Different hematologic phenotypes are associated with the leftward (-alpha 4.2) and rightward (-alpha 3.7) alpha+-thalassemia deletions.

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Research Article

We have compared the phenotypes of the two common deletion forms of alpha+-thalassemia by analysis of umbilical cord blood samples from Melanesia. Homozygotes for the leftward, 4.2-kilobase, deletion (-alpha 4.2) had significantly higher levels of Hb Bart's at birth than homozygotes for the rightward, 3.7-kilobase, deletion (-alpha 3.7). Compound heterozygotes for each deletion had intermediate values. Although deletion forms of alpha 0 thalassemia were not found in this survey, nondeletion alpha-thalassemia was present at low frequency. Since the predominant rightward deletion in this population, -alpha 3.7III, entirely removes the alpha 1-gene and the 4.2-kilobase deletion deletes the alpha 2-gene, these data indicate that the alpha 2-globin gene has a higher output than the alpha 1-gene, on single alpha-gene chromosomes.

Different Hematologic Phenotypes Are Associated with the Leftward ($-\alpha^{4.2}$) and Rightward ($-\alpha^{3.7}$) α^+-Thalassemia Deletions

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Abstract

We have compared the phenotypes of the two common deletion forms of α^+-thalassemia by analysis of umbilical cord blood samples from Melanesia. Homozygotes for the leftward, 4.2-kilobase, deletion ($-\alpha^{4.2}$) had significantly higher levels of Hb Bart's at birth than homozygotes for the rightward, 3.7-kilobase, deletion ($-\alpha^{3.7}$). Compound heterozygotes for each deletion had intermediate values. Although deletion forms of α^0 thalassemia were not found in this survey, nondeletion α-thalassemia was present at low frequency. Since the predominant rightward deletion in this population, $-\alpha^{3.7}$III, entirely removes the α1-gene and the 4.2-kilobase deletion deletes the α2-gene, these data indicate that the α2-globin gene has a higher output than the α1-gene, on single α-gene chromosomes.

Introduction

The human α-globin gene complex on chromosome 16 (1) comprises two adult α-genes, a $\psi\alpha$-gene, and an embryonic ζ- and $\psi\zeta$-gene arranged in the order 5′ − ζ2 − $\psi\zeta$1 − $\psi\alpha$ − α2 − α1 − 3′ (2). Large deletions within this complex removing all or part of the genes are much more common causes of α-thalassemia than point mutations or minor rearrangements that produce the nondeletion forms of this condition (3, 4). Eight deletions causing α-thalassemia have been described. Two of these, which remove a single α-gene and produce α^+-thalassemia are by far the most prevalent (5), one deleting 4.2 kilobases (kb) of DNA ($-\alpha^{4.2}$) and the other 3.7 kb ($-\alpha^{3.7}$) (6). Indeed, the latter is possibly the most common mutation known to produce a genetic disorder. It is prevalent in most tropical and subtropical populations that have been studied including African and American Blacks (7), Mediterraneans (8), Southeast Asians (9), and some Pacific Island populations (10). In contrast the 4.2-kb single gene deletion ($-\alpha^{4.2}$) is very rare in Blacks and Mediterraneans but is more common in Southeast Asia and the Middle East (3). Remarkably, in north coastal Papua New Guinea the $-\alpha^{4.2}$ deletion is found in >80% of the population and appears to be going to fixation (11). These two types of α^+-thalassemia are phenotypically less severe than the α^0 thalassemia determinants that completely abolish α-chain output from the affected chromosome. However, despite their prevalence, no detailed comparison of the phenotypes of $-\alpha^{3.7}$ and $-\alpha^{4.2}$ deletions has been performed. Such a study would be of clinical interest and, because $-\alpha^{4.2}$ deletions remove the α2-gene and $-\alpha^{3.7}$ deletions remove either the entire α1-gene or produce a hybrid α2-α1 gene, might additionally provide some information on the relative expression of the residual α2- or α1-globin genes on chromosomes carrying only a single α-gene ($-\alpha$).

