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ELECTROPHORETIC VARIANTS OF BLOOD PROTEINS IN JAPANESE

VI. TRANSFERRIN

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Summary A multiplicity of transferrin variants have been detected in the course of the biochemical aspect of the study of the genetic effects of atomic bombs. Variants obtained from the studies of 19,770 individuals in Hiroshima and Nagasaki were compared by polyacrylamide slab gel electrophoresis using three kinds of buffer systems with different pH values and thin layer polyacrylamide gel isoelectric focusing. The variants were compared on the basis of their relative mobilities and isoelectric points; seven types of fast-moving variant (B-variant) and nine types of slow-moving variant (D-variant) were detected, involving a total of 154 and 273 individuals, respectively. All the variants were identified as genetic variants by family studies. No variant differed in allele frequency between the two cities. The variants detected in this study were compared with variants detected in residents of Mie district (another Japanese population), Caucasoids, American blacks, and Amerindians. Six additional types of B-variant and four additional types of D-variant, which had not been detected in Hiroshima and Nagasaki, were identified.

INTRODUCTION

Studies on blood proteins of A-bomb survivors and their offspring have been conducted since 1972 to determine genetic effects of A-bomb at the protein level. The accumulated data are now being reported. In the present paper, which is a part of the series, results regarding transferrin (TF) are described.

Since Smithies (1957) detected genetic variants of TF by starch gel electrophoresis (SGE), electrophoretic variants of TF have been reported successively, and no less

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than 22 types have been identified to date, but the frequency of every one of them is low (Kirk, 1968; Giblett, 1969; Sutton and Jamieson, 1972). In Japanese populations, Parker and Bearn (1961), Matsumoto (1964), Omoto and Harada (1972), and Kirk *et al.* (1978) have reported rare electrophoretic variants. Ferrell *et al.* (1977), examining 4,029 Japanese residing in Hiroshima and Nagasaki, reported three types of B-variant and five types of D-variant. However, in the studies reported thus far, accurate comparison of variants was difficult, because the preparation of the gels and the pH values of the buffers used differed by investigator and the kinds of gel-buffers used for mutual comparison of variants were limited.

Since Kühnl and Spielmann (1978) and Thymann (1978) succeeded in separating subtypes of TF C, which cannot be separated by SGE, by employing polyacrylamide gel isoelectric focusing (PAGIF), at least seven subtypes have been detected and all of them have been identified as allelic variants (Constans *et al.*, 1980; Dykes *et al.*, 1982; Kamboth and Kirk, 1983; Pascali and Auconi, 1983). However, there is only one report which compares variants detected by SGE using PAGIF (Kühnl *et al.*, 1979). In the present paper, the authors report on variants detected by SGE and compare them using polyacrylamide slab gel electrophoresis (PAGE) and PAGIF. Furthermore, the results of comparisons with variants obtained in a Japanese population of another area and populations of Caucasoids, American blacks, and Amerindians studied by the same method are also discussed.

MATERIALS AND METHODS

Populations, samples, and family studies in Hiroshima and Nagasaki. The first paper in this series (Satoh *et al.*, 1984a) describes the populations, the circumstances under which samples were collected, and the method of family studies and the preparation of samples. Briefly, data are obtained from two populations, *i.e.*, the "Adult" composed of A-bomb survivors and controls, and the "Child" composed of children of A-bomb survivors. Since all the subjects in the Adult population were born before the bombing, and their protein structure would not have been affected by radiation exposure, the data obtained from exposed and nonexposed individuals were combined (Neel *et al.*, 1978). Furthermore, no measurable genetic effects due to parental exposure experience has been observed so far in the children of A-bomb survivors, so that data obtained from children of A-bomb survivors were combined regardless of their parental dose (Satoh *et al.*, 1984a); the "Representative" population was selected from unrelated individuals in the Adult and Child populations. The frequencies of alleles were calculated from the Representative population. Numbers of examinations for each population were as follows: Adult, 4,638 individuals, Child, 15,132, and Representative, 13,314. Ferrell *et al.* (1977) have already reported the results obtained from 4,020 of the 4,638 adults. At the first screening TF was typed using SGE, as described by Smithies and modified by Weitkamp *et al.* (1972).

Samples from another Japanese population, Caucasoids, American blacks, and Amerindians. Ishimoto *et al.* studied TF variation in plasma obtained from 3,411 students and nurses in Mie district by SGE. They found 74 TF variants which were classified into five types of B-variant and four types of D-variant (unpublished data). In the present study, comparison was made with 24 of these variants, including all nine types.

