
	INS	2	1	2	1	2	2	2	1	1	1	...	
10	PTH	+	−	−	+	+	−	−	−	...		...	
	β-Globin	A	T_1	B	T_2	A	B	B	T_1 X	...		...	
	c-Ha-ras-1	b	c	c	a	b	c	c	b	...		...	
	INS	2	2	1	2	2	1	1	2	...		...	
14	PTH	+	−	−	+	+	+	+	+	...		...	
	β-Globin	A	B	C	S	A X	S	A	S	...		...	
	c-Ha-ras-1	a	d	a	c	d	c	a	c	...		...	
	INS	2	1	1	2	1	2	2	2	...		...	
18	PTH	−	+	−	+	+	+ X	−	−	+	+	−	+
	β-Globin	A	B	C	T	B	C	A	C	B X	T	A	T
	c-Ha-ras-1	a	c	c	a	c X	c	a	c	a X	a	a	a
	INS	1	4	2	3	1	2	1	2	4	3	1	3
17	β-Globin	A	S_1	B	S_2	A	S_2	S_1	S_2 X	...		...	
	c-Ha-ras-1	a	a	b	c	a	c	a	b	...		...	
	INS	1	1	1	2	1	2	1	1	...		...	

NOTE: F: father; M: mother; F_1-1 through F_1-4: children 1–4. For the β-globin gene locus, (β) A, B, C, T, etc., denote different β alleles. For the PTH gene, + and − indicate the presence or absence of the polymorphic Pst I site. For the insulin gene (INS), 1, 2, 3, and 4 denote different polymorphisms detected after digestion with Sac I or Bgl I. For the c-Ha-ras-1 oncogene, a, b, c, and d denote different polymorphic DNA fragments detected after digestion with Msp I. Recombination events are shown with an X in each family.

These DNA polymorphisms are normal inherited variations in DNA that can be used to study the inheritance of DNA sequences near these polymorphisms. Therefore, one can use polymorphisms to mark maternal and paternal alleles, and thus trace their passage within a pedigree.

The frequency of heterozygosity in the length of Msp I fragments cleaved from the region 3′ to the c-Ha-ras-1 locus in our study population of 50 unrelated individuals was 54%. This DNA polymorphism followed Mendelian inheritance in all families examined (see fig. 1 for example). Of 25 families examined for linkage analysis, 14 were informative for linkage between β-globin and c-Ha-

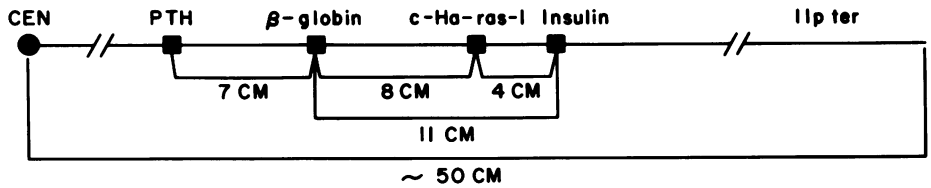

FIG. 2.—Linkage map for human chromosome 11p. The genetic distance in cM found between the *PTH*, β-*globin*, *c-Ha-ras-1*, and *insulin loci* are shown. One cM is defined as the genetic distance equivalent to a recombination fraction θ of .01.

ras-1, eight were informative for linkage between insulin and c-Ha-ras-1, and nine were informative for linkage between PTH and c-Ha-ras-1. Similarly, six families were informative for linkage between PTH, β-globin, and c-Ha-ras-1, and three families were informative for linkage between insulin, β-globin, and c-Ha-ras-1. For linkage between all four loci, four families were informative (see table 2).

A source of error in linkage analysis is nonpaternity. Since individuals were typed at four or more loci of high heterozygosity, most cases of nonpaternity would be detected. We discovered one such case in our analyses, and this family was discarded from the data set.

The lod scores at various recombination fractions indicate that the c-Ha-ras-1 gene is closely linked to both the β-globin and insulin loci (see table 1). The maximum estimate of the recombination fraction between β-globin and c-Ha-ras-1 is $\hat{\theta} = .08$ (95% confidence limits = .06–.11) with a lod score of 5.11. For c-Ha-ras-1 and insulin loci, we find $\hat{\theta} = .04$ (95% confidence limits = .02–.07) with a lod score of 3.31. Although only a small number of families were informative for both c-Ha-ras-1 and PTH, our results indicate that these two loci are loosely linked (see table 2), $\hat{\theta} = .19$ with a lod score of 0.99 (95% confidence limits = .14–.25).

By employing multipoint analysis, we found that the most likely arrangement of the four loci is PTH–β-globin–c-Ha-ras-1–insulin (see fig. 2). The odds in favor of this arrangement vs. the second best arrangement, namely, PTH–β-globin–insulin–c-Ha-ras-1, are 342:1.

DISCUSSION

A number of loci have been assigned to chromosome 11p by in situ hybridization or somatic cell hybrid studies. However, there is considerable controversy about the exact locations of these loci. The β-globin gene cluster was originally assigned to 11p12.05-p12.08 [11]. Recent reports utilizing in situ hybridization and blot hybridization of rearranged chromosome complements [39, 40] have suggested that the β-globin gene is in the 11p15-pter region. Likewise, a number of studies have placed the insulin gene at 11p15-pter, but one study has suggested that insulin is at 11p13-p14 [12, 13, 39, 41]. c-Ha-ras-1 has been assigned to 11p by somatic cell hybrid studies [9, 10], and, recently, by in situ hybridization to 11p14.1 [42] and by blot hybridization to 11p15.1-p15.5 [39, 43]. Now our linkage data strongly indicate that the order of these loci is PTH–β-globin–c-Ha-ras-1–insulin. Since nearly all available studies place the insulin locus at the

very terminus of 11p, and distal to the β-globin gene cluster, it is likely that PTH is the closest of the four loci to the centromere.

It is important to note that our linkage analysis has not addressed the question of the chromosomal location of the four loci we have studied. Furthermore, our genetic map is independent of the exact chromosomal localization of these loci on 11p.

Another laboratory has also addressed the question of the linkage map of these four loci. Their results are similar to those obtained in this study except that no recombination was found between the c-Ha-ras-1 and insulin loci in their families [44].

Studies with other loci on 11p such as the LDH-A gene [45, 46], the catalase gene [47], the locus affecting the amount of F-reticulocyte production [48, 49], and the locus for the aniridia-Wilms tumor syndrome [42, 50–53] should demonstrate linkage with one or more of the loci that we have studied here.

ACKNOWLEDGMENTS

S. E. A. thanks Dr. H. H. Kazazian, Jr., for his continuous advice and support. We also thank Drs. M. Wigler, H. Kronenberg, and A. Ullrich for providing several probes, and Michele Pass and Emily Pasterfield for the preparation of the manuscript.

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