HL-A Antigens and Disease

ACUTE LYMPHOCYTIC LEUKEMIA

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ABSTRACT 50 Caucasian children with acute lymphocytic leukemia (ALL) and 219 members of their families have been genotyped for 15 antigens of the HL-A system. The antigen and gene frequencies for HL-A2 were significantly higher in the patient population than in a 200 member normal Caucasian panel. No other antigen frequencies were significantly elevated. All antigens typed for were found in the patients. No antigen gain or loss was detected in the leukemic cells.

INTRODUCTION

The extraordinary polymorphism of the HL-A leukocyte antigen system strongly implies that natural selection has played a role in its generation. The association of the mouse analogue, H-2, with disease susceptibility, especially leukemia (1, 2), offers one example of how selection may operate. Thus, searches for disease-HL-A antigen associations in man are warranted, although the associations may not be as clear-cut as in the inbred mouse strains. In addition to providing reasons for the polymorphism, the association of particular HL-A antigens with disease may yield some clues to the pathogenesis of these conditions. Moreover, these associations identify individuals at risk and thus may facilitate earlier diagnosis.

Disease-antigen searches should consider first those diseases which are prevalent before or during the reproductive years and, thus, exert a natural selective pressure on the gene pool. Acute lymphocytic leukemia (ALL) [1] is a disease affecting members of the species at this time and is a logical choice for study.

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[1] *Abbreviation used in this paper:* ALL, acute lymphocytic leukemia.

Several investigators have already studied this disease and conflicting results have been published (3–8). The present study differs from the previous investigations in that it presents a larger number of patients and their families who have been completely genotyped. HL-A antigens of 50 Caucasian patients with ALL and their families were assessed. We found a significant increase in HL-A2 in these patients.

METHODS

The lymphocyte cytotoxicity technique of Mittal, Mickey, Singal, and Terasaki (9) with slight modification in the preparation of lymphocyte suspensions was used to assess HL-A antigens. Heparinized blood was poured over nylon columns (1 g for 10–15 ml of blood) and the effluent was sedimented with Plasmagel at 37°C. Lymphocytes were removed by centrifugation of the upper layer of the sedimented blood and contaminating erythrocytes were then agglutinated by chicken anti-human erythrocyte sera (10). The remainder of the preparation of lymphocytes and the cytotoxicity test itself are as described by Mittal et al. (9).

Sera used to detect HL-A antigens were obtained from the Serum Bank maintained by the Transplantation and Immunology Branch of the National Institute of Allergy and Infectious Diseases. Other sera were kindly provided by Doctors M. Jeannet and F. Kissmeyer-Nielsen. Some sera were purchased from Hyland Laboratories, Los Angeles, Calif. Antigens typed for included HL-A1, 2, 3, 5, 7, 8, 9, 10, 11, 12, Lc17 (W28 or Ba*), Thompson (Th, W19), W14, W10, and Te50. In all instances except Lc17, Thompson, and W-14, at least 2 and often as many as 10 sera were used to define each specificity. Sera used to detect HL-A2 included Pinquette (NIH code No. 50-6-03-08-01 and 50-6-03-01-04), Piquard (01-8-03-06-04 and 01-9-07-17-02), Revillard (01-7-02-07-02), Ter. 8 (53-6-01-17-01), Wroten (57-9-03-14-10), D66-17077 IV (03-7-03-21-12), Hyland A2 (code 0966H003A1), and our own serum Stengel. We find that the first listed Piquard serum also detects Lc17; Revillard, Stengel, and Wroten are occasionally positive with non-HL-A2 cells.

An antigen was assigned to a cell when greater than 80% of all sera reacted with the cell. The reproducibility of the procedure was 97% when tested on normal individuals. There was more variability when testing disease subjects, however repeat typings were carried out on many of the patients, and assignment of antigens could be made with a high degree of confidence.

50 Caucasian children and their families (in most instances complete families) were HL-A typed. Genotyping was done on all members of the family. In the few ambiguous situations (e.g., family 50) crossing-over was assumed not to occur. As controls, 200 unrelated normal Caucasian blood bank donors were HL-A phenotyped with the same sera.

