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A Controlled Study of Polymorphisms in Serum Globulin and Glucose-6-Phosphate Dehydrogenase Deficiency in Leprosy [1, 2]

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Few studies of genetically determined traits, other than erythrocyte antigens, or phenylthiocarbamide taste ability ([1, 2, 4, 5, 10]), have been conducted in leprosy. Therefore, as part of an investigation of genetic polymorphism and leprosy conducted under the auspices of the Leonard Wood Memorial, five genetic markers were studied in leprosy patients and controls from Cebu, Philippines. Included were the enzyme glucose-6-phosphate dehydrogenase (G6PD) and four serum proteins, viz., haptoglobins, transferrins, group-specific components (Gc), and the β-lipoprotein (Ag^a).

Haptoglobin is a protein component of the serum that has the capacity to bind hemoglobin. In hemolytic diseases, the hemoglobin from destroyed cells is removed from circulation as a haptoglobin-hemoglobin complex. In such states the haptoglobin content of serum is greatly reduced. Genetic variants of this protein exist and can be detected by differential patterns of electrophoretic mobility. The common genetic types of molecules are designated as Hp 1 and Hp 2. A person homozygous for Hp 1 is called Hp 1:1; one homozygous for Hp 2 is Hp 2:2. The heterozygote is designated Hp 2:1. Transferrin is an iron-binding protein constituent of the serum which also exhibits genetic polymorphism. The most frequent type of transferrin is designated Tfc. Variants are very infrequent and those that migrate faster than Tfc in starch-gel electrophoresis are called Tfb; those slower are Tfd. There are subgroups of Tfb and Tfd, all based on relative mobility. The group specific component (Gc) is an alpha macroglobulin whose structure and function have not been determined. It exhibits gen-

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etic polymorphism that can also be typed by electrophoresis. The Beta lipoproteins represent one of the most complex groups of the human serum proteins. At least two or three independent loci are involved in determining separate lipoprotein systems (Ag, Lp, and others). These appear to be definite polymorphisms, the varying types of which are identified through electrophoretic technics, primarily electrophoresis. Frequency variations in different geographic areas and populations suggest the likelihood of association with differential disease susceptibility.

It is well recognized that inherited deficiency of G6PD, an x-linked trait, may lead to severe hemolytic anemia after ingestion of fava beans or any of a number of drugs such as primaquine (an antimalarial drug), naphthalene, furodantin and sulfonamides. Of interest is the suggestion of Pettit and Chin [12] that deficiency of G6PD might predispose to lepra reaction in sulfone-treated leprosy patients, although Beiguelman *et al.* [2] found no evidence of such a relationship. Since this enzyme deficiency varies considerably in different populations and has been reported in 12.7 per cent of Filipino cannery workers in Alaska [11], it seemed useful to examine the trait in the Cebu study.

The genetic types of haptoglobins, identified by starch gel electrophoresis, are determined by an autosomal multiple allelic series, with the proportions of the three principal phenotypes, 1:1, 2:1, and 2:2, differing in various human populations. In investigations carried out by Schwantes *et al.* [15] in Brazil, and Povey and Horton [14] in India, no differences in haptoglobin distribution were found among patients with different types of leprosy, or between patients and the general population, but this seemed worthy of reexamination.

Like the haptoglobins, the phenotypes of transferrins are also determined by autosomal allelic genes, but unlike the haptoglobins, homozygosity for one type, C, is the most common in all populations. Variants with other mobility (Bo, D1, etc.) have been found in relatively high frequency in some populations, particularly in non-Caucasians. Since leprosy is prevalent in non-Caucasians, it appeared desirable to study the frequency of transferrins in our study population.

Gc types, also determined by autosomal alleles, were first described by Hirschfeld [8], when he modified an earlier immunoelectrophoretic technic. Most of the populations studied since then show three main phenotypes, viz., Gc 1:1, Gc 2:2, and Gc 2:1, with a few rare variants, e.g., Gc Aborigene found in New Guinea and Gc Chippewa in American Indians. Therefore this genetic polymorphism was investigated. Inherited antigenic specificities of the serum beta-lipoproteins (the Ag system) have been detected by the use of antisera that develop in transfused patients [3]. The specificities are detected by precipitin reactions in agar gel double diffusion experiments [6]. Many specificities have now been detected. In this study the original antiserum used in the lipoprotein studies was used (C. de B.); this has now been shown to contain at least three different specificities [9].

