References

1. Fihn SD, McDonell M, Martin D, et al. Risk factors for complications of chronic anticoagulation: a multicenter study. Ann Intern Med 1993; 118:511-20.
2. Fihn SD, Callahan C, Martin D, McDonell M, Henikoff J, White R. The risk for and severity of bleeding complications in elderly patients treated with warfarin. Ann Intern Med 1996; 124:970-9.
3. Kent D, Vermes D, McDonell M, Henikoff J, Fihn SD. A model for planning optimal follow-up for outpatients on warfarin anticoagulation. Med Decis Making 1992; 12:132-41.
4. Mazzolenis D, Colorio C, Rossi A, Pombo G, Carreras LO. Anticoagulant treatment in patients with mechanical heart valves: comparison between acenocoumarol and warfarin [abstract]. Thromb Haemost 1995; 73:1118.
5. Pattacini C, Manotti C, Quintavalla, Dettori AG. A comparative study on the quality of oral anticoagulant therapy (warfarin versus acenocoumarol). Thromb Haemost 1994; 71:188-91.
6. Barcellona D, Vannini ML, Ferru L, Balestieri C, Marongiu F. Warfarin or acenocoumarol: which is better in the management of oral anticoagulants? Thromb Haemost 1998;80:899-902.
7. Rosendaal FR, Cannegetier SC, van der Meer FJM, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993; 69:236-9.
8. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort study, prospective collaborative study (ISCOAT). Lancet 1996; 348:423-8.
9. Maugeri N, Kempfer AC, Evangelista V, Cerletti Ch, de Gaetano G, Lazzari MA. Enhanced response to chemotactic activation of polymorphonuclear leukocytes from patients with heart valve replacement. Thromb Haemost 1997; 77:71-4.
10. Chenoweth DE, Cooper SW, Hugli TE, Stewart RW, Blackstone EH, Kirklin J. Complement activation during cardiopulmonary by-pass. Evidence for generation of C3a and C5a anaphylatoxins. N Engl J Med 1981; 304:497-503.

The frequency of allele α^{LELY}, a low expression allele of the gene encoding erythroid spectrin α-chain, in the Greek population

Sir,

α^{LELY}, a low expression allele of the *SPTA1* gene, encodes the α-chain of erythroid spectrin.[1] It is characterized by a C→G mutation at position α1857 in exon 40;[2] it is functionally neutral, but yields major peptide map abnormalities,[3] and a C→T (nt12) mutation in intron 45. This second mutation is responsible for the partial skipping of exon 46,[4] which is essential for the nucleation of spectrin α/β-chain dimerization. Although α^{LELY} does not cause symptoms in either heterozygotes or homozygotes, it enhances the expression of deleterious α-alleles and, thus, has clinical importance.

Allele α^{LELY} is encountered in distinct ethnic groups, Caucasians, African Blacks, Japanese, Chinese, Brazilians and Parakana Indians, with a rather uniform frequency.[5,6] Among French Caucasians its frequency was estimated to be 0.31.

We investigated 175 individuals randomly selected from all parts of Greece. Exon 40 and intron 45 mutations were screened using a polymerase chain reaction.[5] Chi-square test was used to determine whether frequencies in certain groups were significantly dif-

Table 1. Statistical analysis of the frequencies of allele α^{LELY} between distinct ethnic groups considered by pairs (Caucasians (Greek + French)) vs. non-Caucasians.

	*Caucasians*Blacks*	*Africans*	*Japanese*	*Chinese*	*Brazilians*	*Parakana Indians*
n	454	86	100	36	108	82
u	0.289	0.209	0.20	0.222	0.241	0.159
Caucasians*[a]		nsd	nsd	nsd	nsd	sd
African Blacks[b]			nsd	nsd	nsd	nsd
Japanese[b]				ns	nsd	nsd
Chinese[b]					nsd	nsd
Brazilians[c]						nsd
Parakana Indians[c]						

**Greek + French Caucasians. [a]Marechal et al. 1995, and this work. [b]Marechal et al., 1995. [c]Basseres et al., 1998.*
Abbreviations: n: numbers of SPTA1 alleles investigated; Σn = 866. u: frequencies of allele α^{LELY} in individual populations. The frequencies of allele α^{LELY} were significantly different (s.d.) or not significantly different (n.s.d.) at p<0.05 between any particular pair of groups.

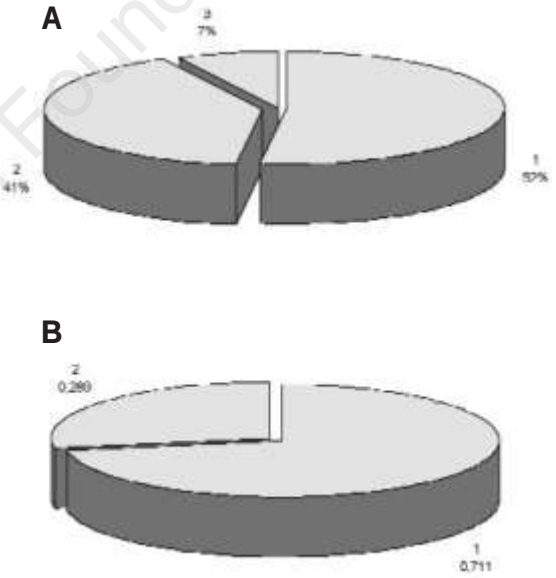

Figure 1. The allelic distribution of α/α (1), α/α^{LELY} (2) and $\alpha^{LELY}/\alpha^{LELY}$ (3) in the Greek population (A: values as percentages) and of the α (1) and α^{LELY} alleles (2) (B: values as frequencies).

ferent (p<0.05) from the overall mean frequency of allele α^{LELY}, and whether frequencies were significantly different (p<0.05) within any particular pair of groups, the m±2s interval being used in all cases.