Gene frequencies for the various HL-A antigens were assessed by direct counting in the ALL population and by the method of iterative maximum likelihood estimation assuming the Hardy-Weinberg Law (11, pp. 165–172) in the normal population. In each of the two segregational series, the over-all test of possible difference in gene frequencies between the two groups was done by Fisher's discrepancy chi-square (11, pp. 186–7). The differences in individual gene and antigen frequencies were tested by individual normal deviate tests in which the standard errors are computed from the standard formulas evaluated under the null hypothesis of no difference in the two groups. Throughout the paper, the statistical tests are of the two-sided kind with the significance levels adjusted by correcting for the number of alleles in each segregational series (12).

RESULTS

The genotypes of the 50 families are listed in the Appendix. Gene and antigen frequencies for the patients and normal controls are listed in Tables I and II. In all groups and both segregational series, the numbers of genotypes and phenotypes are consistent with the Hardy–Weinberg Law as tested by the chi-square goodness of fit test. No loss or gain of the HL-A antigens was found in the patients. Due to the small number of cases and the fact that the normal controls were not genotyped, comparisons of the frequencies of haplotypes could not be made.

For the first segregational series (in Table I A) the gene frequencies for the ALL population differ significantly from the normal controls ($P \sim 0.002$) as tested by the discrepancy chi-square. The individual gene frequencies are tested one-by-one while adjusting the significance level for the nine statistical tests being made. We find the ALL group's gene frequency for HL-A2 is 0.420 and for the normal group it is 0.235. Under the null hypothesis of no difference, the common gene frequency for the two groups combined is 0.277. Using this frequency, we recompute the standard errors for the ALL and control groups to be 0.0237 and 0.0448, respectively. The normal deviate test for the gene frequencies of HL-A2 is thus $(0.420-0.235)/\sqrt{\{(0.0237)^2+(0.0448)^2\}} = 3.65$, which after proper adjustment yields $P \sim 0.002$. The similarly adjusted test of the antigen frequencies, 0.720 vs. 0.415, also yields a significant results, $P \sim 0.001$. On the other hand, the gene frequency of the undefined antigen(s), X, of the first segregational series is significantly less in the ALL group, 0.040 vs. 0.149, with $P \sim 0.041$. HL-A9 was not found as frequently in the ALL group, but this difference does not reach significance.

In the second segregational series no significant differences are found between the ALL and the normal groups either overall or individually in the gene or antigen frequencies.

40 of the 50 ALL patients have siblings with clearly defined genotypes available for comparison of genotype frequencies. The 40 families included all those listed in the Appendix except Nos. 7, 11, 16, 18, 19, 23, 34, 43, and 50. These families were excluded because of ambiguous typings of the closest sibling in age, because the patients was a sole child, or because the only sibling was an identical twin. Family 34 was excluded because of ambiguity in assigning HL-A7 to one maternal haplotype in the closest sibling although we have assumed its presence in the genotype presented. Family 43 was excluded because Th. was not typed for in the closest sibling. In Table II this subset of 40 are compared with their closest siblings in age as well as to all 106 of their siblings.

For HL-A2, the gene and antigen frequencies of the sibs are intermediate between the normal and ALL groups. This suggests comparing the frequency of HL-A2 in the ALL patients with their sibs. A paired sample statistical test for the presence or absence of HL-A2 was done between each of the 40 patients and his closest sib (13, pp. 213–215); no significant difference was found. A second statistical test (13, pp. 253–6) was performed comparing each patient as to the presence of HL-A2 with all his sibs. This was not significant. For no allele in either segregational series did either of these statistical tests reach significance when properly adjusted for the number of alleles.

As with the whole ALL group, the subset of 40 patients differ significantly overall from the normals for the first segregational series ($P \sim 0.007$) and the gene and antigen frequencies of HL-A2 differ significantly ($P \sim 0.01$) from the normal groups. These are the only significant differences found between any of the groups of Table II and the 200 normal controls.

In all the comparison noted above, the P values are adjusted to take into account the number of alleles being compared within each of the two segregational series. Adjustment to the consideration of both series simultaneously requires multiplication of P by a factor approximately equal to two. Thus the results on the enhanced frequency of HL-A2 in the ALL groups remain highly significant when both series are considered simultaneously.