MATERIALS AND METHODS

Sampling, specimen collection and handling. The study sample consisted of 557 leprosy patients and 434 control subjects. Among the leprosy patients, 256 were lepromatous (46.0%), 224 were tuberculoid (40.2%), and 77 showed other forms of the disease or were unclassified (13.8%). Information on the presence or absence of lepra reaction over the four years prior to the study, was available on 229 lepromatous cases; 144 (62.9%) had a record of lepra reaction. The distribution of the total sample by age, sex, and birthplace is given in Table 1.

Specimens of blood were drawn from patients at the Eversley Childs Sanitarium in Mandawe (near Cebu City), the Cebu Traveling Skin Clinics, and the Leonard Wood Memorial Epidemiologic Unit in Cebu City. The control specimens were obtained on a voluntary basis from medical students at the Cebu Institute of Technology (134 specimens, or 30.9% of the control specimens), and in a sequential manner from patients consulting at the Cebu Skin

TABLE 1. *Age, sex, and birthplace distribution for controls and cases.*

	Total	Sex				Age[a]				Birthplace[b]							
		Males		Females		<40 yrs.		≥40 yrs.		Vizayas		Mindanao		Other provinces or not reported			
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%		
Controls	434	277	63.8	157	36.2	333	76.7	99	22.8	294	67.7	17	3.9	123	28.3		
Cases	557	341	61.2	216	38.8	380	68.2	177	31.8	487	87.4	56	10.1	14	2.5		

[a] Age unknown for 2 controls.
[b] For controls whose birthplace is reported: 93% Vizayas-born
5.4% Mindanao-born
1.6% born in other provinces

Dispensary for dermatologic conditions other than leprosy (69.1% of the control specimens). Because of insufficient quantity of serum in some specimens, 1 per cent of the sample was not typed for haptoglobins, 1.6 per cent for Gc, 5.6 per cent for transferrins, and 4.6 per cent for the Ag system. It should also be noted that since G6PD is sex-linked, only males were studied for this marker, viz., 223 cases and 269 controls. These were similar in age and birthplace distribution to the total sample. The sampling methods, diagnostic criteria and technics of blood collection and shipment have been described in more detail in a previous paper ([10]).

Laboratory technics. Standard laboratory procedures were used for analysis of phenotypes. Deficiency of G6PD was determined in Cebu on freshly drawn samples. The spot test method described by Fairbanks and Beutler ([7]) was used.

Typing for serum proteins was carried out over a period ranging from one to two years after blood collection, during which time the serum was kept frozen at —20°C. For the haptoglobin and Gc determinations the vertical starch gel electrophoresis method of Smithies ([16]) was used. For the transferrins the starch gel system of Smithies ([16]) and Poulik's discontinuous buffer ([13]) were employed. A micro-Ouchterlony technic was used for the lipoprotein (Ag) specifities ([6]).

To avoid observer bias, the specimens were labeled with code numbers. The laboratory technicians, therefore, had no way of distinguishing the code numbers of cases from those of the controls.

Data processing and analysis. Epidemiologic and clincial information, as well as laboratory results, were coded for computer processing. Phenotypic differences were examined for possible association with leprosy, type of leprosy, lepra reaction, and their possible relationships to age, sex, duration of disease, and province of origin. Two tests of statistical significance were performed, viz., the chi-square test on the distribution of phenotypes and the Z test on differences in the proportions of the phenotypes. Because of the small sample size, a number of the statistical comparisons could not be

TABLE 2. *Phenotypic distribution of haptoglobins, Gc, transferrins, and β-lipoproteins Ag (a +), according to disease status, type of leprosy, lepra reaction, and sex.*

