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Review articles

Ethnic variation in vitamin D-binding protein (GC): a review of isoelectric focusing studies in human populations

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Summary. Since the discovery in 1977 that the GC1 gene could be resolved into two common subcomponents on an isoelectric focusing (IEF) gel, a large number of ethnic groups have been screened to analyze the extent of genetic variation in human populations. Using the IEF technique, approximately 50,000 individuals from 160 different populations have been tested for the GC polymorphism. A marked variation in common GC suballele frequencies in different geographic areas seems to correlate with skin pigmentation and intensity of sun light. Pigmented (black) and keratinized (yellowish) skin type populations have a relatively high frequency of the *GC*IF* allele as compared to white skin populations. By comparison non-pigmented and non-keratinized white skin populations are generally characterized by having the maximum values of the *GC*IS* allele. The anthropologic significance of the GC locus has been enhanced further by detecting additional unique GC variants which provide useful information about evolutionary links between different populations. However, the presence of some electrophoretically identical unique variants in genetically and geographically distinct populations demand further investigation of these allelic variants to shed more light on their origins.

Introduction

In the last three decades, since the discovery by Smithies (1955) that mixtures of proteins can be separated by electrophoresis in starch gels, biologic anthropologists and forensic scientists have developed other electrophoretic support media, including polyacrylamide, agarose and cellulose acetate, to resolve genetically determined variations in proteins and enzymes from blood and other body fluids. About one third of the loci studied by these electrophoretic methods have been found to be polymorphic in human populations (Harris 1980).

In conventional electrophoresis the separation of protein components depends on relative differences in net charge, shape, and molecular size, and the separation usually takes place at constant pH and ionic strength. However, these conventional methods of electrophoresis do not permit adequate differentiation in macromolecules having similar or identical molecular size and conformation, but slightly different isoelectric points. The development of the isoelectric focusing (IEF) technique utilizing different supporting media (Svensson 1961, 1962; Vesterberg and Svensson 1966; Fawcett 1968; Riley and Coleman 1968) has made possible the discrimination of such protein molecules by allowing differentiation of proteins having a difference of isoelectric point as small as 0.01 pH units.

Using conventional methods of electrophoresis, approximately one third of the possible amino acid substitutions can be detected by differences in electrophoretic migration (Harris 1980; Ayala 1982). The IEF technique can detect differences in the isoelectric point conferred on a protein indirectly by amino acid substitutions which do not directly involve amino acids with a charged side chain (Constans et al. 1983b).

In IEF a voltage gradient is applied to a complex mixture of buffer components known as carrier ampholytes (a mixture of aliphatic amino-carboxylic acids with molecular weight between 300–600). The electric field produces a pH gradient between a strong base as catholyte and a strong acid as anolyte. When a protein is introduced in this pH gradient it migrates along the pH gradient until the differences between its isoelectric point and the pH of the gradient approaches zero. In this way very small differences in isoelectric points between protein molecules can be detected. The high resolution achieved by IEF is due to an inherent concentrating effect which counteracts the diffusion which occurs in conventional electrophoresis. The detailed mechanism of IEF has been discussed by Righetti and Drysdale (1976).

The routine application of IEF has added a new dimension in population genetic studies by the detection, not only of additional alleles at many loci, but also by revealing additional polymorphic variation at loci which had appeared to be monomorphic when examined by conventional methods of electrophoresis. For example alpha-1-antitrypsin or proteinase inhibitor (PI) and transferrin (TF) – two serum proteins – were considered to be monomorphic in most human populations. With the application of the IEF technique these proteins have turned out to be highly polymorphic. Likewise, the heterozygosities of the vitamin D-binding protein or group-specific component (GC) and phosphoglucomutase-1 (PGM1) have been increased by the discoveries of new alleles at these loci.

In addition to these four systems the data on IEF for other blood genetic markers is increasing rapidly. However, the literature best documents the application of IEF to these four systems and an enormous amount of population data has ac-

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cumulated. It is beyond the scope of this paper to cover all these systems. Therefore, we have attempted to review current IEF data on GC in a large number of population groups. In addition to the common allelic forms the significance of some unique variants at the GC locus in population differentiation is discussed.