TABLE I A

Analyses of 50 Leukemic Patients and Normals

Antigen	Gene frequencies ±SE		Antigen frequencies ±SE	
	200 Normals	50 ALL patients	200 Normals	50 ALL patients
HL-A1	0.191±0.020	0.160 ±0.037	0.350±0.034	0.320 ±0.066
-A2	0.235±0.022	0.420*±0.049	0.415±0.035	0.720‡±0.063
-A3	0.114±0.016	0.150 ±0.036	0.215±0.029	0.300 ±0.065
-A9	0.142±0.018	0.070 ±0.026	0.265±0.031	0.140 ±0.049
-A10	0.049±0.011	0.020 ±0.014	0.095±0.021	0.040 ±0.028
-A11	0.042±0.010	0.050 ±0.022	0.085±0.020	0.100 ±0.042
Th.	0.055±0.012	0.080 ±0.027	0.105±0.022	0.160 ±0.052
Lc 17	0.023±0.008	0.010 ±0.010	0.045±0.015	0.020 ±0.020
X	0.149±0.022	0.040§±0.020	—	—
Goodness of fit test for Hardy-Weinberg Law	X^2 = 30.69 (28 d.f.) $P \sim 0.35$	X^2 = 33.65 (36 d.f.) $P \sim 0.60$	— —	— —
Discrepancy chi-square for difference between groups	X^2 = 24.59 (8 d.f.) $P \sim 0.002$		— —	— —

d.f., degrees of freedom.

* Significantly different from normals, $P \sim 0.002$.

‡ Significantly different from normals, $P \sim 0.001$.

§ Significantly different from normals, $P \sim 0.041$.

TABLE I B

Analyses of 50 Leukemic Patients and Normals

Antigen	Gene frequencies ±SE		Antigen frequencies ±SE	
	200 Normals	50 ALL patients	200 Normals	50 ALL patients
HL-A5	0.062±0.012	0.120±0.032	0.120±0.023	0.240±0.060
-A7	0.145±0.018	0.180±0.038	0.270±0.031	0.340±0.067
-A8	0.114±0.016	0.110±0.031	0.215±0.029	0.220±0.059
-A12	0.174±0.020	0.130±0.034	0.315±0.033	0.240±0.060
Te 50	0.111±0.016	0.140±0.035	0.205±0.029	0.260±0.062
W 10	0.084±0.014	0.020±0.014	0.160±0.026	0.040±0.028
W 14	0.038±0.010	0.030±0.017	0.075±0.019	0.060±0.034
X	0.272±0.025	0.270±0.044	—	—
Goodness of fit test for Hardy-Weinberg Law	X^2 = 21.48 (21 d.f.) $P \sim 0.43$	X^2 = 18.71 (28 d.f.) $P \sim 0.90$	— —	— —
Discrepancy chi-square for difference between groups	X^2 = 10.57 (7 d.f.) $P \sim 0.16$		— —	— —

23 of the 50 patients had at least one genotypically identical normal sibling. 18 had one, 2 had two, and 3 had three identical siblings. On the basis of chance alone, given the average size of these families, 23 of 50 patients would be expected to have at least one identical sibling (14). Hence, there does not appear to be a preferential genotype for the patients in the individual families.

TABLE II A

Analyses of 40 Leukemics and Their Siblings

Antigen	Gene frequencies ±SE		Antigen frequencies ±SE		
	40 All patients	40 Siblings	40 All patients	40 Siblings	106 Siblings
HL-A1	0.188 ±0.044	0.188±0.044	0.375 ±0.077	0.375±0.077	0.387
-A2	0.412*±0.055	0.350±0.053	0.700*±0.072	0.600±0.077	0.566
-A3	0.138 ±0.039	0.100±0.034	0.275 ±0.071	0.175±0.060	0.189
-A9	0.038 ±0.021	0.050±0.024	0.075 ±0.042	0.100±0.047	0.133
-A10	0.025 ±0.017	0.062±0.027	0.050 ±0.034	0.125±0.052	0.104
-A11	0.062 ±0.027	0.025±0.017	0.125 ±0.052	0.050±0.034	0.075
Th.	0.075 ±0.029	0.075±0.029	0.150 ±0.056	0.125±0.052	0.179
Lc 17	0.012 ±0.012	0.038±0.021	0.025 ±0.025	0.075±0.042	0.038
X	0.050 ±0.024	0.112±0.035	—	—	—
Goodness of fit test for Hardy-Weinberg Law	$X^2 = 32.31$ (36 d.f.) $P \sim 0.65$	$X^2 = 25.53$ (36 d.f.) $P \sim 0.90$	— —	— —	— —
Discrepancy chi-square from normal group	$X^2 = 20.85$ (8 d.f.) $P \sim 0.007$	$X^2 = 10.28$ (8 d.f.) $P \sim 0.25$	— —	— —	— —

* Significantly different from normals, $P \sim 0.01$.

