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S Allele of L-*MYC* Oncogene is Associated with Metastatic Lung Cancer in Patients from Moldova

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THE L-MYC oncogene is known to possess a polymorphic EcoRI site in the second intron, resulting in the appearance of S ('small', EcoRI-cleaved) or L ('large', EcoRI-resistant) alleles. Studies of Japanese lung cancer patients have reported an increase of S allele frequency among cases with metastases [1, 2], whereas similar investigations on Caucasians failed to find such a correlation for Americans [3], Norwegians [4] and Australians [5]. Thus, race was commonly suspected to influence the clinical significance of L-*MYC* genotype [6]. However, recent publications have demonstrated the first exceptions, with a lack of a negative impact of S alleles in a Chinese study [7] and an association of S alleles with metastatic lung cancer for Russians [8]. The present study aimed to test L-*MYC* allele distribution in Caucasians from another former member of the Soviet Union, Moldova, which is closely related to Romania, Southern Russia and Ukraine by ethnic, historical and geographical links.

43 lung cancer cases and 77 healthy volunteers were recruited for the analysis. DNA was isolated from peripheral blood cells, digested by EcoRI, electrophoretically separated on an agarose gel, transferred on to Nylon membranes, and hybridised to a 1.8 kb SmaI-EcoRI L-MYC radiolabelled probe [9]. Data on S (6.6 kb) and L (10 kb) allele frequencies are shown in Table 1. A striking uniformity of the incidence of L and S variants among Caucasians and Orientals was confirmed [1–8]. Furthermore, as in all other reports, there was no difference in L-*MYC* genotype distribution between lung cancer cases and non-affected controls [1–8]. However, despite the rather small number of patients, the chi-squared test with Yates' correction revealed statistically significant variations between different clinical subgroups. In particular, both S allele and SS genotype occurrence were higher in node-positive individuals than in node-negative ones ($P < 0.02$ and $P < 0.05$, respectively). In addition, the S variant was over-represented in cases with distant metastases (M_1) as compared with M_0 patients ($P < 0.05$).

Thus, the associations between L-*MYC* genotype and lung cancer progression seem to be mediated not by purely racial but rather by more complex ethnico-geographical factors. It is not yet known whether this EcoRI polymorphism in the non-coding region of the gene has its own functional importance, or if the described relationships reflect a linkage disequilibrium between L-*MYC* and a 'true' lung cancer locus. Evidence for geographical variability of L-*MYC* clinical impact may favour the latter explanation.

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Table 1. *L*-MYC *allele distribution in lung cancer patients and healthy donors*

Patients and controls	L-*MYC* genotypes (%)				L-*MYC* alleles (%)		
	SS	LS	LL	Total	S	L	Total
Lung cancer	10 (23)	25 (58)	8 (19)	43 (100)	45 (52)	41 (48)	86 (100)
Primary tumour							
T_1	0 (0)	3 (75)	1 (25)	4 (100)	3 (38)	5 (63)	8 (100)
T_2	5 (26)	9 (47)	5 (26)	19 (100)	19 (50)	19 (50)	38 (100)
T_3	5 (25)	13 (65)	2 (10)	20 (100)	23 (58)	17 (43)	40 (100)
Nodal involvement							
N_0	0 (0)	8 (67)	4 (33)	12 (100)	8 (33)	16 (67)	24 (100)
N_1	3 (27)	7 (64)	1 (9)	11 (100)	13 (59)	9 (41)	22 (100)
N_2	7 (41)	8 (47)	2 (12)	17 (100)	22 (65)	12 (35)	34 (100)
N_X	0 (0)	2 (67)	1 (33)	3 (100)	2 (33)	4 (67)	6 (100)
Distant metastases							
M_0	5 (17)	16 (55)	8 (28)	29 (100)	26 (45)	32 (55)	58 (100)
M_1	5 (36)	9 (64)	0 (0)	14 (100)	19 (68)	9 (32)	28 (100)
Healthy donors	21 (27)	38 (49)	18 (23)	77 (100)	80 (52)	74 (48)	154 (100)

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