The samples of Caucasoids and American blacks were collected at the Women's Hospital, University of Michigan, Ann Arbor, Michigan, from 2,144 unrelated individuals including 1,764 Caucasoids, 155 American blacks, and 225 Orientals. By PAGE, B-variants were detected in 30 Caucasians and one Oriental, while D-variants were detected in two Caucasians, nine American blacks, and three Orientals. All were confirmed to be genetic variants by family studies. Among these, 18 B-variants (all of them from Caucasians) and eight D-variants (two from Caucasians and six from American blacks) were compared in this study.

The TF variants of Amerindians were detected in three of 21 tribes studied, the Baniwa, Guaymi, and Piaroa; the variants had been identified as TF D_{chi} and TF D_{GUA1} (Neel, 1978). In the present study, comparison studies were carried out with nine cases of TF D_{chi}, consisting of three detected in each tribe, and two samples of TF D_{GUA1}.

Comparison of variants. a) Polyacrylamide slab gel electrophoresis (PAGE): Electrophoresis was performed employing Pharmacia apparatus Mark II; a polyacrylamide gel (80 × 140 × 0.27 mm) was composed of running gel (T, 8.0%; C, 2.5%), stacking gel (T, 5.5%; C, 3.64%), and sampling gel (T, 3.5%; C, 4.3%). Three kinds of buffers with different pH values were used: 1) 0.04 M Tris-glycine, pH 8.5, 2) 0.05 M Tricine-Tris, pH 7.5, and 3) 0.035 M TES-Tris, pH 6.5. Both tank and gel buffers were identical.

b) Thin layer polyacrylamide gel isoelectric focusing (PAGIF): All the samples were partially purified using 0.6% Rivanol and concentrated by adding Sephadex G-25 powder (Pharmacia). For PAGIF, a gel of 1.0 mm thickness was prepared (4.85% acrylamide, 0.15% bisacrylamide). A 2.0% Ampholine, pH 5–7 was chosen. The electrode strips were soaked with 1 M H_3PO_4 solution (anode) and 1 M monoethanolamine solution (cathode). For the focusing run on a multiphor LKB 2117, the power supply (LKB 7103) was set at 1,000 V, 12 mA, and 7.5 W. After a three-hour prerun, filter papers (5 × 10 mm, Wattman 3 MM) soaked in the purified samples were applied on the gel 2 cm apart from the cathodal strip and the run was continued for one hour. The filter paper was then removed and focusing was continued for two hours. The gel was fixed and stained according to the LKB application note 250.

For immunofixation, cellulose acetate strips were soaked in an anti-TF-immunoglobulin (Behring Inst.) mixed with 0.15 M NaCl (1 : 6). Incubation was carried out for one hour at room temperature and followed by washing overnight in 0.15 M NaCl.

Relative mobility of variants on PAGE. After electrophoresis, the distance between peaks of TF C and variants was measured by a densitometer. Regardless of which the three kinds of buffers used, the distance between TF C and TF B_{HR2} (the most frequent B-variant in Hiroshima and Nagasaki, nomenclature described below) was regarded as the standard for the B-variants and the distance between TF C and TF D_{chi} as the standard for the D-variants. Mobilities of other variants are shown as relative mobilities to these standards.

Nomenclature of rare variants. Rare variants were named by city in the order of their discovery according to the method of Ferrell *et al.* (1977) except that the abbreviations for Hiroshima and Nagasaki were shortened to HR and NG, respectively. Variants detected in Mie district with mobility different from those detected in Hiroshima and Nagasaki were named ME, and those from Michigan, AA by the senior author (the Mie and Ann Arbor TF variants are hitherto unpublished).