TABLE II B

Analyses of 40 Leukemics and Their Siblings

Antigen	Gene frequencies ±SE		Antigen frequencies ±SE		
	40 ALL patients	40 Siblings	40 ALL patients	40 Siblings	106 Siblings
HL-A5	0.125±0.037	0.075±0.029	0.250±0.068	0.150±0.056	0.160
-A7	0.150±0.040	0.125±0.037	0.275±0.071	0.250±0.068	0.274
-A8	0.138±0.039	0.150±0.040	0.275±0.071	0.300±0.072	0.255
-A12	0.112±0.035	0.175±0.042	0.225±0.066	0.300±0.072	0.292
Te 50	0.150±0.040	0.062±0.027	0.275±0.071	0.125±0.052	0.142
W 10	0.025±0.017	0.050±0.024	0.050±0.034	0.100±0.047	0.132
W 14	0.038±0.021	0.075±0.029	0.075±0.042	0.150±0.056	0.113
X	0.262±0.049	0.288±0.051	—	—	—
Goodness of fit test for Hardy-Weinberg Law	$X^2 = 24.88$ (28 d.f.) $P \sim 0.65$	$X^2 = 27.98$ (28 d.f.) $P \sim 0.46$	— —	— —	— —
Discrepancy chi-square from normal group	$X^2 = 9.54$ (7 d.f.) $P \sim 0.21$	$X^2 = 5.63$ (7 d.f.) $P \sim 0.58$	— —	— —	— —

Since susceptibility to murine leukemia viruses depends to a certain degree on homozygosity of the H-2 antigens, a search was made for homozygosity in the affected subjects. There were no haplotype homozygotes. HL-A2 was found in homozygous state six times. This is not significantly higher than what would be expected, given the gene frequencies of the parents. HL-A7 and HL-A12 were homozygous once each. There was no excess homozygosity in the parents.

Only one of the patient-mother combinations was haplotypically identical (see Fig. 1). All of the other 49 such combinations were not identical.

TABLE III

Comparison of Various Antigen Frequencies Reported in the Literature

Study	No. of ALL patients	Antigen frequencies in leukemics				
		HL-A1	HL-A2	HL-A9	HL-A10	HL-A12
Kourilsky et al. (3)	102	0.24	0.50	—	—	0.37
Thorsby et al. (4)	11	0.273	0.727	0.190	0.091	0.364
Walford et al. (5)	10	0.000	0.700	0.200	0.100	0.900
Lawler et al. (6)	58	0.36	0.45	0.16	0.14	0.38
Batchelor et al. (7)	17	—	0.765	0.000	—	—
This paper	50	0.320	0.720	0.140	0.040	0.240
	No. of controls	Antigen frequencies in controls				
		HL-A1	HL-A2	HL-A9	HL-A10	HL-A12
Kourilsky et al. (3)	234	0.23	0.53	—	—	0.43
Dausset et al. (23)	308	0.244	0.451	0.247	0.117	0.295
Albert et al. (2)	5072*	0.28	0.48	0.21	0.11	0.27
Pegrum et al. (8)	180	0.31	0.49	0.20	—	—
This paper	200	0.350	0.415	0.265	0.095	0.315

* Except for HL-A10 which is based on 438 individuals.

DISCUSSION

A significant increase in HL-A2 was seen among children and young adults suffering from ALL in our study. The results of the smaller series of Thorsby, Bratlie, and Lie (4) Walford, Finkelstein, Neerhout, Konrad, and Shanbrom (5) and Batchelor, Edwards, and Stuart (7) are all very close to our results (Table III). Sanderson[2] also reports a significant increase in HL-A2 among his ALL group. In contrast, the studies of Kourilsky, Dausset, Feingold, Duprey, and Bernard (3) and Lawler, Klonda, Hardisty, and Till (6) do not demonstrate this. The reason for the difference may reside in differing diagnostic criteria for ALL. Alternatively, the populations of Kourilsky et al. (3) and Lawler et al. (6) may differ in ways, environmental or genetic, which are unrelated to HL-A but important for susceptibility to leukemia.