Historical background

The group-specific component (GC) in human serum was first detected immunologically by Hirschfeld (1959). In the same year Thomas et al. (1959) reported a vitamin D-binding α-globulin (DBP) present in human serum. The biologic function of GC remained unknown until Daiger et al. (1975) showed that GC is the serum transport protein of vitamin D and its metabolites, and it is now well established that DBP and GC are identical proteins (Bouillon et al. 1976; Haddad and Walgate 1976; Imawari and Goodman 1977; Cleve and Patutschnick 1977; Svasti and Bowman 1978; Kawakami and Goodman 1981).

GC is a serum α_2-globulin. It consists of a single polypeptide chain of molecular weight 52,000–56,000 (Svasti et al. 1979; Coue et al. 1983) and contains one vitamin D-related sterol binding site per molecule of protein. GC is produced primarily in the liver. It circulates in the serum essentially as an apoprotein which is the form free of ligands. The normal concentration of GC in plasma is 300–600 ug/ml (see Kawakami and Goodman 1981). However, there is a slight decrease in these values in liver cirrhosis patients (Cleve and Dencker 1966; Kawai et al. 1983). Apo GC can be detected after electrophoresis of serum followed by print-immunofixation using a specific GC antibody (Constans et al. 1979a).

The GC protein displays genetic polymorphism. Three common phenotypes GC 1-1, GC 2-1, GC 2-2 were first detected by immunoelectrophoresis (Hirschfeld 1959) and subsequently inheritance data showed that these phenotypes are controlled by two autosomal codominant alleles, *GC*1* and *GC*2* at the GC locus (Hirschfeld et al. 1960). In addition to the immunoelectrophoresis technique, GC phenotypes may also be visualized by starch gel electrophoresis (see Cooper 1978), agarose gel electrophoresis followed by immunofixation (Johnson et al. 1975), and polyacrylamide gel electrophoresis (Kitchin 1965). Gel electrophoresis shows that the GC 1-1 phenotype consists of two protein bands, GC 1fast and GC 1slow, with almost equal intensities, whereas the GC 2-2 phenotype is manifested by one major band. The difference between GC 1fast and GC 1slow is posttranslational in nature, involving a difference in the number of sialic acid residues (Svasti and Bowman 1978; Cleve and Patutschnick 1979), while the difference between GC 1 and GC 2 is due to a difference in primary structure (Svasti et al. 1979).

In addition to the difference in sialic acid residues between the fast and slow GC 1 components, Constans et al. (1983a) have observed an extra sialic acid residue in the GC 1 protein present in patients with alcoholic cirrhosis. Similarly, it has been reported now that the fast and slow components of three new GC 1 mutants contain different numbers of sialic acid residues (Thymann et al. 1985). In contrast, although it is well known that the single band GC variants remain unaltered after neuraminidase treatment, recently Nakasono et al. (1983, 1985) described two new GC single band variants which contain neuraminidase sensitive sialic acid residues.

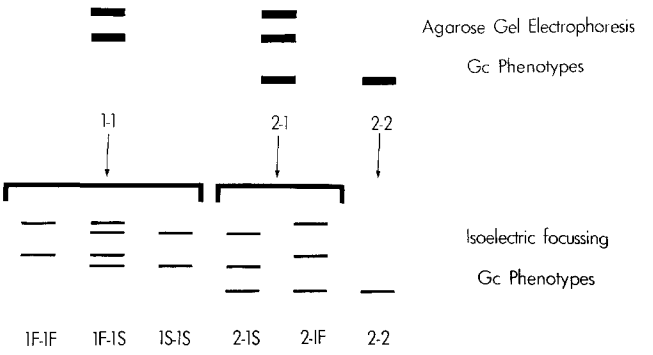

Fig. 1. Diagrammatic representation showing the difference in the numbers of common GC phenotypes obtained by IEF and conventional agarose gel electrophoresis

In addition to the occurrence of two common alleles, there are a number of other variants, most of which are rare (Cleve 1973; Cooper 1978). With the introduction of IEF the GC polymorphism was extended from two to three common alleles due to the discovery of the *GC*1* subtypes, *GC*1F* and *GC*1S* (Constans and Viau 1977). This allows six common phenotypes, 1F, 1S, 1F1S, 2-1F, 2-1S, and 2 (Fig. 1) to be identified. At an international workshop on the GC system held in July 1978 (Constans et al. 1979b), a new nomenclature was developed for the designation of the increasing number of GC variants. Double band variants were called GC 1 and single band variants GC 2. Furthermore, the cathodal band of GC 1S was considered as the reference for double-banded variants. All double-banded variants, which are anodal to GC 1S, are called GC 1A and all double-banded variants which are cathodal to GC 1S are called GC 1C. Similarly, any single-banded variant more anodal than GC 2 is called GC 2A and more cathodal to GC 2 is called GC 2C.