We have compared the phenotype of these conditions by α-globin gene mapping and quantitation of the level of Hb Bart's (4, 12, 13) in newborns from the Melanesian archipelago of Vanuatu in the South West Pacific. Measurement of γ-chain tetramers, Hb Bart's, in umbilical cord blood is a relatively simple and sensitive means of detecting an α-globin chain deficit at birth, and the percentage of Hb Bart's has been shown to provide a measure of the severity of the associated α-thalassemia defect (4). The population of Vanuatu is particularly suited to such a comparison because both the $-\alpha^{3.7}$ and $-\alpha^{4.2}$ deletions are found at high frequencies and α^0 determinants are either very rare or absent. Furthermore, the predominant $-\alpha^{3.7}$ deletion in this population is of the $-\alpha^{3.7}$III subtype (14, 10) that leaves the entire α2-gene intact, allowing comparison of the phenotype of chromosomes with a single α2-gene ($-\alpha^{3.7}$III) with those having only a single α1-gene ($-\alpha^{4.2}$).

Methods

1,396 umbilical cord blood samples were collected at the Central Hospital, Port Vila, Vanuatu, and Luganville Hospital, Espiritu Santo, Vanuatu, from 1979–1984. A small number of cord bloods from Madang, north coastal Papua New Guinea, were also studied. All samples were frozen soon after collection. Initial screening by hemoglobin electrophoresis on cellulose acetate was done using Titan III H cellulose acetate plates (Helena Laboratories, Beaumont, TX). Samples with detectable amounts of Hb Bart's were then quantitated in duplicate on long cellulose acetate strips as described (15). DNA extraction and gene analysis by the Southern blot technique were as described previously (15). All of the early samples (95 in the preliminary screen and 236 in the next survey) were digested with both Bam HI and Bgl II and hybridized with the α- and ζ-globin-specific probes (below). Chromosomes with a single α-gene deletion were detected by the presence of a 10–10.5-kb Bam HI α-specific band. Hybridization with the ζ-probe after Bgl II digestion allowed differentiation of $-\alpha^{4.2}$ chromosomes, which produce an 8-kb band, from $-\alpha^{3.7}$ chromosomes, which produce a 16-kb band (10). Further samples with high levels of Hb Bart's (potential homozygotes) were digested with Bgl II only and hybridized with the ζ-probe. The α-probe was a 1.5-kb Pst I fragment containing the α1-gene and the ζ-probe, a 2.8-kb Eco RI/Bam HI fragment containing the entire ζ2-gene. Triplicated and single ζ- and γ-gene chromosomes were detected as described elsewhere (16–18).

Results

In a preliminary screen to determine the approximate frequency of α-thalassemia in the archipelago of Vanuatu, 95 umbilical cord blood samples were analyzed by Southern blot DNA anal-

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ysis with the restriction enzymes Bam HI and Bgl II (3, 10). Of these 190 chromosomes, 44 (23%) had a single α-gene deletion, $-\alpha$, two had the triplicated α-gene arrangement, $\alpha\alpha\alpha$, and there were 144 normal $\alpha\alpha$-chromosomes. Interestingly, the Southeast Asian α° thalassemia deletion, $--^{SEA}$ (9), that removes both linked α-genes and is prevalent in Southeast Asia, was not found. However, both types of single α-gene deletion, $-\alpha^{3.7}$ (26 chromosomes) and $-\alpha^{4.2}$ (16 chromosomes), were present at appreciable frequency, unlike other populations where either one or the other predominates (10). Hemoglobin electrophoresis of a small number of samples showed high levels of Hb Bart's in the homozygotes ($-\alpha/-\alpha$), as expected, but also revealed the presence of Hb Bart's in some individuals without an α-gene deletion.

Genotype–phenotype correlation. In view of these preliminary findings we undertook a further survey of 236 additional samples to correlate the percentage of Hb Bart's in each sample with the restriction enzyme genotype. The results are shown in Tables I and II and Fig. 1. The gene frequency of $-\alpha$ is 0.19, of which 28% were of the 4.2-kb deletion type (Table I). Correlation of the DNA genotype with the amount of Hb Bart's (Table II) showed that most samples without a gene deletion had no detectable Hb Bart's. However, 26 samples without deletions showed Hb Bart's at levels of 0.44–3.7%, which suggests the presence of nondeletion forms of α-thalassemia in this population. An approximate figure for the frequency of such chromosomes may be derived by assuming that these 26 individuals are heterozygotes for nondeletion α-thalassemia, leading to a gene frequency of (26/472) 0.055.