		Haptogloblins				Gc				Transferrins			Ag (a +)		
		No. tested	1:1	2:1	2:2	No. tested	1:1	2:1	2:2	No. tested	CC	Others	No. tested	Neg.	Pos.
Controls	Males	275	0.153	0.451	0.396	277	0.188	0.704	0.108	272	0.978	0.022	272	0.055	0.945
	Females	155	0.116	0.484	0.400	157	0.217	0.650	0.134	153	0.987	0.013	154	0.091	0.909
	Total	430	0.140	0.463	0.398	434	0.198	0.684	0.118	425	0.981	0.019	426	0.068	0.932
Cases	Males	338	0.281	0.411	0.308	337	0.185	0.721	0.095	316	0.981	0.019	316	0.060	0.940
	Females	214	0.294	0.383	0.322	214	0.164	0.715	0.121	194	0.985	0.015	193	0.073	0.927
	Total	552	0.286	0.400	0.313	551	0.176	0.719	0.105	510	0.982	0.018	509	0.065	0.935
Lepromatous cases		253	0.277	0.427	0.296	252	0.167	0.718	0.115	233	0.983	0.017	232	0.086	0.914
Tuberculoid cases		222	0.261	0.392	0.347	222	0.176.	0.739	0.086	208	0.981	0.019	208	0.048	0.952
Lepromatous with lepra reaction		143	0.287	0.427	0.287	142	0.155	0.725	0.120	132	0.985	0.015	131	0.061	0.939
Lepromatous without lepra reaction		83	0.277	0.422	0.301	83	0.181	0.711	0.108	79	0.975	0.025	79	0.101	0.899

performed, and, unless the probability of occurrence was 0.05 or less, differences were disregarded.

RESULTS

The phenotypic distributions of G6PD deficiency, and haptoglobin, transferrin, Gc and Ag types, are presented by disease status, type of leprosy, history of lepra reaction, and sex in Table 2, by age in Table 3, and by duration of disease in Table 4. Gene frequencies of cases and controls are given in Table 5. The frequency of G6PD deficiency in cases and controls by age is presented in Table 6.

Glucose-6-phosphate dehydrogenase. No significant differences in the frequency of G6PD deficiency were found to be associated with leprosy, even when type of leprosy and presence or absence of lepra reaction were considered.

Haptoglobins. Among the cases, neither type of leprosy nor lepra reaction was detectably associated with variations in the distribution of haptoglobin phenotypes, although subclassification by age did reveal some deviations. In pooled cases, the proportion of Hp 2:1 heterozygotes was significantly lower in patients below 40 years of age than in older patients ($P < 0.01$) (Table 3).

When case-control comparisons were examined, an excess of Hp 1:1 homozygotes was observed in all the patient groups, i.e., total cases, lepromatous cases, tuberculoid cases, patients with lepra reaction, and patients without reaction. This excess was significant at the 0.01 probability level (Table 2). Moreover, total cases and lepromatous cases had a corresponding deficit of Hp 2:2 homozygotes when compared with controls.

Comparisons repeated between groups matched for age (under 40 and 40 or over) showed that in each age group total cases, as well as tuberculoid and lepromatous cases considered separately, had a significantly higher proportion of Hp 1:1 than controls (Table 3). A corresponding deficit in the proportion of Hp 2:2 homozygotes was found among the lepromatous cases in each age group and among the total cases of the younger age group. Also, in this

TABLE 3. *Phenotypic distribution according to disease status, type of leprosy and age (under 40 years or 40 and over).*

	Age (yrs.)	Haptoglobins				Gc			Transferrins			Ag (a +)		
		No. tested	1:1	2:1	2:2	No. tested	1:1	2:1	2:2	No. tested	CC	Others	No. tested	Neg.	Pos.
Controls	<40	332	0.148	0.464	0.389	434	0.162	0.707	0.132	326	0.975	0.025	327	0.058	0.942
	≥40	98	0.112	9.459	0.429	100	0.320	0.160	0.070	99	1.000	0.0	99	0.101	0.899
Cases	<40	374	0.310	0.364	0.326	373	0.172	0.724	0.105	339	0.982	0.018	338	0.056	0.944
	≥40	177	0.237	0.480	0.282	178	0.185	0.708	0.107	171	0.982	0.018	171	0.082	0.918
Lepromatous	<40	171	0.304	0.398	0.298	170	0.153	0.729	0.118	154	0.987	0.013	153	0.078	0.922
	≥40	82	0.220	0.488	0.293	82	0.195	0.695	0.110	79	0.975	0.025	79	0.101	0.899
Tuberculoid	<40	147	0.279	0.354	0.367	147	0.170	0.748	0.082	134	0.978	0.022	134	0.030	0.970
	≥40	75	0.227	0.467	0.307	75	0.187	0.720	0.093	74	0.986	0.014	74	0.081	0.919

TABLE 4. *Phenotypic distribution according to the type of leprosy, age, and duration of disease since reported onset, 3 years or less and 10 years and over.*