Several other new variants, unresolved by conventional electrophoresis, have been delineated by IEF and the total number of mutant alleles at the GC locus now exceeds 80. An up-to-date list of GC variants is given in Table 1 and their diagrammatic representation is presented in Fig. 2.

World distribution of GC variants

A survey of the literature reveals IEF data for GC gene frequencies on 160 population groups (Table 2). This makes GC the most intensively studied blood genetic marker using IEF. The extended polymorphism at the GC locus shows three common alleles and a large number of unique variants which are markers of certain racial groups. Due to the importance of both common and specific genes in population differentiation we will discuss them separately.

Common alleles

The classification based on traditional methods permits only two common alleles, *GC*1* and *GC*2*, to be recognized at the GC locus. The variation in the *GC*2* allele frequency was considered to be the criteria to differentiate between populations. In general the *GC*2* allele frequency is higher in Caucasians and their derivatives than in Black populations. The only population completely devoid of the *GC*2* allele are the Tuareq Kel Kummar of Mali from the Southern Sahara. The absence of *GC*2* in this small group is best explained by ge-

Table 1. List of GC variants

GC Variant	Reference
1A1	Cleve et al. (1963)
1A2	Daiger and Cavalli-Sforza (1977)
1A3	Matsumoto (Ref. Constans et al. 1979b)
1A4	Cox et al. (1978)
1A5	Constans et al. (1979b)
1A6	Constans et al. (1979b)
1A7	Constans et al. (1979b)
1A8	Constans et al. (1979b)
1A9	Constans et al. (1979b)
1A10	Cleve et al. (1981)
1A11	Cleve et al. (1981)
1A12	Cleve et al. (1981)
1A13	Cleve et al. (1981)
1A14	Cleve et al. (1981)
1A15	Constans et al. (1983b)
1A16	Constans et al. (1983b)
1A17	Constans et al. (1983b)
1A18	Constans et al. (1983b)
1A19	Constans et al. (1983b)
1A20	Constans et al. (1983b)
1A21	Kamboh et al. (1984)
1A22	Kamboh et al. (1984)
1A26	Goedde et al. (1985)
1F	Constans and Viau (1977)
1S	Constans and Viau (1977)
1C1	Constans et al. (1978a)
1C2	Constans et al. (1979b)
1C3	Constans et al. (1979b)
1C4	Constans et al. (1979b)
1C5	Constans et al. (1979b)
1C6	Constans et al. (1979b)
1C7	Constans et al. (1979b)
1C8	Constans et al. (1979b)
1C9	Litwiak and Henningsen (1977)
1C10	Constans et al. (1979b)
1C11	Cleve et al. (1981)
1C12	Dykes and Polesky (1982)
1C13	Thymann et al. (1982)
1C14	Thymann et al. (1982)
1C15	Constans et al. (1983b)
1C16	Constans et al. (1983b)
1C17	Constans et al. (1983b)
1C18	Constans et al. (1983b)
1C19	Constans et al. (1983b)
1C20	Constans et al. (1983b)
1C21	Constans et al. (1983b)
1C22	Constans et al. (1983b)
1C23	Dykes et al. (1983)
1C24	Kamboh et al. (1984)
1C25	Constans et al. (1983b)
1C26	Constans et al. (1983b)
1C27	Constans et al. (1983b)
1C28	Constans et al. (1983b)
1C29	Constans et al. (1983b)
1C30	Constans et al. (1983b)

Table 1 (continued)

