Hum Genet (1985) 70:95–99

Human Genetics

DNA polymorphism and molecular pathology of the human globin gene clusters

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Hum Genet (1985) 69:1–14

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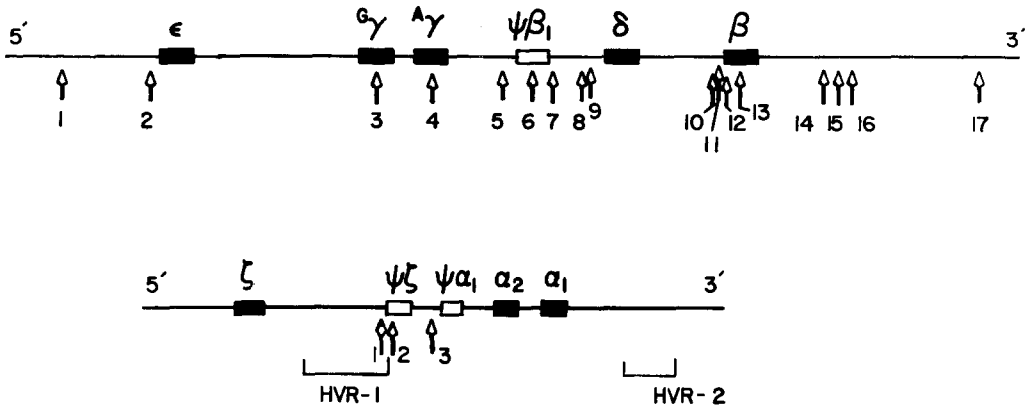

Fig. 2. A Location of the useful polymorphic restriction sites in the β-globin gene cluster. Each polymorphic site is shown by an *open arrow*. The sites are: 1. Taq I (16), 2. Hinc II (1), 3. Hind III (38), 4. Hind III (38), 5. Pvu II (65), 6. Hinc II (1), 7. Hinc II (1), 8. Rsa I (58), 9. Taq I (58), 10. Hinf I (62), 11. Rsa I (97), 12. HgiA I (72), 13. Ava II (1), 14. Hpa I (41), 15. Hind III (108), 16. Bam HI (45), 17. Rsa (16). **B** Location of the DNA polymorphisms in the globin gene cluster. HVR: Highly variable region. The sites are: 1. EcoRI (10), 2. Sac I (32), 3. Bgl II (110)

Table 1. Frequency of presence of DNA polymorphic sites in the β-globin gene cluster in different groups[a]

Polymorphisms	Greeks		Italians		Am. Blacks		Indians		S.E. Asians	
	β^A	β^{thal}	β^A	β^{thal}	β^A	β^S	β^A	β^{thal}	β^A	β^E
Taq I (1)	1.00	1.00	1.00	1.00	0.88	0.41	1.00	1.00	1.00	1.00
Hinc II	0.46	0.85	0.76	0.54	0.10	0.02	0.78	0.75	0.72	0.20
Hind III (3)	0.52	0.14	0.26	0.48	0.41	0.35	0.30	0.26	0.27	0.73
Hind III (4)	0.30	0.07	0.06	0.37	0.16	0.05	0.06	0.09	0.04	0.00
Pvu II (5)	0.27	0.16					0.62	0.04		
Hinc II (6)	0.17	0.07	0.20	0.11	0.15	0.04	0.17	0.10	0.19	0.73
Hinc II (7)	0.48	0.12	0.28	0.31	0.76	0.81	0.27	0.17	0.27	0.73
Rsa I (8)	0.37		0.77		0.50		0.79			
Taq I (9)	0.68		0.23		0.53		0.27			
Hinf I (10)	0.97	0.92	0.95	0.92	0.70	0.10	1.00	0.86	0.98	1.00
Rsa I (11)										
HgiA (12)	0.80	0.90	0.86	0.73	0.96	0.96	0.82	0.38	0.44	0.73
Ava II (13)	0.80	0.90	0.86	0.73	0.96	0.96	0.78	0.38	0.44	0.73
Hpa I (14)	1.00	1.00	1.00	1.00	0.93	0.35	1.00	1.00		1.00
Hind III (15)	0.72		0.73		0.63		0.56			
Bam HI (16)	0.70	0.78	0.74	0.82	0.90	1.00	0.82	0.84	0.70	0.73
Rsa I (17)	0.37	0.21	0.18	0.17	0.10	0.00	0.18	0.08		

[a] Computation of these data was performed in collaboration with Dr. A. Chakravarti and K. Buetow of the Department of Biostatistics at the University of Pittsburgh

blacks although they are very rare in other racial groups. In general, there is not a striking difference between the frequency of the presence (+) of a polymorphism in β^A and $\beta^{variant}$ chromosomes. However, in some cases there is linkage disequilibrium between the presence of a polymorphic site and the β-globin allele. For example, the Hinf I site (number 10 in Fig. 2) is present in 70% of β^A chromosomes examined in American Blacks but only in 10% of the β^S chromosomes in this population. Other sites that show linkage disequilibrium with the β-globin allele include the Hpa I site (site 14) and the β^S allele in American and West African Blacks, and the Hind III sites (3 and 4) and the β^{thal} alleles in Greeks.