RESULTS

1) Hiroshima and Nagasaki population

B-variants were detected in 34 adults and 120 children. These variants, involving a total of 154 individuals, were classifiable into seven types, *i.e.*, TF B_{HR1}, TF B_{HR2}, TF B_{HR3}, TF B_{HR4}, TF B_{HR5}, TF B_{HR6}, and TF B_{NG1}. Except for one homozygous phenotype TF B_{HR2}, all the other variants encountered were heterozygous for a normal allele, *TF*C*, and variant alleles. TF B_{HR4} and TF B_{NG1} were detected only in one family in Hiroshima and in one family in Nagasaki, respectively, and TF B_{HR1} and TF B_{HR6} were observed only in Hiroshima (Table 1). Ferrell *et al.* (1977) have reported earlier that in examinations of 4,020 adults, three variants, TF B3, TF B_{HIR2}, and TF B_{HIR4}, were detected. However, the present authors reexamined TF B3 using PAGE and PAGIF, and confirmed that it could be classified into two different types of variants, TF B_{HR1} and TF B_{HR5}. TF B_{HR5} is a unique variant in that its mobility in pH 6.5 PAGE and isoelectric point (pI) cannot be distinguished from those of TF C. Similarly, TF B_{HIR2} could be subclassified into TF B_{HR2} and TF B_{HR3}, the difference between them being that when the relative mobility (RM) of the former in pH 8.5 PAGE was set at 1.0, the RM of the latter was 1.15. The RM of TF B_{NG1} in pH 8.5 PAGE was 1.17, a value only a little different from 1.15 for TF B_{HR3}, but the distinction between the two was clear in studies using pH 6.5 PAGE, where the respective RM values were 1.27 and 1.12. The RM of TF B_{HR6} in pH 8.5 and pH 7.5 PAGE was 1.40, the same value as that of TF B_{HR4} but in pH 6.5 PAGE it was 1.27, a value different from 1.38 of TF B_{HR4} but the same as the RM of TF B_{NG1} (Table 2). These three variants showed different pI (Fig. 1).

The allele frequencies of the B-variants are shown in Table 1. The frequency of *TF*BHR2* was relatively high, but there was no difference between Hiroshima and Nagasaki. Neither was any difference observed between the two cities in the frequency of any of the other B-variants. In Hiroshima a homozygous phenotype of TF B_{HR2} was encountered in a child of unrelated parents.

D-variants were detected in 65 adults and 208 children. These variants were

Table 1. Transferrin phenotypes observed in the Adult, Child, and Representative populations[a] and allele frequencies among the Representative population.

Phenotype	Adult	Child	Representative			Allele	Combined	HR	NG
			Combined	HR[b]	NG[b]				
TF C	4,539	14,804	13,033	7,788	5,245	*TF*C*	.98937	.9882	.9910
TF C/B_{HR1}	3	7	5	5	0	*TF*BHR1*	.00013	.0003	0
TF C/B_{HR2}	13	77	64	44	20				
TF B_{HR2}	0	1	1	1	0	*TF*BHR2*	.00247	.0028	.0019
TF C/B_{HR3}	8	19	22	12	10	*TF*BHR3*	.00083	.0008	.0009
TF C/B_{HR4}	1	1	1	1	0	*TF*BHR4*	.00003	.0001	0
TF C/B_{HR5}	9	11	12	6	6	*TF*BHR5*	.00045	.0004	.0006
TF C/B_{HR6}	0	3	1	1	0	*TF*BHR6*	.00003	.0001	0
TF C/B_{NG1}	0	1	1	0	1	*TF*BNG1*	.00003	0	.0001
TF C/D_{HR1}	2	8	7	2	5	*TF*DHR1*	.00026	.0001	.0005
TF C/D_{HR2}	1	0	1	1	0	*TF*DHR2*	.00003	.0001	0
TF C/D_{HR3}	1	4	3	3	0	*TF*DHR3*	.00011	.0002	0
TF C/D_{HR4}	3	2	4	4	0	*TF*DHR4*	.00015	.0003	0
TF C/D_{HR5}	0	8	3	3	0	*TF*DHR5*	.00011	.0002	0
TF C/D_{HR6}	2	1	2	1	1	*TF*DHR6*	.00007	.0001	.0001
TF C/D_{NG1}	1	0	1	0	1	*TF*DNG1*	.00003	0	.0001
TF C/D_{NG2}	0	1	1	0	1	*TF*DNG2*	.00003	0	.0001
TF C/D_{chi}	55	183	151	100	51				
TF D_{chi}	0	1	1	1	0	*TF*Dchi*	.00573	.0064	.0048
Total	4,638	15,132	13,314	7,973	5,341				

[a] See text for definition of populations. [b] HR and NG are abbreviations for Hiroshima and Nagasaki, respectively.

classifiable into nine types, *i.e.*, TF D_{chi}, TF D_{HR1}, TF D_{HR2}, TF D_{HR3}, TF D_{HR4}, TF D_{HR5}, TF D_{HR6}, TF D_{NG1}, and TF D_{NG2}. Except for one homozygous phenotype TF D_{chi}, all the other variants were heterozygous for a normal allele, *TF*C*, and variant alleles. TF D_{HR2} was detected only in one family in Hiroshima and TF D_{NG1} and TF D_{NG2} each only in one family in Nagasaki. TF D_{HR3}, TF D_{HR4}, and TF D_{HR5} were observed only in Hiroshima (Table 1). Earlier, Ferrell *et al.* (1977) reported TF D_{chi}, TF D_{HIR1}, TF D_{HIR2}, TF D_{HIR3}, and TF D_{NGS1}. However, the authors' reexaminations revealed that TF D_{HIR3} could be classified into two different types of variant, *i.e.*, TF D_{HR3} and TF D_{HR4}. The RM values of TF D_{HR3} and TF D_{HR4} were 1.08 and 1.18, respectively, in pH 8.5 PAGE, but were 0.94 and 1.55 in pH 6.5 PAGE and their pI clearly differed from each other. The pI of TF D_{HR6} was the same as that of TF D_{HR2}, but the RM values of the two were different in PAGE at any pH level.