As has been found in surveys in Jamaica (12) and South Africa (19) there were several $-\alpha$-heterozygotes in which no Hb Bart's was detectable. In 3 of the 15 cases this is probably due to the presence of a triplicated α-gene arrangement (20, 21) on the other chromosome (giving a total of four α-genes), which should compensate for the α-chain deficit due to the deletion. In the other 12 cases of genotype $-\alpha/\alpha\alpha$, the α-chain deficiency is presumably insufficient to produce a detectable amount of Hb Bart's.

Comparison of the amount of Hb Bart's present in individuals with different genotypes (Fig. 1) showed two related findings.

Table I. α-Globin Genotypes in Cord Bloods from Vanuatu

Genotypes	No.
$\alpha\alpha/\alpha\alpha$	152
$\alpha\alpha/\alpha\alpha\alpha$	4
$-\alpha^{3.7}/\alpha\alpha\alpha$	3
$-\alpha^{3.7}/\alpha\alpha$	44
$-\alpha/\alpha\alpha$	2
$-\alpha^{4.2}/\alpha\alpha$	21
$-\alpha^{3.7}/-\alpha^{3.7}$	7
$-\alpha^{3.7}/-\alpha^{4.2}$	1
$-\alpha^{4.2}/-\alpha^{4.2}$	2
	236

Number of individuals with each genotype identified in the cord blood survey. Two $-\alpha$-haplotypes were not classified because of insufficient DNA. All $\alpha\alpha\alpha$-chromosomes were of the $\alpha\alpha\alpha^{anti\ 3.7}$ type (20). In five of the $-\alpha^{3.7}/\alpha\alpha$ cases and one of the $-\alpha^{3.7}/\alpha\alpha\alpha$ cases, Hb $J^{Tongariki}$ (24) was found on hemoglobin electrophoresis. 45 of these $-\alpha^{3.7}$ deletions were subtyped; 38 were $-\alpha^{3.7}$III; and 7 were $-\alpha^{3.7}$I deletions.

Table II. Association of Hb Bart's with α–Gene Deletions

		No.
No deletion	Hb Bart's absent	130
No deletion	Hb Bart's present	26
Single deletion	Hb Bart's absent	15
Single deletion	Hb Bart's present	55
Homozygous deletion	Hb Bart's absent	0
Homozygous deletion	Hb Bart's present	10
		236

Number of samples found with each genotype–Hb Bart's combination. The 26 individuals without a gene deletion who have Hb Bart's are presumed to be cases of nondeletion α-thalassemia. Of the 15 single gene deletion heterozygotes without Hb Bart's, three had the $-\alpha/\alpha\alpha\alpha$-genotype so that the additional α-gene in trans may have compensated for the reduced output of the $-\alpha$-haplotype. In the other three individuals with $\alpha\alpha\alpha$-chromosomes, all were of $\alpha\alpha\alpha/\alpha\alpha$-genotype and Hb Bart's was absent.

Firstly, the 12 individuals of genotype $-\alpha/\alpha\alpha$ without Hb Bart's had predominantly the 3.7-kb deletion (nine cases) rather than the 4.2-kb deletion (one case); two deletions were not typed because of insufficient sample. Secondly, the two homozygotes for the $-\alpha^{4.2}$ deletion had higher levels of Hb Bart's than any of the