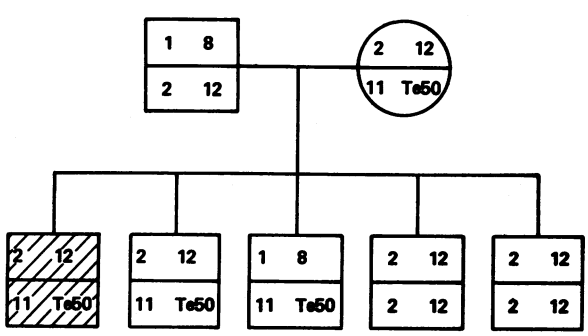

FIGURE 1 The genotypes of a patient with ALL and his family. The patient's genotype is marked with diagonal lines.

In the usual analyses of retrospective studies (15), the increase in HL-A2 can be expressed as a relative risk of ALL of 3.62 in our study for those individuals with HL-A2 to those without HL-A2. Kourilsky et al. (3) found a relative risk of only 0.89, not significantly different from one. These two relative risks are significantly different (16), so these results cannot be explained by chance. In fact not only does the antigen frequency of HL-A2 among leukemics differ significantly between the two studies, but the control groups also differ significantly for this antigen. This discrepancy may be explained for the control groups by the fact that HL-A2 in Kourilsky et al. is probably the combination of the HL-A2 and Lc17 alleles. However, this does not explain the decreased frequency of HL-A2 antigen among the leukemic group in Kourilsky et al. compared with this study (3).

Pegrum, Balfour, Evans, and Middleton (8) do not distinguish among the diagnoses of acute leukemia, so their data cannot be compared with the rest. However, their control group is seen to be comparable with ours.

Walford et al. (5) reported a decrease in HL-A1 antigen frequencies among his leukemic group. Our results agree with Kourilsky et al. (3) and Lawler et al. (6) in finding no such decrease. Similarly Sanderson[2] did not find any significant difference between his leukemic and control groups for this antigen.

Sanderson found significant decreases in HL-A9 and HL-A10 among his leukemic group. However, if his statistical tests are adjusted for the number of tests

[2] Sanderson, A. R. Personal communication.

being made, their P values rise to about 0.3, so that their results are comparable with those of this paper. The other papers reporting on these antigens do not confirm any marked decrease of these antigens among the leukemic patients.

Turning to the second segregational series, we find that our results for HL-A12 are in contrast to Walford et al., who found this antigen to be more frequent in his leukemic series (5). However, his study was small, and the antiserum used, Merritt, apparently contains other antibodies than anti-12. We note in Table III that our results for HL-A12 are very similar to those of Kourilsky et al. (3), Thorsby et al. (4), and Lawler et al. (6). Sanderson[9] reports a significant increase in this antigen among his 48 leukemics, a significance which is sustained by the adjusted statistical analysis. We do not have his detailed data available so we cannot test statistically whether this difference from our results may be due to chance.

Of note, however, is the family illustrated in Fig. 1. If the A2-A12 haplotype was associated with leukemia, one would expect a person homozygous for it to be very susceptible. Such was not the case in this family, as two unaffected siblings are A2, A12 homozygous. In 11 other families (Nos. 5, 14, 15, 20, 24, 25, 29, 36, 40, 47, 50) at least one unaffected sibling had the A2, A12 haplotype. In only 6 of these 11 families did the patient have the A2, A12 haplotype. From these data we conclude that this haplotype is not associated with ALL.

Our data and that of others (4, 5, 7, footnote 2) suggest an association between HL-A2 and acute lymphocytic leukemia. If this is so, it is more likely that A2 confers susceptibility to leukemia, than another antigen conferring resistance, since in our series no other single defined antigen is significantly decreased in frequency in the ALL population. To be sure, antigen(s) X (first segregational series) is significantly lower in this population, but X represents a multiplicity of as yet undefined antigens low in frequency and most people would not possess X. In contrast, most people are resistant to leukemia.

The association of an HL-A antigen with leukemia suggests an etiologic relationship. Four possibilities, all speculation, come to mind. These have been previously stated by Snell (17) and Lilly (18). One, the antigen molecule may serve as a receptor for the leukemia virus. Secondly, the molecule may be immunochemically similar to the virus or to a tumor-specific antigen induced by the virus allowing for persistent infection or tumor growth by the mechanism of cross tolerance. Thirdly, the presence of the HL-A antigen molecule in the cell membrane may be a structural necessity for cell surface changes which lead to malignant behavior. Finally, the gene determining the HL-A antigen may be linked to a gene which controls the host's immune response to a leukemia virus or to a tumor-specific cell surface antigen.