	Duration (yrs.)	Age (yrs.)	Haptoglobins				Gc				Transferrins			Ag (a +)		
			No. tested	1:1	2:1	2:2	No. tested	1:1	2:1	2:2	No. tested	CC	Others	No. tested	Neg.	Pos.
Cases	≤ 3	<40	68	0.324	0.294	0.382	67	0.164	0.776	0.060	59	0.983	0.017	59	0.085	0.915
		≥40	38	0.132	0.553	0.316	38	0.184	0.658	0.158	36	1.000	0.0	36	0.083	0.917
		Total	106	0.255	0.387	0.358	105	0.171	0.733	0.095	95	0.989	0.011	95	0.084	0.916
	≥10	<40	109	0.284	0.376	0.339	108	0.250	0.630	0.120	99	0.990	0.010	98	0.051	0.949
		≥40	74	0.257	0.446	0.297	74	0.230	0.703	0.068	73	0.986	0.014	73	0.068	0.932
		Total	183	0.273	0.404	0.322	182	0.242	0.659	0.090	172	0.988	0.012	171	0.058	0.942
Lepromatous	≤ 3	<40	23	0.304	0.391	0.304	23	0.130	0.826	0.043	20	1.000	0.0	20	0.150	0.850
		≥40	7	0.0	0.429	0.571	7	0.0	0.857	0.143	6	1.000	0.0	6	0.0	1.000
		Total	30	0.233	0.400	0.367	30	0.100	0.833	0.067	26	1.000	0.0	26	0.115	0.885
	≥10	<40	66	0.318	0.348	0.333	65	0.215	0.661	0.123	59	0.983	0.017	58	0.069	0.931
		≥40	51	0.294	0.490	0.216	51	0.235	0.667	0.098	50	0.980	0.020	50	0.080	0.920
		Total	117	0.308	0.410	0.282	116	0.224	0.655	0.121	109	0.982	0.018	108	0.074	0.926
Tuberculoid	≤ 3	<40	33	0.273	0.303	0.424	32	0.125	0.781	0.094	27	0.963	0.037	27	0.037	0.963
		≥40	25	0.160	0.560	0.280	25	0.160	0.680	0.160	24	1.000	0.0	24	0.125	0.875
		Total	58	0.224	0.414	0.362	57	0.140	0.737	0.123	51	0.980	0.020	51	0.078	0.922
	≥10	<40	28	0.214	0.464	0.321	28	0.286	0.607	0.107	27	1.000	0.0	27	0.0	1.000
		≥40	20	0.150	0.500	0.350	20	0.250	0.750	0.0	20	1.000	0.0	20	0.050	0.950
		Total	48	0.187	0.417	0.396	48	0.270	0.667	0.063	47	1.000	0.0	47	0.021	0.979

younger group, a deficit of heterozygotes appeared in total cases as well as lepromatous and tuberculoid cases.

The suggested excess of heterozygotes among older cases as compared with younger cases, in the absence of such a deviation among the controls, is, however, puzzling and raises the questions (1) whether the haptoglobin 2:1 phenotype may yield a selective advantage in leprosy and thus preferential survival, (2) whether haptoglobin heterozygotes may be susceptible to a more persistent type of disease and have a lower recovery rate (longer duration), or (3) whether this observed difference is merely a sampling artifact. The resolution of this problem requires a longitudinal study of leprosy patients blood-grouped and diagnosed at onset.

As might be expected from the comparisons involving phenotypes, gene frequencies revealed a considerable excess of the Hp 1 gene (and a corresponding deficit of the Hp 2 gene) in the total cases of both younger and older groups in comparisons with controls of the corresponding age groups (Table 5). The differences between the lepromatous cases and the controls were statistically significant, although the differences for the tuberculoid cases compared with controls were of borderline significance and were restricted to the older age group (the frequencies of the Hp 1 gene being respectively 0.335 and 0.460 in the controls and in the tuberculoid cases aged 40 and over).

Transferrins. No differences were observed between leprosy cases and controls in the frequencies of the phenotype Tfcc. The low frequency of other phenotypes precluded statistical analysis by the various parameters used in the haptoglobin analysis.

Group-specific components. Since the Gc component is readily degraded by contaminants in handling, specimens processed in several different laboratories, shipped and stored for long periods of time, may give ambiguous results. Therefore, the observations of this study are presented with the understanding that caution must be used in interpreting them.