We found that the distribution of α/α, α/α^{LELY} and $\alpha^{LELY}/\alpha^{LELY}$ individuals was: 91(52%), 71(41%) and 13(7%), respectively (Figure 1a). Out of 350 SPAT1 genes (Figure 1b), we found 97α^{LELY} alleles, which corresponds to a frequency of 0.28. Exon 40 and exon 45 mutations were always found to be linked. The frequency of allele α^{LELY} in Greek Caucasians was thus almost identical to that recorded among French Caucasians. The overall mean of all available frequencies,[5,6] including this work, (n=866 *SPTA1* allele), was m=0.22±0.087. The only statistically significant difference (0.01< p<0.05) was that for the pair of Caucasians and Parakana Indian groups (Table 1).

The Greek and French populations are both of Caucasian origin[7] and thus could be expected to have similar frequencies of the α^{LELY} and this expectation is supported by all experimental evidence (ref. #5 and present study). Allele α^{LELY} also appears with similar frequencies in remote ethnic groups[5,6] yet not as uniform as within Caucasians.

The significant difference between the Caucasian population and Parakana Indians (0.01<p<0.05), noted here, shows that the α^{LELY} polymorphism, although relatively constant throughout the world, is less so in very isolated populations. Parakana Indians form a very ancient population and have a very restricted range of polymorphisms for several genetic markers.[8]

α^{LELY} is deleterious only in *trans* of *SPTA1* alleles that cause HE and may reach a non-negligible proportion in black populations;[9] this issue has not yet been evaluated in Greek populations.

The presumably universal character of α^{LELY} is consistent with a very ancient origin. The present study underscores the high stability of allele α^{LELY} among Caucasians and even non-Caucasians with exception of the Parakana Indians.

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Key Words

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References

1. Kotula L, Laury-Kleintrop LD, Showe L, et al. The exon-intron organization of the human erythrocyte α-spectrin gene. Genomics 1991; 9:131-40.
2. Wilmotte R, Marechal J, Morle L, et al. Low expression allele α^{LELY} of red cell spectrin is associated with mutations in exon 40 ($\alpha^{V/41}$ polymorphism) and intron 45 and with partial skipping of exon 46. J Clin Invest 1993; 91:2091-6.
3. Alloisio N, Morle L, Marechal J, et al. Spa$^{V/41}$: a common spectrin polymorphism at the αIV-αV domain junction. Relevance to the expression level of hereditary elliptocytosis due to α-spectrin variants located in trans. J Clin Invest 1991; 87: 2169-77.
4. Wilmotte R, Harper SL, Ursitti J, et al. The exon 46-encoded sequence is essential for stability of human erythroid α-spectrin and heterodimer formation. Blood 1997; 90:4188-96.
5. Marechal J, Wilmotte R, Kanzaki A, et al. Ethnic distribution of allele α^{LELY}, a low-expression allele of red-cell spectrin α-gene. Br J Haematol 1995; 90:553-6.
6. Basseres DS, Salles TSI, Costa FF, Saad STO. Presence of allele α^{LELY} in an Amazonian Indian population. Am J Hematol 1998; 57:212-4.
7. Cavalli-Sforza LL, Piazza A. Human genomic diversity in Europe: a summary of recent research and prospects for the future. Eur J Hum Genet 1993; 1:3-18.
8. Black FL, Salzano FM, Layrisse Z, Franco MHLP, Harris NS, Weimer TA. Restriction and persistence of polymorphisms of HLA and other blood genetic traits in the Parakana Indians of Brazil. Am J Phys Anthropol 1981; 52:119-32.
9. Glele-Kakai C, Garbarz M, Lecomte MC, et al. Epidemiological studies of spectrin mutations related to hereditary elliptocytosis and spectrin polymorphisms in Benin. Br J Haematol 1996; 95:57-66.

Acute myeloid leukemia occurring in a patient with polycythemia vera in treatment with hydroxyurea

Sir,

Hydroxyurea is a non-alkylating chemotherapeutic agent used in the treatment of patients with polycythemia vera (PV). The leukemogenic risk associated with treatment with hydroxyurea alone is considered to be relatively low but the probability of development of acute leukemia has been recognized as a long-term side-effect.[1] We report the case of a patient with PV who developed acute myeloblastic leukemia (AML) after three years of treatment with hydroxyurea.

A 62-year old man was admitted because of leukocytosis and thrombocytosis in February 1995. Clinical examination revealed only splenomegaly of 3 cm. Full blood count was erythrocytes 5.630×10^9/L; hemo-