The first three of these hypotheses require only the presence of HL-A2 on the cell membrane and do not require that the subject be homozygous for the gene controlling HL-A2. Our data, which show that 30 of 36 HL-A2 bearing leukemics are heterozygous for the antigen, could fit well with these hypotheses.

The first hypothesis is attractive. HL-A antigens are cell surface molecules and cell surface molecules do act as viral attachment sites. However, this explanation alone is inadequate to explain leukemogenesis as 28% of our population of ALL patients were negative for A2. Presumably, they would not have the receptor unless some closely related but serologically different molecule could substitute for A2. At present, the only serologically cross-reacting, and thus structurally related, specificity for A2 is Lc17. Those patients in the present study who are negative for A2 were also negative for Lc17. On the other hand, it is of note that the amino acid composition of soluble HL-A antigen derived from an A2-positive cell line (RPMI 4265) is very similar to that derived from an A2-negative cell line (RAJI) (19). It may well be that the basic HL-A molecule is constant enough in most of its structure and that the virus is flexible enough to allow for some minor (serologically detectable) differences in receptor molecule specificity.

The second and third hypotheses are also attractive but suffer from the same criticism as the first, i.e., not all leukemics have HL-A2. Since a human leukemia virus has not been isolated, the second hypothesis cannot be tested. A test of the third may be possible by careful quantitative assessment of HL-A2 content on normal and neoplastic lymphocytes, as changes in the amount of the antigen may indicate participation in cell membrane structural realignments that result in malignancy.

The final hypothesis seems unlikely on the surface. Since there was no single HL-A antigen which was significantly decreased in the ALL group, we cannot conclude that our patients lack an immune response gene which confers resistance to leukemia. However, it is possible that the gene controlling HL-A2 is linked to an immune response gene which allows a low (or absent) response to leukemia antigens. In order for the HL-A2 heterozygote to be susceptible to leukemia, this low response gene would have to be at least codominant. Most of the histocompatibility linked immune response genes studied thus far (20) show recessive behavior of genes controlling low or absent response to antigen. But it is possible that low immune response gene co-

dominance could be simulated upon challenge by a virulent tumor, i.e., the process of leukemogenesis could override the immune response conferred on an HL-A2 heterozygote by the presence of anti-leukemia immune response genes linked to other HL-A antigens. If this were the case, our data would fit this hypothesis also.

There are several facts from this study which cannot be overlooked and which prevent us from accepting any one of these more simple hypotheses per se as the explanation of the association of HL-A2 and leukemia. These are the following: (*a*) not all leukemics have HL-A2, although it is possible that certain subcategories of ALL may be identified in which HL-A2 frequency reaches 100%; (*b*) 42% of the normal population have HL-A2 and the vast majority of these people do not have leukemia; and (*c*) the identical HL-A genotypes of the leukemic patients are found in normal numbers in their healthy siblings. Thus, other factors must be operating. They necessarily are genetic or environmental. The mouse leukemia model of Lilly, Boyse, and Old (1) requires at least one other gene not linked to H-2 to explain the fact that, although F_1 hybrids between susceptible and resistant strains are resistant to leukemia, the H-2 heterozygotes in the F_2 and back-cross generations are not completely resistant. The high but not 100% concordance rate of ALL in identical twins argues in favor of environmental factors being of some importance. Of interest will be the occurrence of leukemia in one allele or no allele-different siblings of patients with leukemia. If HL-A has any bearing on leukemogenesis, the HL-A identical normal siblings should have a higher incidence of leukemia than the HL-A nonidentical siblings, especially the two allele-different ones.

Since A2 appears associated with ALL, those races with lower gene frequencies of A2 would be expected to have a lower leukemia incidence. This is true of the negro race which has both low A2 gene frequency and low incidence of leukemia (21, 22). From the data of gene frequencies of A2 among whites and negroes and the relative risk of ALL among whites with and without the A2 allele, it is possible to predict the relative risk of ALL among white and negroes. This requires the assumption that race per se is not a factor. Let P_1 be the incidence of ALL among individuals with A2 and P_2 be the incidence of ALL among individuals without A2 regardless of their race. Let $R = P_1/P_2$. Let p_1 be the antigen frequency of A2 among whites and p_2 be the antigen frequency of A2 among negroes. The relative risk of ALL among whites to that among negroes is then easily shown to be,

$$R_r = \frac{p_1P_1 + (1 - p_1)P_2}{p_2P_1 + (1 - p_2)P_2} = \frac{p_1R + (1 - p_1)}{p_2R + (1 - p_2)}.$$