With all ages pooled, no differences were

TABLE 5. *Gene frequencies for cases and controls according to sex, and age and for lepromatous and tuberculoid cases.*

	Controls					Cases						
	Total	M	F	<40 yrs.	≥40 yrs.	Total	M	F	<40 yrs.	≥40 yrs.	L	T
Hp 1	0.371	0.378	0.358	0.379	0.335	0.487	0.488	0.486	0.492	0.477	0.490	0.457
Hp 2	0.629	0.622	0.642	0.621	0.665	0.513	0.512	0.514	0.508	0.523	0.510	0.543
Gc 1	0.540	0.540	0.541	0.515	0.625	0.535	0.545	0.521	0.534	0.539	0.526	0.545
gc 2	0.460	0.460	0.459	0.485	0.375	0.465	0.455	0.479	0.466	0.461	0.474	0.455
Tf CC	0.990	0.989	0.993	0.987	1.0	0.991	0.990	0.992	0.991	0.991	0.991	0.990
Aga +	0.261	0.235	0.302	0.241	0.319	0.255	0.245	0.270	0.237	0.286	0.293	0.219

found between total cases and controls. Yet, when compared with controls of corresponding age group, lepromatous cases, 40 years old and over, showed a deficiency in the frequency of homozygotes (Z= 1.95). It is possible, however, that this deviation derives from the significantly higher proportion of $Gc_{1:1}$ homozygotes in controls aged 40 or over compared to younger controls ($P < 0.01$), whereas no such differences were observed within the group of total cases or within the respective case groups of different disease type (Table 4).

In addition to the age-associated heterogeneity of the controls with respect to observed Gc type, differences in this marker trait appeared to be associated with birthplace: patients born in Vizayas Islands showed an excess of $Gc_{2:1}$ heterozygotes as compared with patients born in Mindanao. Thus, in view of these internal discrepancies, no real conclusions may be drawn concerning any relationship of Gc components with leprosy.

Lipoproteins. Because of the low frequency of the Ag (a-), statistical analysis of lipoprotein associations was limited. No differences were detectable.

DISCUSSION

In any epidemiologic study, the significance of the findings must be evaluated in terms of the reliability of control selection, i.e., their representativeness and lack of bias. Two sources of controls were used in this investigation, viz., medical students and patients consulting at the dispensary for skin diseases other than leprosy. These two groups showed no differences in the distribution of the haptoglobin phenotypes, when, singly or together, they were tested against expected phenotypic frequencies based on the assumption of the Hardy-Weinberg equilibrium (χ^2 for dermatologic patients = 0.14, for medical students 0.54, and for total controls 0.02). Thus internal heterogeneity of the sample cannot account for the observed haptoglobin differences, i.e., the excess of Hp 1:1 phenotype and Hp 1 gene, even more marked in lepromatous leprosy than in tuberculoid. That the association seems to stem from an excess of either Hp 1:1 homozygotes or the Hp 1

TABLE 6. *Frequency of G6PD deficiency in controls, cases, and lepromatous and tuberculoid patients, according to age.*

	TOTAL		<40 yrs.		≥40 yrs.		Vizayas-born.		Born in other provinces	
	No. tested	% deficient	No. tested	% deficient	No. tested	% deficient	No. tested	% deficient	No. tested	% deficient
Controls	270	2.6	212	2.8	58	1.7	151	2.6	119	2.5
Cases	222	5.0	148	4.7	74	5.4	186	3.8	36	11.1
Lepromatous	69	2.9	47	4.3	22	0.0	49	2.0	20	5.0
Tuberculoid	119	5.9	73	5.5	46	6.5	110	5.5	9	11.1
With lepra reaction	36	2.8	—	—	—	—	—	—	—	—
Without lepra reaction	17	5.9	—	—	—	—	—	—	—	—

gene, rather than a deficit of Hp 2:2 homozygotes or Hp 2 allele, is indicated by analysis of the distribution of controls, lepromatous patients, and tuberculoid patients among the various phenotypes. This analysis reveals significant differences in the frequency of the Hp 1:1 homozygotes, both under 40 years ($\chi^2 = 15.75$; $P < 0.01$) and over 40 years ($\chi^2 = 12.49$; $P < 0.01$), but no such deviations are noted for the Hp 2:2 homozygotes and the Hp 2:1 heterozygotes.

Confirmation of these observations is necessary, since with so many comparisons a certain number would be expected to reach levels of "statistical significances" by chance.