GC Variant	Reference
1C31	Dykes et al. (1983)
1C32	Dykes et al. (1983)
1C33	Dykes et al. (1983)
1C34	Constans et al. (1983b)
1C35	Yuasa et al. (1983b)
1C35 Aborigines	Kamboh et al. (1984)
1C36	Yuasa et al. (1983a)
1C37	Constans et al. (1983b)
2A1	Constans et al. (1979b)
2A2	Vavrusa and Cleve (1974)
2A3	Constans et al. (1978b)
2A4	Constans et al. (1979b)
2A5	Constans et al. (1979b)
2A6	Speiser et al. (1972)
2A7	Cleve et al. (1981)
2A8	Weidinger et al. (1981)
2A9	Thymann et al. (1982)
2A10	Constans et al. (1983b)
2A11	Constans et al. (1983b)
2A12	Constans et al. (1983b)
2A13	Constans et al. (1983b)
2AR	Nakasono et al. (1985)
2C1	Constans et al. (1979b)
2C2	Cleve et al. (1966)
2C3	Weidinger et al. (1981)
2C4	Constans et al. (1983b)
2C5	Thymann et al. (1982)
2C6	Thymann et al. (1982)
2C7	Constans et al. (1983b)
2C8	Constans et al. (1983b)
2C9	Constans et al. (1983b)
2C10	Constans et al. (1983b)

netic drift or founder effect (Constans et al. 1980a). Although the frequency of *GC*2* gives some indication of overall population variation, its similar frequency in Europeans and Mongoloids cannot differentiate these groups. However, two sub-alleles of GC 1, *GC*1F,* and *GC*1S* clearly separate these two genetically distinct populations.

There is significant variation in the distribution of the two sub-allele frequencies in different ethnic groups. Europeans and closely related populations are characterized by having the maximum values of the *GC*1S* allele which vary from 50 to 60%. By comparison, Negroes from Africa and America have a low incidence of the *GC*1S* allele. However, they demonstrate a common feature in having the highest frequencies of the *GC*1F* allele. The range of *GC*1F* frequencies in Black Americans is more or less uniform and varies from 67 to 79%. However there is extreme geographical variation in the frequency of the *GC*1F* allele among African populations. North and East Africans have a *GC*1F* frequency slightly lower than 50% and in some cases nearly equal to the *GC*1S* frequency. The frequencies of *GC*1F* and *GC*1S* in these groups indicate gene flow from Middle East populations. The *GC*1F* allele frequency is higher in South and West Africa, ranging from 60 to 83%.