From (21) we have $p_1 = 0.48$ and $p_2 = 0.29$. The results of the present study gives $R = 3.62$. Substituting these values in the equation we find the predicted relative risk between races to be $R_r = 1.28$. We find from (22) that the 1969 incidence of ALL among white children was 2.11/100,000 and among negroes it was 1.44/100,000. Thus the observed relative risk of ALL between races is $2.11/1.44 = 1.47$. These two figures are well within statistical limits. The close correspondence between these figures seems to indicate that the A2 frequencies account for a large part of the difference in the incidence of ALL between whites and negroes.

Comparisons of disease incidence and HL-A antigen types should be conducted in various racial groups and in isolated populations, as they may shed light on the association of these important cell surface molecules and disease resistance or susceptibility.

Appendix

Genotypes of Families

Family number	Father	Mother	Patient*	Normal siblings
1	1, 8/2, 12	2, 12/11, Te50	2, 12/11, Te50	2, 12/11, Te50; 1, 8/11, Te50; *2, 12/2, 12*;‡ 2, 12/2, 12
2	X§, 5/X, X	1, 8/X, 12	X, X/1, 8	X, X/1, 8; X, X/X, 12; *X, 5/X, 12*
3	1, 7/1, 12	2, X/3, 7	1, 7/3, 7	1, 7/3, 7; *1, 12/2, X*; 1, 12/3, 7
4	1, 8/11, 12	3, 7/X, X	1, 8/3, 7	1, 8/3, 7; 1, 8/X, X; 1, 8/X, X; *11, 12/X, X*
5	(2, W14/2, X)	1, 8/2, 12	2, X/1, 8	*2, W14/1, 8*; 2, W14/1, 8; 2, X/2, 12; 2, X/2, 12
6	2, 5/3, 5	1, Te50/X, 12	3, 5/1, Te50	*3, 5/1, Te50*; 2, 5/X, 12; 2, 5/X, 12
7	1, ?/2, Te50	11, Te50/Th, 7	2, Te50/Th, 7	2/Te50/Th, 7¶; 2, Te50/Th, 7; 2, Te50/Th, 7; 2, Te50/Th, 7; 1, ?/11, Te50; *1, ?/11, Te50*
8	1, Te50/X, X	9, X/Lc17, W14	1, Te50/9, X	*X, X/Lc17, W14*; X, X/Lc17, W14
9	2, X/3, X	2, X/11, Te50	2, X/11, Te50	2, X/11, Te50; *2, X/2, X*
10	1, W14/Th, W10	10, X/X, 5	1, W14/X, 5	1, W14/X, 5; 1, W14/X, 5; *1, W14/10, X*; Th, W10/X, 5