None of the other genetic markers investigated yielded significant differences, except the Gc deviations, which must be considered open to question. In addition to the statistically discernible age-associated Gc heterogeneity within the control series and birthplace-associated Gc heterogeneity within the case series, comparison of the phenotypic distribution of group-specific components revealed considerable deviation from Hardy-Weinberg expectancies ($\chi^2 = 47.60$, $P < 0.01$, and 15.99, $P < 0.01$ respectively).

In view of the consistencies of the control series with Hardy-Weinberg expectancies in haptoglobin frequencies and the lack of evidence for bias in the control or case samples with respect to other serum protein or erythrocyte antigen phenotypes ([10]), it is probable that the Gc discrepancies do not actually derive from sampling or epidemiologic problems, but rather from a technical problem in that the laboratory procedures presently used for Gc determinations are probably unsatisfactory on nonsterile samples.

Therefore, while it is desirable for the other findings (G6PD, haptoglobins, transferrins, etc.) to be confirmed in a prospective investigation, as well as in other cross-sectional studies, before they are accepted as conclusive, it is clearly necessary that the observations with regard to Gc be restudied in a situation where fresh blood specimens can be examined.

SUMMARY

As a part of a study of genetic polymorphism and leprosy, conducted under the auspices of the Leonard Wood Memorial, five genetic markers were investigated in leprosy patients and controls from Cebu, Philippines.

The sample consisted of 557 patients, among whom 256 were affected with lepromatous leprosy, 224 with tuberculoid leprosy, and 77 with other types of the disease or unclassified disease. There were 434 controls without manifestations of leprosy, comprised of medical students and patients attending the Cebu Skin Clinics for cutaneous diseases other than leprosy. The markers investigated were haptoglobins, transferrins, Ag, Gc, and G6PD. This last marker, which is sex-linked, was studied only in males. The phenotypic distributions were analyzed in relation to leprosy, type of leprosy, and the acute episode of lepromatous leprosy known as lepra reaction. Age, sex, duration of disease, and province of birth in the Philippines, were also considered. Gene frequencies were derived.

An association between the haptoglobin polymorphism and leprosy is suggested by an excess of Hp 1:1 phenotypes and/or the Hp 1 gene, observed particularly in lepromatous but also in tuberculoid or total cases when compared with controls. No differences, however, were observed for transferrins, Ag, and G6PD. Because of technical problems, no conclusions can be drawn concerning Gc types.

Other cross-sectional studies in areas where leprosy is highly prevalent are recommended.

RESUMEN

Como parte de un estudio sobre polimorfismo genético y lepra, llevado a cabo bajo el auspicio de Leonard Wood Memorial, cinco marcadores genéticos fueron investigados en enfermos de lepra y controles en Cebú, Filipinas.

La muestra consistió de 557 enfermos, entre los cuales 256 estában afectados con lepra lepromatosa, 224 con lepra tuberculoide, y 77 con otro tipo de enfermedad o enfermedad no clasificada. Hubo 434 controles sin manifesta-

ciones de lepra, constituidos por estudiantes de medicina y los enfermos que concurren a la Clínica Dermatológica de Cebú para enfermedades cutáneas diferentes de lepra. Los marcadores investigados fueron haptoglobinas, transferinas, Ag, Gc, y G6PD. Este último marcador, el cual es relacionado con el sexo, se estudió solamente en hombres. La distribución de los fenotipos se analizó en relación con lepra, tipo de lepra, y episodios agudos de lepra lepromatosa conocida como reacción leprótica. Edad, sexo, duración de la enfermedad, y provincia de nacimiento en Filipinas, fueron factores que también fueron considerados. La frecuencia de los genes fué establecida.

Una relación entre polimorfismo de haptoglobina y lepra se manifiesta por un exceso de Hp 1:1 fenotipo y/o el gene Hp 1, observado particularmente en formas lepromatosas pero también en tuberculoides o en el total de los casos cuando se comparó con los controles. No se observaron diferencias, sin embargo, para transferinas, Ag, y G6PD. A causa de problemas técnicos, no se dedujeron conclusiones relativas al tipo Gc.

Otros estudios estratificados en áreas donde la lepra es altamente prevalente se recomiendan.