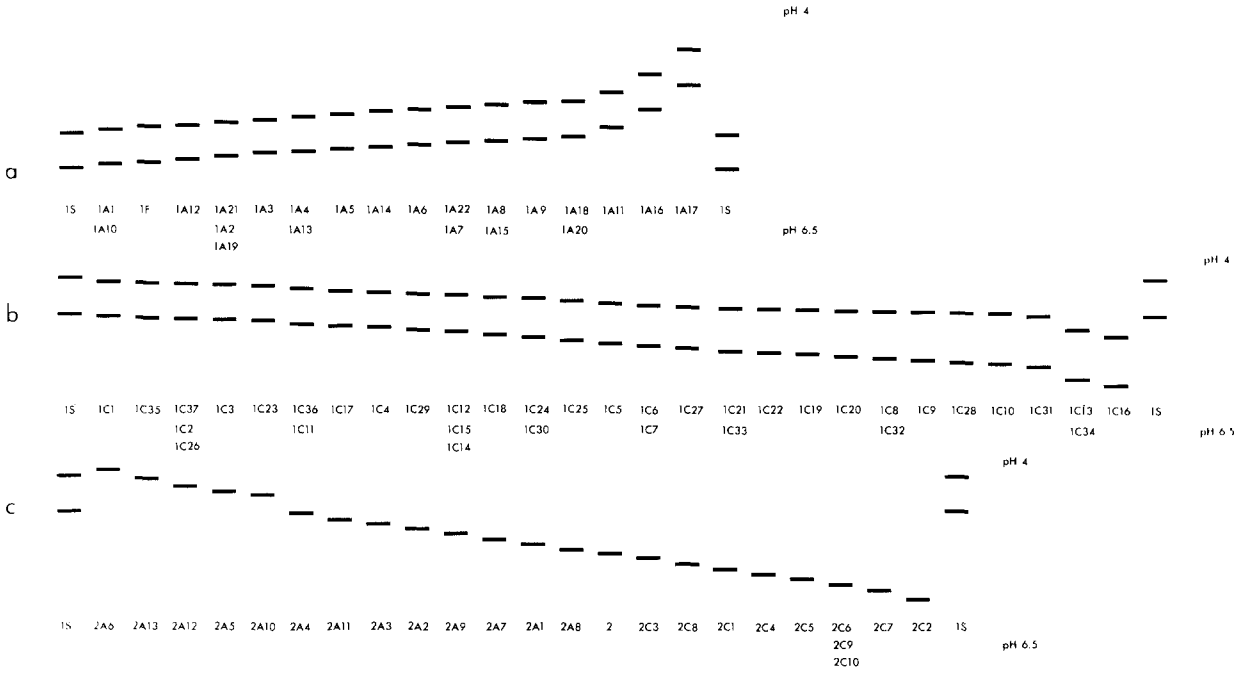

Fig. 2a–c. Diagrammatic representation of GC patterns detectable on IEF: **a** double-banded *GC*1* variants anodal to the GC 1S; **b** double-banded *GC*1* variants cathodal to the GC 1S; **c** single-banded *GC*2* variants anodal and cathodal to the GC 2

The Black Caribs from Central America, an African-Amerindian hybrid population, have a *GC*1F* frequency of less than 50%, but Black Carib populations are known to show strong founder effects for alleles at several genetic loci. In North American Indians the *GC*1F* frequencies vary from 30 to 40% whereas South American Indians have particularly low frequencies for the *GC*1F* allele, ranging between 20–33%.

There are only two published reports on GC subtyping for Eskimos residing in Alaska and they do not coincide. Our unpublished data on Eskimos from Kodiak Island, Alaska also indicate some variation and this probably reflects different sampling localities with variable local white admixture.

East and Southeast Asian populations have a *GC*1F* frequency of about 50% and similar values are also present in most Pacific populations. Exceptionally high values of *GC*1F* (72–79%) and correspondingly low values of allele *GC*2* (5–6%) have been observed in two samples from Malaysia in Malay and Bidayal (Tan et al. 1981). The same authors have reported consistently higher frequencies of *GC*1F* in Indonesians and Chinese than have been observed by others (Table 2). The reported pattern of GC frequencies in Malaysia is very similar to those in Blacks. However, it would be interesting to look at more populations in Southeast Asia before making any suggestion about possible Black ancestry or admixture in these groups.

Most of the populations in the Pacific region including Australia have very similar frequencies for the two GC suballeles. In Polynesians the range of the *GC*1S* and *GC*1F* values is between 27–36% and Melanesians have relatively high values varying from 31–40%. The Australian Aborigines have about 40% frequency of both the *GC*1F* and *GC*1S* alleles.

The pattern of GC allele frequency variation is presented in a simple graphical way in Fig. 3. The triangular display presents the frequencies for the three common GC alleles (data from Table 2). Only representative populations from each ethnic group have been chosen for this analysis. However, average values have been calculated in certain cases to remove discrepancies in allele frequencies. The most apparent divergence in Fig. 3 is in the extreme and distinct clusters of Blacks and Europeans. This difference is mainly due to their extreme frequencies for *GC*1F* and *GC*1S* alleles. The European cluster includes Asiatic Indians on one side and Middle Easterns on the other, all sharing similar GC frequencies. Amerindians occupy rather an isolate position but again not far away from the European cluster. A third and distinct cluster of populations include East and Southeast Asians together with Polynesians. It is interesting to note in this context that a close relationship between east Asians and Polynesians has been observed previously using data from a single locus or multiple loci (Kirk 1982a, b; Serjeantson et al. 1982, 1983; Kamboh et al. 1983). These genetic results coincide with archaelogical studies reviewed by Bellwood (1978). The scattered positions of Micronesians (Nauru and Kiribati), Melanesians (Fiji and New Caledonia), and Australian Aborigines indicate differences between them. However, their sequential distribution provide evidence of a genetic relationship between Pacific populations.

Unique alleles

Like other blood traits GC has also several unique alleles which are potentially important in population discrimination. However, most of the rare allelic variants have a highly restricted distribution. We will discuss here those mutants which provide information about population movements and antiquity and ignore those identified only in single families or isolated groups.