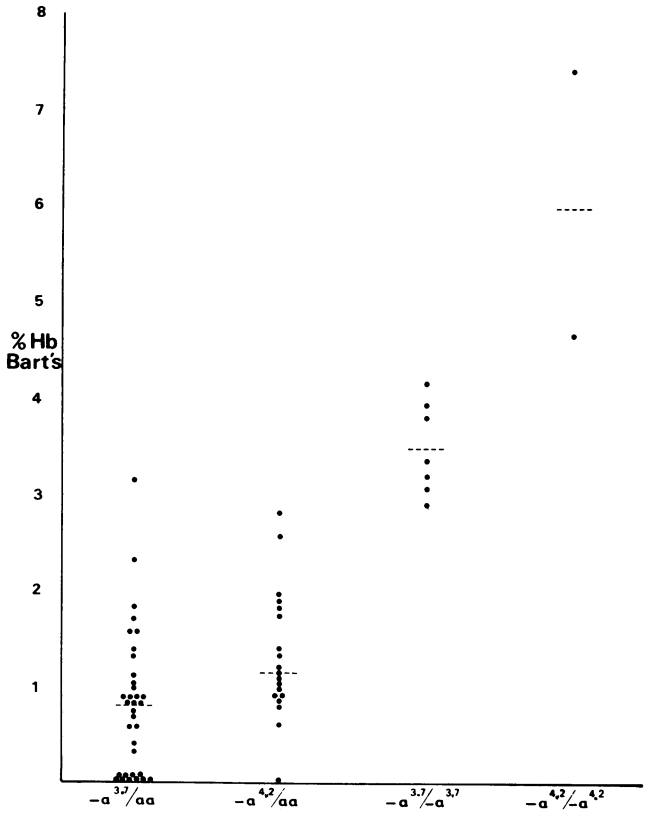

Figure 1. Levels of Hb Bart's in heterozygotes and homozygotes for α^+-thalassemia. Mean Hb Bart's levels are shown as a dashed line. In both heterozygotes and homozygotes the $-\alpha^{3.7}$ deletion is associated with a lower mean Hb Bart's level. One compound heterozygote ($-\alpha^{3.7}/-\alpha^{4.2}$) was found with 3.8% Hb Bart's.

$-\alpha^{3.7}/-\alpha^{3.7}$ homozygotes. Both of these findings suggested that the $-\alpha^{4.2}$ might produce a more severe α-chain deficit than the $-\alpha^{3.7}$ deletion.

Genotyping of individuals with high levels of Hb Bart's. To investigate further the apparent difference in phenotype produced by the $-\alpha^{3.7}$ and $-\alpha^{4.2}$ deletions we measured Hb Bart's levels in a large series of homozygotes and compound heterozygotes for each deletion to maximize measurable differences in levels of Hb Bart's and to eliminate the possible presence of nondeletion α^+-thalassemia determinants on the $\alpha\alpha$-chromosome in heterozygotes. To find sufficient homozygotes we screened 1,065 further cord blood samples from Vanuatu by hemoglobin electrophoresis and determined the genotype in all samples with >2% Hb Bart's as well as some with 1.5–2%. In addition we screened a small number of cord blood samples from north coastal Papua New Guinea where the $-\alpha^{4.2}$ deletion is present at high frequency (11). The results on the 61 samples thus obtained are summarized in Fig. 2. The mean level of Hb Bart's in the $-\alpha^{4.2}/-\alpha^{4.2}$ homozygotes was 5.97%, significantly different from both the $-\alpha^{3.7}/-\alpha^{4.2}$ compound heterozygotes, mean 4.81%, and the $-\alpha^{3.7}/-\alpha^{3.7}$ homozygotes, mean 3.46%. For purposes of comparison with the Hb Bart's data, the red cell indices associated with different α-genotypes in our survey of older children and adults from Vanuatu (22) are summarized in Table III. There are no significant differences between individuals with the $-\alpha^{3.7}$ and $-\alpha^{4.2}$ haplotypes.

11 further cases of individuals with normal α-globin maps and high levels of Hb Bart's (1.65–6.15%) were detected in this "high Hb Bart's" group. None had the Southeast Asian α° deletion ($--^{SEA}$) (9). These are presumably examples of nondeletion