Genotypes of Families—Continued

Family number	Father	Mother	Patient*	Normal siblings
11	1, 7/3, ?	2, X/?, W10	1, 7/2, X	
12	2, 7/9, Te50	1, 5/10, X	9, Te50/1, 5	9, Te50/1, 5; 2, 7/10, X; 9, Te50/50, X; *9, Te50/10, X*
13	2, 8/Th, X	2, 5/X, X	2, 8/2, 5	2, 8/2, 5; Th, X/X, X; Th, X/X, X; 2, 8/X, X
14	2, 12/Lc17, ?	Th, 7/Lc17, 7	2, 12/Lc17, 7	2, 12/Lc17, 7; *2, 12/Th, 7*
15	3, 7/X, 5	2, Te50/2, 12	X, 5/2, Te50	*X, 5/2, Te50*; X, 5/2, Te50; X, 5/2, 12
16	2, Te50/?, 5	3, 7/11, ?	2, Te50/3, 7	
17	2, X/3, X	2, X/?, 7	3, X/2, X	*2, X/?, 7*
18	3, X/2, X	2, X/1, X	2, X/2, X	
19	2, 5/3, ?	2, Te50/9, 12	2, 5/9, 12	2, 5/9, 12¶
20	3, 7/2, 7	2, 12/9, 7	2, 7/2, 12	3, 7/2, 12
21	2, ?/11, Te50	10, 12/3, 7	11, Te50/10, 12	*2, X/10, 12*
22	(10, 5/2, Te50)	2, X/Lc17, W14	10, 5/2, X	*2, Te50/Lc17, W14*
23	3, 7/Th, X	3, W10/9, 12	Th, X/9, 12	
24	2, 12/Th, Te50	1, X/3, Te50	Th, Te50/3, Te50	Th, Te50/1, X; *2, 12/1, X*; 2, 12/1, X
25	1, W10/2, 12	11, Te50/Lc17, 12	1, W10/11, Te50	2, 12/11, Te50; *2, 12/Lc17, 12*
26	3, Te50/2, W10	3, 7/2, X	2, Te50/2, X	*2, W10/3, 7*
27	2, X/10, 7	3, X/Th, 12	2, X/3, X	10, 7/3, X; *10, 7/Th, 12*
28	2, 7/Th, W10	1, 8/Th, Te50	2, 7/1, 8	2, 7/Th, Te50; *Th, W10/1, 8*
29	2, 12/3, 7	3, Te50/Th, W10	2, 12/3, Te50	2, 12/3, Te50; 2, 12/Th, W10; *3, 7/3, Te50*; 3, 7/Th, W10; 3, 7/Th, W10
30	1, X/9, 12	2, X/X, W10	9, 12/2, X	9, 12/2, X; 9, 12/X, W10; *1, X/X, W10*
31	2, 7/3, X	2, X/Th, X	2, 7/2, X	3, X/Th, X; 3, X/2, X/2, 7/Th, X; 2, 7/Th, X
32	2, 7/3, W10	3, W14/11, X	2, 7/3, W14	*2, 7/11, X*
33	2, X/?, W14	1, 8/2, 12	2, X/1, 8	*2, X/1, 8*
34	1, 7/2, X	1, 7/3, 7	2, X/3, 7	*1, 7/1, 7*
35	3, 7/?, ?	1, 8/?, ?	3, 7/1, 8	*3, 7/1, 8*
36	1, 8/11, W14	2, 12/X, X	1, 8/X, X	*1, 8/X, X*; 1, 8/2, 12
37	2, 7/X, W14	1, X/3, 8	2, 7/1, X	2, 7/1, X; 2, 7/1, X; 2, 7/1, X; *X, W14/1, X*
38	1, 8/?, ?	2, 5/9, W10	1, 8/2, 5	1, 8/2, 5; *1, 8/9, W10*; 1, 8/9, W10; 1, 8/1, W10
39	11, X/9, X	2, 7/?, ?	11, X/2, 7	11, X/2, 7; 11, X/2, 7; *9, X/2, 7*
40	1, Te50/2, 12	2, X/Th, X	2, 12/Th, X	*2, 12/2, X*
41	1, 8/2, 5	1, 8/2, X	2, 5/2, X	*1, 8/2, X*
42	2, X/3, X	X, 7/Th, W14	2, X/Th, W14	2, X/Th, W14; *2, X/X, 7*; 2, X/X, 7; 2, X/X, 7; 3, X/X, 7
43	9, 5/X, X	2, 12/3, 7	9, 5/3, 7	*X, X/3, 7*
44	2, 7/Th, 8	Th, 12/10, X	2, 7/Th, 12	*Th, 8/Th, 12*; 2, 7/10, X
45	1, X/2, 8	3, X/9, 12	2, 8/3, X	*2, 8/3, X*; 2, 8/3, X; 2, 8/3, X; 1, X/3, X; 1, X/3, X; 1, X/9, 12
46	3, X/Th, W10	2, X/3, 12	Th, W10/2, X	Th, W10/2, X; Th, W10/3, 12; *3, X/2, X*
47	1, 8/3, 5	2, 12/9, W14	3, 5/2, 12	1, 8/2, 12; *1, 8/9, W14*; 1, 8/9, W14
48	2, 8/10, X	1, 5/Th, 5	2, 8/Th, 5	*2, 8/1, 5*; 2, 8/1, 5; 10, X/Th, 5
49	2, 5/2, X	2, X/10, X	2, X/2, X	*2, 5/10, X*; 2, X/10, X
50	2, ?/9, 12	2, 12/X, W14	9, 12/2, 12	*2, ?/2, 12*; 9, 12/X, W14

* The paternal chromosome's haplotype is listed first in the patient and the normal siblings.
‡ The normal sibling (italicized) is the closest in age to the patient.
§ X is an unknown antigen.
‖ Parentheses indicate a deduced genotype in a parent who was not typed.
¶ Identical twin with the patient.

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