One of the first and most important GC variants, which has gained considerable attention from physical anthropolo-

Table 2. World distribution of GC allele frequencies

Population	Number tested	1F	1S	2	Others	Reference
Europe						
Germany						
South Germany	1523	0.14	0.60	0.26	<0.01	Weidinger et al. (1981)
Düsseldorf	1156	0.16	0.55	0.29	<0.01	Scheil et al. (1980)
Munich	440	0.14	0.59	0.26	<0.01	Cleve et al. (1978)
Marburg	146	0.17	0.55	0.27	<0.01	Cleve et al. (1978)
Hessen	261	0.13	0.60	0.27	–	Kühnl et al. (1978)
United Kingdom						
English	100	0.16	0.57	0.26	–	Papiha et al. (1982a)
Asians	243	0.19	0.52	0.29	–	Karlsson et al. (1983b)
France						
Toulouse	256	0.13	0.54	0.31	<0.01	Constans et al. (1979b)
Lille	114	0.20	0.55	0.24	–	Constans et al. (1979b)
Basques	200	0.06	0.55	0.39	–	Constans et al. (1979b)
Pyrenean	290	0.08	0.51	0.41	–	Constans et al. (1978a)
Alps (Savore)	285	0.14	0.53	0.30	<0.01	Constans et al. (1979a)
Strasbourg	112	0.12	0.59	0.27	<0.01	Constans et al. (1979a)
Belgium						
Liege	267	0.16	0.54	0.29	–	Hoste (1979)
Italy						
Latium	1235	0.14	0.57	0.28	–	Petrucci and Congedo (1983)
Italy	147	0.14	0.58	0.26	–	Cleve et al. (1978)
Sweden	3394	0.14	0.61	0.25	<0.01	Svensson and Hjalmarsson (1981)
Spain						
Basques	190	0.09	0.57	0.34	–	Constans et al. (1985)
Denmark						
Copenhagen	1674	0.15	0.57	0.26	<0.01	Thymann (1981)
Copenhagen	390	0.14	0.60	0.25	–	Constans et al. (1979a)
Iceland	382	0.10	0.63	0.26	–	Karlsson et al. (1983a)
USSR						
Siberia	227	0.52	0.28	0.20	–	Dykes and Polesky (1984)
North America						
USA Whites						
Pennsylvania	110	0.14	0.57	0.27	–	Kueppers and Harpel (1979)
Minnesota	7247	0.15	0.56	0.27	–	Dykes et al. (1983)
Mennonites	611	0.11	0.56	0.31	–	Dykes et al. (1983)
Minneapolis	1376	0.17	0.56	0.26	–	Dykes and Polesky (1982)
California	404	0.28	0.49	0.21	<0.01	Garber et al. (1983)
USA Blacks						
Philadelphia	273	0.68	0.17	0.13	0.02	Kueppers and Harpel (1979)
Georgia	219	0.79	0.12	0.08	0.01	Kueppers and Harpel (1979)
Minnesota	540	0.67	0.18	0.10	0.03	Dykes et al. (1983)
Baltimore	126	0.67	0.17	0.13	0.03	Constans et al. (1985)
USA Amerindians						
Apache	457	0.31	0.59	0.08	–	Dykes et al. (1983)
Aache	127	0.29	0.66	0.03	–	Dykes et al. (1983)

Table 2 (continued)