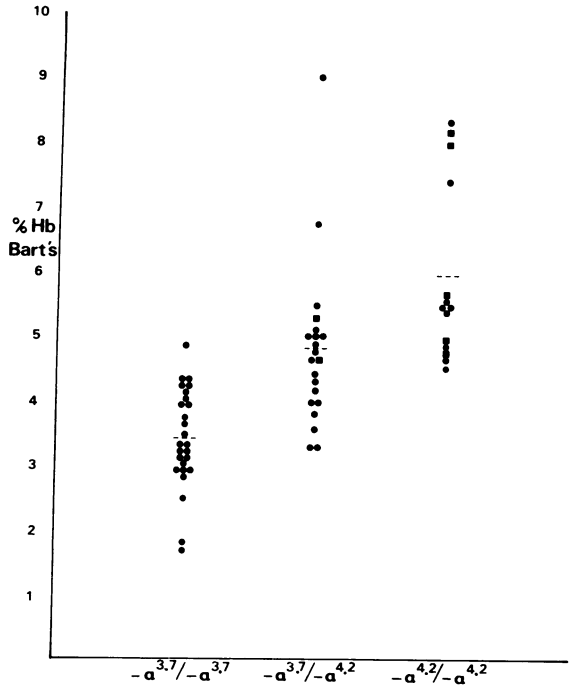

Figure 2. Levels of Hb Bart's in 61 homozygotes for single α-gene deletions. 54 samples were from Vanuatu (*circles*) and 7 from Papua New Guinea (*squares*). The mean and standard deviation for each genotype is: $-\alpha^{3.7}/-\alpha^{3.7}$, 3.46±0.77; $-\alpha^{3.7}/-\alpha^{4.2}$, 4.81±1.26; $-\alpha^{4.2}/-\alpha^{4.2}$, 5.97±1.4. Using Student's *t* test all genotype pairs were highly significantly different, $P < 0.01$ to $P < 0.001$.

Table III. Red Cell Indices in Each α-Globin Genotype

	10–15 yr age group			Adults		
Genotype	No.	MCV	MCH	No.	MCV	MCH
$\alpha\alpha/\alpha\alpha$	79	86.3±5.4	27.1±1.3	92	89.4±4.7	29.2±1.5
$-\alpha^{3.7}/\alpha\alpha$	24	81.4±5.9	24.9±1.3	65	83.6±6.3	26.6±2.3
$-\alpha^{4.2}/\alpha\alpha$	4	79.5±4.4	24.7±0.3	17	84.5±4.2	26.4±1.3
$-\alpha^{3.7}/-\alpha^{3.7}$	7	71.1±3.6	21.8±1.8	8	74.3±3.3	22.7±0.6
$-\alpha^{3.7}/-\alpha^{4.2}$	5	72.8±7.8	21.6±1.4	5	75.0±7.5	22.3±2.6
$-\alpha^{4.2}/-\alpha^{4.2}$	0			3	74.7±7.0	22.3±2.1

The mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) for each genotype group is shown as mean±SD. Although MCH values were consistently slightly lower in association with the $-\alpha^{4.2}$-compared with the $-\alpha^{3.7}$-haplotypes, none of the observed differences between these haplotypes were significant at the 5% level. These hematologic data together with hemoglobin levels are reported in full elsewhere (22).

α-thalassemia, in keeping with the prevalence of such determinants in this population indicated above.

Subtyping of $-\alpha^{3.7}$ deletions. We have shown, by detailed restriction enzyme mapping, that $-\alpha^{3.7}$ deletions may be divided into three subtypes produced by independent recombination events (14). One of these, type I, is a single α1-like gene; the second, type II, is a hybrid α2-α1 gene, whereas the type III deletion is produced by a crossover at the extreme 3′ end of the α-gene homology block and leaves a single intact α2-gene. In contrast, the $-\alpha^{4.2}$ deletion removes the entire α2-gene and leaves the α1-gene intact (6).

21 of the $-\alpha^{3.7}/-\alpha^{3.7}$ homozygotes and 16 of the $-\alpha^{3.7}/-\alpha^{4.2}$ compound heterozygotes shown in Fig. 2 were subtyped using the restriction enzymes Apa I and Rsa I (14). 18 of the 21 $-\alpha^{3.7}$ homozygotes were homozygous for the type III deletion, and the other 3 were compound heterozygotes for a type I and type III $-\alpha^{3.7}$ deletion. Amongst the $-\alpha^{3.7}/-\alpha^{4.2}$ compound heterozygotes, 12 had $-\alpha^{3.7}$III and 4 $-\alpha^{3.7}$I deletions. There was no apparent difference in levels of Hb Bart's between the $-\alpha^{3.7}$III and the small number of $-\alpha^{3.7}$I deletions; the mean level of Hb Bart's in the four individuals of genotype $-\alpha^{3.7}$I$/-\alpha^{4.2}$ was 4.94%, and in the three individuals of genotype $-\alpha^{3.7}/-\alpha^{3.7}$III 3.55%.