2.3 Random versus non-random association of polymorphic sites

If two polymorphic sites are randomly associated with each other, the probability of the presence of both sites (++) is equal to the product of the probability of the presence of each site. For example, let us suppose that polymorphic site I is present in 50% of the chromosomes examined in a given population, and polymorphic site II is present in 30% of the chromosomes examined in the same population. The theoretical probability of the presence of both sites (++) in the chromosomes of the particular population will be 50% × 30% = 15%, if the two sites are randomly associated. If they are non-randomly associated, the probability of the presence of both will be significantly different from the expected. This non-randomness of association is termed linkage disequilibrium. The pattern or combination of polymorphic restriction sites for any chromosome is called a haplotype [1]. For a given number *n* of polymorphic restriction sites there is a maximum of 2^n possible combinations of sites with an expected frequency for each of those haplotypes equal to the product of the probabilities for every individual site.

ruptions is maintained for short stretches [54]. Overall nearly 4kb of DNA within the α-globin complex is highly homologous and duplicated. This is in marked contrast to the β-globin gene cluster in which homologous regions are limited to portions of the exons. The high degree of broad homology in the alpha complex provides a large target size for recombination or crossing-over events in the DNA.

Acknowledgements. The authors thank Mrs. Emily Pasterfield for the preparation of this manuscript. We would especially like to express our thanks to C. D. Boehm, P. G. Waber, T. C. Cheng, P. V. Giardina, A. Li, S. Charache, J. Sexton, S. Goff, A. F. Scott, J. A. Phillips, K. Buetow, A. Chakravarti who contributed to much of the work reviewed here. We also are appreciate of our colleagues who shared with us preprints and unpublished data. This work was supported by grants from the NIH to HHK and SHO. SEA in the recipient of a New Investigator Research Award from the NIH.

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Received June 19, 1984

Note added in proof (November 6, 1984)

Since the submission of this review several new mutations have been found in the β-globin gene cluster.

1. β^+ thalassemia gene due to a transcriptional mutation in a Japanese patient. The mutation is an A-T change in position −31 in the TATA box of the β-globin gene (Fukumaki Y, Yamada H, Kimura A, Nakamura T, Matsunaga E, Takihara Y, Tagaki Y. A new deletion in β thalassemia and a new TATA box mutation in β^+ thalassemia in Japan 1984. Abstract, 4th Conference on Hemoglobin Switching, Airlie, Virginia).
2. β° thalassemia gene due to a splicing mutation in a Greek patient. The mutation is a G-T change in IVS-1 nt 5 (Forget BG, Weissman SM, 1984, personal communication).
3. β° thalassemia gene due to a splicing defect in a patient from Kuwait. The mutation is a deletion of 17 nts which abolishes the acceptor splice site of IVS-1.
4. One form of $^{A}\gamma$ HPFH in Greeks is due to a G-A change in position −117 from the $^{A}\gamma$ gene. This change occurs just 2 nts upstream of the distal CAT box of the $^{A}\gamma$ gene (Gelinas R, Stamatoyannopoulos G, et al, 1984, Abstract, 4th Conference on Hemoglobin Switching, Airlie, Virginia and Collins FS, Weissman SM, Forget BG, et al, 1984, Abstract, 4th Conference on Hemoglobin Switching, Airlie, Virginia).

In addition, a few new deletions in the β-globin gene cluster have also been described at the recent 4th Hemoglobin Switching meeting.

1. δβ thalassemia in an American Black. This deletion starts 5′ to δ, but after two Alu I sequences 5′ to δ (Anagnou N, Nienhuis AW, NIH, 1984).
2. HPFH type III in an Indian patient. This deletion extends 5′ to HPFH type II, but the $^{A}\gamma$ gene is intact (Mager D, Smithies O, Madison, Wisc. 1984).
3. $(^{A}\gamma\delta\beta)^\circ$ thalassemia in a German patient. The deletion starts between $^{G}\gamma$ and $^{A}\gamma$ and extends 3′ to β-globin gene (Anagnou N, Nienhuis AW, NIH, 1984).
4. δβ thalassemia in a Japanese patient. The deletion starts between $^{A}\gamma$ and $\psi\beta_1$ and extends an unknown distance 3′ to β-globin gene (Fukumaki Y, et al, Fukuoka, Japan, 1984).
5. HPFH type IV in an Italian patient. The deletion starts in a narrow region of 70 nts of the non-repetitive DNA between the two Alu I repeats 5′ to δ globin gene and extends an unknown distance to β-globin gene (Ottolenghi S et al, Milan, 1984).