Table 2. Relative mobilities of transferrin variants on polyacrylamide slab gel electrophoresis with three buffer systems.

Variant	System		
	PAGE pH 8.5	PAGE pH 7.5	PAGE pH 6.5
TF B_{HR1}	0.71	0.76	0.66
TF B_{HR2}	1.00	1.00	1.00
TF B_{HR3}	1.15	1.12	1.12
TF B_{HR4}	1.40	1.40	1.38
TF B_{HR5}	0.69	0.68	0.00
TF B_{HR6}	1.40	1.40	1.27
TF B_{NG1}	1.17	1.20	1.27
TF B_{ME1}	0.85	0.87	0.66
TF B_{ME2}	1.20	1.22	0.89
TF B_{AA1}	0.90	0.90	0.80
TF B_{AA2}	1.00	0.95	0.90
TF B_{AA3}	1.00	1.05	1.05
TF B_{AA4}	1.47	1.47	1.45
TF D_{HR1}	0.48	0.71	0.81
TF D_{HR2}	0.67	0.81	0.81
TF D_{HR3}	1.08	1.04	0.94
TF D_{HR4}	1.18	1.19	1.55
TF D_{HR5}	1.87	1.94	1.97
TF D_{HR6}	0.90	0.90	0.94
TF D_{NG1}	0.67	0.84	0.61
TF D_{NG2}	1.18	1.13	1.23
TF D_{chi}	1.00	1.00	1.00
TF D_{ME1}	1.58	1.60	1.55
TF D_1	1.04	1.03	1.00
TF D_{AA1}	1.06	1.04	1.00
TF D_{GUA1}	1.23	1.25	1.05

TF D_{NG2} showed the same RM as TF D_{HR4} in pH 8.5 PAGE, but the former showed an RM of 1.23 and the latter 1.55 in pH 6.5 PAGE. Also, the pI definitely differed (Table 2 and Fig. 1).

The frequency of *TF*Dchi*, which varied widely in Mongoloids, was 0.0064 in Hiroshima and 0.0048 in Nagasaki, an insignificant difference; nor was there any significant difference in the frequency of any of the other D-variants between the two cities (Table 1).

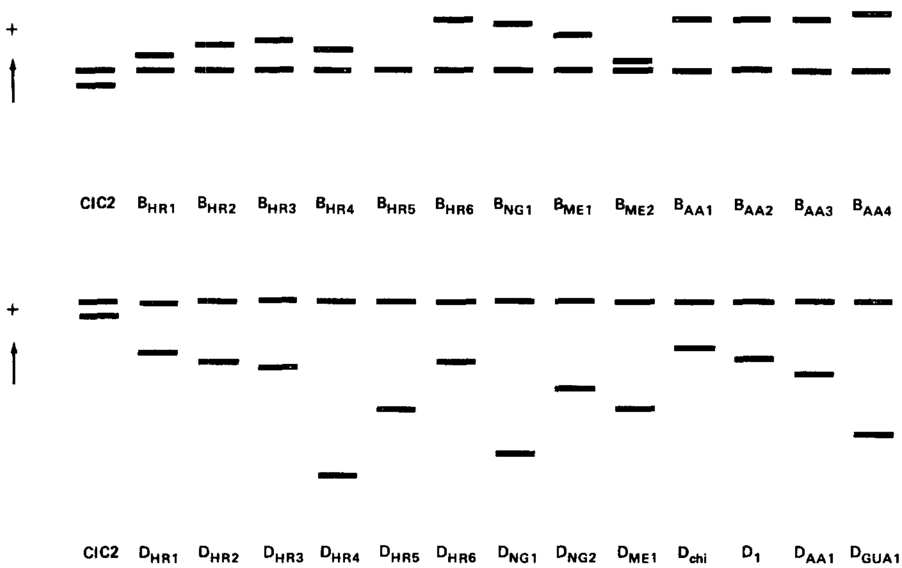

Fig. 1. Diagram of heterozygous transferrin variants on thin layer polyacrylamide gel isoelectric focusing. Only the name of variants are shown in the diagram though it is drawn on the basis of phenotypes heterozygous with C1.