Because of the known molecular structure of these deletion chromosomes, by comparing the phenotype of the $-\alpha^{3.7}$III deletion with that of the $-\alpha^{4.2}$ deletion and assuming that levels of Hb Bart's faithfully reflect α-chain deficiency, we are effectively comparing the α-globin output of chromosomes with a residual intact α2-gene to those with an intact α1-gene. It follows that on these chromosomes with a single α-gene the α2-gene produces more α-globin than the α1-gene.

Interaction with other globin gene variants. Since several globin gene variants at both the β- and α-loci are known to be present in this Melanesian population (22), we have been able to study the effects of these on Hb Bart's levels. All of the unselected 236 samples in the survey described above were analyzed with γ and ζ probes for the presence of the single and triplicated γ- and ζ-gene arrangements (16–18). As reported elsewhere, single and triple γ-gene chromosomes had no significant effect on the amount of Hb Bart's associated with different α-genotypes (23). Similarly, seven heterozygotes for triple ζ-gene chromosomes and three heterozygotes for single ζ-gene chromosomes

produced Hb Bart's levels appropriate to their α-genotype (data not shown). Hence, deletion or insertion of 11 kb of DNA upstream of the α-genes had no detectable effects on the activity of these genes at birth.

Discussion

High frequencies of single α-gene deletions are found in many tropical areas, but usually either the rightward ($-\alpha^{3.7}$) or, less commonly, the leftward ($-\alpha^{4.2}$) deletion predominates (3, 10). In Vanuatu, each is present at a significant frequency, allowing comparison of their phenotypes. Analysis of the red cell indices of adults heterozygous and homozygous for these deletions failed to show significant differences between the two types of deletion (Table III) (22). However, measurement of levels of Hb Bart's at birth provides a more sensitive index of α-chain deficiency, and this is not known to be complicated by other factors that may affect red cell indices in the tropics. The higher levels at birth of Hb Bart's associated with the $-\alpha^{4.2}$ deletion indicates that this defect generates a greater α-chain deficit than the $-\alpha^{3.7}$III deletion. The data on Melanesians heterozygous for the $-\alpha^{3.7}$ defect are in agreement with studies in Jamaica and South Africa (12, 19), which found that this defect is not always associated with detectable amounts of Hb Bart's in cord blood. Interestingly, in Southeast Asia, where both the $-\alpha^{3.7}$ and $-\alpha^{4.2}$ deletions are found, Hb Bart's was more often detectable in $-\alpha^{4.2}$ heterozygotes (13).

Analysis of the percentage of variant hemoglobins in individuals with both an α-chain variant and one or two deletion chromosomes might provide some indication of the relative expression of the $-\alpha^{3.7}$ and $-\alpha^{4.2}$ chromosomes in adult life. Limited data on the Hb $J^{Tongariki}$ (24) and Hb Q (25) variants suggest that the $-\alpha^{4.2}$ deletion may produce a slightly more severe phenotype, but many further such examples would be required to confirm this. Comparison of the phenotypes of individuals with Hb H disease who have either the $-\alpha^{3.7}$ or $-\alpha^{4.2}$ deletion as well as an α°-chromosome, should provide further data on this question. However, from the red cell indices data (Table III) it is clear that any difference between the phenotypes in adult life must be small.

Studies of the proportions of α-chain variants in heterozygotes and homozygotes first suggested that the human α-globin gene was duplicated, and indicated that the output of each of the two genes was similar (26, 27). However, because of possible differences in affinities for β-chains, rates of synthesis, and stabilities of α-chain variants, it is difficult to extrapolate from the percentage of a variant to the level of expression of its gene. Furthermore, in the case of most α-variants on αα-chromosomes it is not known which gene carries the mutation (28). Hence, small differences in the level of expression of the two α-genes would not have been apparent from these studies. DNA sequence analysis and restriction enzyme mapping have shown that whereas the $-\alpha^{4.2}$ deletion leaves the α1-gene intact, the $-\alpha^{3.7}$III deletion found in Vanuatu leaves a single intact α2-gene (14, 29). Hence, the Hb Bart's data indicate that, on these single α-gene chromosomes, the α2-gene produces more α-globin than the α1-gene. Although this is consistent with other observations which suggest that the α2-gene may also be more active on αα-chromosomes (30, 31), it is not valid to make such a simple extrapolation. For example, it has recently been demonstrated that there is a compensatory increase in expression of the single α-gene in heterozygotes for the $-\alpha^{3.7}$ deletion (32). This could in part explain the observation that these heterozygotes do not always have detectable levels of Hb Bart's at birth (Fig. 1) (12), and further similar studies on $-\alpha^{4.2}$ heterozygotes will be of interest.