RÉSUMÉ

Dans le cadre d'une étude du polymorphisme génétique dans la lèpre, menée sous les auspices du Leonard Wood Memorial, cinq indicateurs génétiques ont été étudiés chez des malades de la lèpre et chez des témoins, à Cebu, Philippines.

L'échantillon était constitué de 557 malades, parmi lesquels 256 étaient atteints de lèpre lépromateuse, 224 de lèpre tuberculoïde, et 77 présentaient d'autres types de lèpre, ou chez lesquels le type clinique n'avait pas été précisé. L'échantillon témoin était constitué par 434 individus ne présentant pas de manifestations de lèpre, et comprenait des étudiants en médecine et des personnes fréquentant le dispensaire de Cebu pour maladies cutanées (Cebu Skin Clinics) pour des affections dermatologiques autres que la lèpre. Les indicateurs étudiés étaient des suivants: haptoglobines, transferrines, Ag(a), "group specific components" (Gc), glucose-6-phosphate dehydrogenase. Ce dernier indicateur, qui est lié au sexe, n'a été étudié que chez des sujets masculins. Les distributions phénotypiques ont été étudiées en fonction de la lèpre, du type de lèpre et de la réaction lépreuse. D'autres facteurs ont été également considérés, à savoir, l'âge, le sexe, la durée de la maladie, et la province d'origine. Les fréquences des différents gènes ont été calculées.

Un excès du phénotype Hp 1:1, ainsi que du gène Hp1, par rapport aux témoins, a été constaté surtout chez les lépromateux, mais aussi chez les tuberculoïdes et dans l'ensemble des cas. Ceci suggère l'existence d'une association entre le polymorphisme des haptoglobines et la lèpre. Par contre, aucune différence n'a été observée pour les transférrines, Ag(a), et G6PD. Par suite de problèmes techniques, aucune conclusion n'a pu être tirée concernant l'indicateur Gc.

Des études complémentaires de ce type (cross-sectional studies) ainsi que des études longitudinales, devraient être menées dans des régions où la prévalence de la lèpre est élevée.

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APPENDIX I. *Comparisons made, with results of chi-square test.*

Groups compared		Chi square				Observations
		Hp	Gc	Tf	Ag(a+)	
Controls	Cases	30.75				Excess Hp 1:1 in cases; excess Hp 2:2 in controls
Controls	Lepromatous	20.72		Inv.		Excess Hp 1:1 in lepromatous; excess Hp 2:2 in controls
Controls	Tuberculoids	14.66		Inv.		Excess Hp 1:1 in tuberculoids
Controls	Lepra reaction	17.07		Inv.		Excess Hp 1:1 in reaction; excess Hp 2:2 in controls
Controls	No lepra reaction	10.08	n.p.	n.p.	n.p.	Excess Hp 1:1 in no reaction
Lepromatous	Tuberculoids			Inv.		
Tuberculoids	Lepra reaction			Inv.		
Lepra reaction	No lepra reaction			Inv.		
Controls <40 y.	Controls ≥40 y.		13.28	Inv.		Excess Gc 1:1 in ≥40 y.
Cases <40 y.	Cases ≥40 y.	7.03		Inv.		Excess Hp 1:2 heterozygotes in ≥40 y.
Leprom. <40 y.	Leprom. ≥40 y.			Inv.		
Tuberc. <40 y.	Tuberc. ≥40 y.			Inv.	Inv.	
Cases ≤3 d.	Cases ≥10 d.			Inv.		
Cases ≤3 d. <40 y.	Cases ≥10 d. <40 y.		(4.26)	Inv.	Inv.	Excess Gc 1:2 heterozygoyes in ≥10 d.
Cases ≤3 d. ≥40 y.	Cases ≥10d. ≥40 y.		Inv.	Inv.	Inv.	
Cases ≤3 d. <40 y.	Cases ≤3 d. ≥40 y.	8.04	Inv.	Inv.	Inv.	Excess Hp 1:1 in <40 y.; excess Hp 1:2 heterozygotes in ≥40 y.
Cases ≥10 d. <40 y.	Cases ≥10 d. >40 y.			Inv.	Inv.	
Leprom. ≤3 d.	Leprom. ≥10 d.		Inv.	Inv.	Inv.	
Leprom. ≤3 d. <40 y.	Leprom. ≥10 d. <40 y.		Inv.	Inv.	Inv.	
Leprom. ≤3 d. ≥40 y.	Leprom. ≥10 d. ≥40 y.	Inv.	Inv.	Inv.	Inv.	
Leprom. ≤3 d. <40 y.	Leprom. ≤3 d. ≥40 y.	Inv.	Inv.	Inv.	Inv.	
Leprom. ≥10 d. <40 y.	Leprom. ≥10 d. ≥40 y.			Inv.	Inv.	
Tuberc. ≤3 d.	Tuberc. ≥10 d.		Inv.	Inv.	Inv.	
Tuberc. ≤3 d. <40 y.	Tuberc. ≥10 d. <40 y.		Inv.	Inv.	Inv.	
Tuberc. ≤3 d. ≥40 y.	Tuberc. ≥10 d. ≥40 y.	Inv.	Inv.	Inv.	Inv.	
Tuberc. ≤3 d. <40 y.	Tuberc. ≤3 d. ≥40 y.	(3.89)	Inv.	Inv.	Inv.	Excess Hp 1:1 in <40 y.
Tuberc. ≥10 d. <40 y.	Tuberc. ≥10 d. ≥40 y.	Inv.	Inv.	Inv.	Inv.	
Controls, males	Controls, females			Inv.		