The new nine variants encountered in this study, *i.e.*, TF B_{HR1}, TF B_{HR3}, TF B_{HR5}, TF B_{HR6}, TF B_{NG1}, TF D_{HR4}, TF D_{HR5}, TF D_{HR6}, and TF D_{NG2}, were confirmed to be inheritable by family studies. Even though the differences that distinguish one variant from another are small, they are evident on either PAGE or PAGIF, in samples from carrier parent.

2) Comparison with TF variants detected in another Japanese population, Caucasoids, American blacks, and Amerindians

The variants discovered in Mie district were compared in the same gels with those of Hiroshima and Nagasaki. Of nine from Mie, three had different mobilities from any of Hiroshima and Nagasaki variants, being named TF B_{ME1}, TF B_{ME2}, and TF D_{ME1}. Six of these were identical with TF B_{HR1}, TF B_{HR4}, TF B_{HR5}, TF D_{HR5}, TF D_{NG1}, and TF D_{chi}. Among the variants in Japanese population, TF B_{HR5} and TF D_{chi} were observed in the three districts, while TF B_{HR2} with relatively high frequencies in Hiroshima and Nagasaki was not found in Mie.

Six types of TF variant, *i.e.*, TF B_{AA1}, TF B_{AA2}, TF B_{AA3}, TF B_{AA4}, TF D1, and TF D_{AA1} were identified in samples from Ann Arbor. TF D1 was detected in Caucasians and American blacks, while TF D_{AA1} was only detected in Caucasians. TF B_{AA1}, TF B_{AA2}, and TF B_{AA3} showed the same pI as TF B_{HR6}, while TF B_{AA2} and TF B_{AA3} showed the same RM as TF B_{HR2} in pH 8.5 PAGE. However TF B_{AA2} and TF B_{AA3} were distinguishable in pH 7.5 or 6.5 PAGE (Table 2 and Fig. 1).

None of Ann Arbor variants corresponded to any of those found in Japanese population.

TF D_{chi} found in Amerindians had the same mobility as the one detected in Japanese population on PAGE or PAGIF. TF D_{GUA1} differed in its mobility from those de tected in other populations.

DISCUSSION

The present study has demonstrated, in a sample of 19,770 persons from two Japanese cities, 16 different TF variants. This figure approximates the total number of such variants that have thus far been differentiated by SGE and PAGE in reports from all over the world, as illustrated by the summaries of Giblett (1969) (17 variants) and Sutton and Jamieson (1972) (20 variants) excluding those subtypes detected by PAGIF. The question immediately arises whether the Japanese are unusually variable in this respect or whether any carefully conducted study of this magnitude on a civilized population with great internal mobility would yield similar findings. The answer is not known, but the fact that the average indices of heterozygosity for some 23 proteins scored in Caucasians and Japanese were 0.078 and 0.077, respectively (Neel *et al.*, 1978), does not suggest unusual genetic variability in Japanese.

It is in this connection important that the validity of the variants we are reporting is in all instances backed up by family studies indicating a variant of identical mobility in some other member of the propositus' family, and also by repeated, direct comparisons of fresh or well preserved samples of the various variants. Thus we doubt that any of the small differences on which the distinctions between certain variants are based are artifactual in nature.

None of the variants reported here achieve polymorphic proportions, but the *TF*Dchi* allele, polymorphic in many Mongoloid populations, does have an allele frequency of 0.0057. The next highest allele frequency is that of *TF*BHR2*, of 0.0024. Most of the remaining variants are quite rare, five having been thus far encountered in only a single family. Among the variable loci in Japanese, the TF 'variant profile' thus appears intermediate between a locus such as phosphoglucomutase-1, with relatively many rare variants but also two polymorphisms (Satoh *et al.*, 1984b), and the glucose-6-phosphate dehydrogenase locus (Kageoka *et al.*, 1985), with many rare variants but all in very low frequencies, even lower than the TF variants.

We note that only one of the eight variants from Amerindians, Caucasoids, and American blacks from the Ann Arbor collection corresponds in mobility to a Japanese variant, this being the polymorphic TF D_{chi} encountered in Amerindians. This finding further attests to the multiplicity of low frequency variants at this locus. (Apparently identical electrophoretic behaviors would not of course assure variant identity, but clear differences in well-preserved samples do establish nonidentity.)

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