There are now several lines of evidence which suggest that the α2-gene may produce more globin than the α1-gene, on αα- as well as $-\alpha$-chromosomes. Firstly, two independent studies have shown that, in normal (αα/αα) individuals, the amount of α2-messenger RNA (mRNA) exceeds that of α1 by 1.5–2.8-fold, probably due to increased transcription of the α2-gene (30, 31). α1-mRNA has been shown to have a higher translational efficiency than α2-mRNA and it was suggested that this balances the increased transcription of the α2-gene, so that each gene produces an equal amount of α-globin (33). However, the precision of such studies, particularly given the range of estimated α_2/α_1 mRNA levels, is insufficient to exclude a slightly higher output from the α2-gene. Clearly, it would be of interest to perform similar analyses on these Melanesian individuals, though this would necessitate a more sophisticated method of sample collection than has so far been possible in these remote island populations. Secondly, it is remarkable that all of the nondeletion α-thalassemias which have been analyzed to date (reviewed in references 3 and 28) have been associated with a mutation in the α2-gene. (One also has an additional mutation in the α1 gene [3]). Since there is no other evidence for increased mutation in the α2 compared with the α1 gene this may reflect a selection bias. If the α2-gene is normally more active, point mutations in this gene would produce a more severe phenotype than α1-mutations and might be more likely to be selected and detected. Interestingly, these nondeletion mutations affecting the α2-gene produce a more severe phenotype than single α-gene deletions (3, 34), presumably because of a compensatory increase in the expression of the residual α1-gene in the $-\alpha^{4.2}$ deletion (32). Similarly, the α2-gene chain termination mutant, Hb Constant Spring, produces a relatively severe form of α^{+}-thalassemia (35). Although none of these studies provide unequivocal evidence, taken together they are consistent in suggesting a higher output from the α2-gene.

Because the sequence of both the α2- and α1-genes and the structure of each type of deletion chromosome have been defined (2, 6, 14, 29), it is possible to identify the sequence differences between the $-\alpha^{3.7}$III and $-\alpha^{4.2}$ chromosomes that are presumably responsible for the difference in expression between the two. These differences are 20-point mutations and a 7 basepair deletion at the 3′ end of the α-gene, and more substantial differences 1 kb 5′ to the gene in the region of the Y homology box (2, 29). The relative importance of these two regions of sequence difference could be indicated by comparison of the phenotype of the $-\alpha^{3.7}$I deletion, which has the same 3′ region as the $-\alpha^{4.2}$ chromosome and the same 5′ region as the $-\alpha^{3.7}$III chromosome, with the $-\alpha^{3.7}$III and the $-\alpha^{4.2}$ phenotypes. The $-\alpha^{3.7}$I chromosomes identified in this study suggest that this deletion is more similar to the $-\alpha^{3.7}$III than the $-\alpha^{4.2}$ deletion, which indicates that the upstream sequence differences may be of more importance. Hence, although the $-\alpha^{3.7}$I deletion leaves a residual α-gene that is α1-like in sequence, its phenotype may differ from that of the $-\alpha^{4.2}$ deletion because of the presence of upstream sequences in the $-\alpha^{3.7}$III that are deleted on the $-\alpha^{4.2}$ chromosome. However, because of the small number of $-\alpha^{3.7}$I deletions detected in this study, further comparison of the $-\alpha^{3.7}$I and $-\alpha^{4.2}$ phenotypes is required.

At present it is not possible to develop a unifying model to

account for the phenotypes of the different $-\alpha$-deletions in terms of the particular sequences that determine transcriptional and translational efficiencies. However, because of the very limited sequence differences between these duplicated genes, further analysis both in vitro and in vivo of the expression of each of the four types of $-\alpha$-chromosome should further our understanding of gene expression and its control in man.

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