APPENDIX I.—*Continued*

Groups compared		Chi square				Observations
		Hp	Gc	Tf	Ag(a+)	
Cases, males	Cases, females			Inv.		
Controls, Vizayas	Controls, Mindanao	Inv.	Inv.	Inv.	Inv.	
Controls, Viz. males	Controls, Mind. males	Inv.	Inv.	Inv.	Inv.	
Controls, Viz. females	Controls, Viz. females	Inv.	Inv.	Inv.	Inv.	
Controls, derm. pts.	Controls, med. students			Inv.	Inv.	
Cases, Vizayas	Cases, Mindanao			Inv.	Inv.	
Cases, Viz. males	Cases, Mind. males		Inv.	Inv.	Inv.	
Cases, Viz. females	Cases, Mind. females		Inv.	Inv.	Inv.	
Lepromatous <40 y.	Tuberculoid <40 y.			Inv.		
Lepromatous ≥40 y.	Tuberculoid ≥40 y.			Inv.		
Lepromatous ≤3 d.	Tuberculoid ≤3 d.		Inv.	Inv.	Inv.	
Lepromatous ≥10 d.	Tuberculoid ≥10 d.		Inv.	Inv.	Inv.	
Leprom. ≤3 d. <40 y.	Tuberc. ≤3 d. <40 y.		Inv.	Inv.	Inv.	
Leprom. ≥10 d. <40 y.	Tuberc. ≥10 d. <40 y.		Inv.	Inv.	Inv.	
Leprom. ≤3 d. ≥40 y.	Tuberc. ≤3 d. ≥40 y.	Inv.	Inv.	Inv.	Inv.	
Leprom. ≥10 d. ≥40 y.	Tuberc. ≥10 d. ≥40 y.	(5.72)	Inv.	Inv.	Inv.	Excess Hp 1:2 heterozygotes in tuberc.
Cases ≤40 y.	Controls <40 y.	25.87	n.p.	n.p.	n.p.	Excess Hp 1:1 in cases; excess Hp 1:2 heterozygotes in controls
Cases ≥40 y.	Controls ≥40 y.	10.21	n.p.	n.p.	n.p.	Excess Hp 1:1 in cases; excess Hp 2:2 in controls
Lepromatous <40 y.	Controls <40 y.	17.34		Inv.		Excess Hp 1:1 in lepromatous; excess Hp 2:2 in controls
Lepromatous ≥40 y.	Controls ≥40 y.	6.27		Inv.		Excess Hp 1:1 in lepromatous; excess Hp 2:2 in controls
Tuberculoid <40 y.	Controls <40 y.	12.19	n.p.	n.p.	n.p.	Excess Hp 1:1 in tuberculoid; excess Hp 1:2 heterozygotes in controls
Tuberculoid ≥40 y.	Controls ≥40 y.	(5.91)	n.p.	n.p.	n.p.	Excess Hp 1:1 in tuberculoids

Statistical comparisons made and levels of significance:
— = Not significant at the 0.05 probability level.
Inv. = Test not valid because of small size of sample (expected values below 5)
n.p. = Not performed.
d. = Duration of disease since reported onset.
y. = Years of age.
Figures refer to chi square. When the chi square is indicated in parenthesis it is not significant, but the Z-test on the differences of proportions is significant.