Population	Number tested	1F	1S	2	Others	Reference
USA Amerindians						
Blackfeet	74	0.18	0.61	0.19	–	Dykes et al. (1983)
Cocopa	135	0.37	0.44	0.18	–	Dykes et al. (1983)
Chippewa	249	0.31	0.46	0.19	0.04	Dykes and Polesky (1984)
Lumbee	242	0.20	0.48	0.32	<0.01	Constans et al. (1985)
Pima	58	0.47	0.41	0.11	–	Constans et al. (1985)
Maricopa	68	0.39	0.42	0.18	–	Dykes et al. (1983)
Navajo	103	0.40	0.52	0.06	–	Dykes et al. (1983)
Pima	332	0.44	0.41	0.14	–	Dykes et al. (1983)
Walapi	115	0.34	0.57	0.07	–	Dykes et al. (1983)
Yakima	92	0.31	0.56	0.13	–	Dykes et al. (1983)
USA Eskimos						
Alaska	307	0.26	0.35	0.33	0.06	Dykes et al. (1983)
Alaska	328	0.27	0.49	0.19	0.05	Matsumoto et al. (1980)
Kodiak Island	219	0.17	0.51	0.31	0.01	Kamboh and Ferrell (unpublished)
South America						
Indians						
Brazil						
Gorotire	155	0.20	0.42	0.35	0.03	Constans and Salzano (1980)
Kraho	136	0.33	0.29	0.38	–	Constans and Salzano (1980)
Caingang	106	0.20	0.48	0.32	–	Constans and Salzano (1980)
Napoleao	60	0.43	0.50	0.07	–	Salzano et al. (1984)
Guariba	82	0.43	0.43	0.14	–	Salzano et al. (1984)
Tanajuara	107	0.52	0.40	0.08	–	Salzano et al. (1985)
Santo Andre	109	0.39	0.34	0.27	–	Salzano et al. (1985)
Toconao	176	0.30	0.47	0.23	–	Goedde et al. (1985)
Bolivia						
Aymara-Quechua	253	0.23	0.64	0.12	0.01	Constans and Salzano (1980)
Guyana						
Palikour	104	0.14	0.61	0.17	0.08	Constans et al. (1985)
Peru						
Machiguenga	180	0.10	0.60	0.28	–	Matsumoto et al. (1980)
Quechua	97	0.27	0.59	0.11	<0.01	Matsumoto et al. (1980)
Central America						
Mexico						
La Manita	128	0.35	0.50	0.14	–	Dykes et al. (1983)
Chamizal	102	0.34	0.48	0.17	–	Dykes et al. (1983)
Black Caribs						
St. Vincent	311	0.49	0.36	0.12	0.01	Dykes et al. (1983)
Livingston	215	0.63	0.25	0.10	–	Dykes et al. (1983)
Stann Creek	274	0.53	0.31	0.15	–	Dykes et al. (1983)
Punta Gorda	217	0.55	0.30	0.14	–	Dykes et al. (1983)
Guatemala (Lxil)	108	0.37	0.51	0.12	–	Constans et al. (1985)
North and East Africa						
Tunisia	98	0.26	0.52	0.21	–	Lefranc et al. (1981)
Mali						
Tuareg Kel Kummer	260	0.31	0.67	–	<0.01	Constans et al. (1980a)

Table 2 (continued)

Population	Number tested	1F	1S	2	Others	Reference
North and East Africa						
Djibouti Republic						
Harratins	161	0.48	0.44	0.05	0.01	Constans et al. (1980a)
Issa	92	0.43	0.43	0.12	0.01	Constans et al. (1980a)
Afar	95	0.46	0.35	0.17	–	Constans et al. (1980a)
Algeria						
Tuareg Issequamaren	160	0.42	0.54	0.01	0.01	Constans et al. (1980a)
Ethiopia						
Erythrean	126	0.50	0.36	0.13	0.01	Constans et al. (1985)
Equatorial Africa						
Central African Empire						
Sara	291	0.83	0.09	0.06	<0.01	Constans et al. (1980a)
Pygmies Bi-Aka	751	0.61	0.18	0.07	0.12	Constans et al. (1980a)
Pygmies Bi-Aka	267	0.58	0.19	0.06	0.16	Constans et al. (1978a)
Pygmies Bi-Aka	335	0.60	0.18	0.08	0.12	Constans et al. (1981b)
South Africa						
Transkei (Bantu)	126	0.84	0.10	0.05	0.01	Papiha et al. (1985)
Malagasy (East/West Coast)	247	0.68	0.12	0.16	0.04	Constans et al. (1985)
West Africa						
Senegal						
Peulhs	357	0.78	0.11	0.05	0.05	Constans et al. (1978b)
Gambia						
Keneba	186	0.85	0.10	0.03	0.02	Papiha et al. (1985)
Manduar	84	0.88	0.08	0.02	0.02	Papiha et al. (1985)
Cameroon (Bantu)	123	0.82	0.08	0.09	0.01	Constans et al. (1985)
Asia						
India						
Delhi	488	0.14	0.55	0.31	–	Kamboh et al. (1984)
Madras	235	0.15	0.54	0.31	–	Kamboh et al. (1984)
Soliga (tribal)	79	0.08	0.74	0.18	–	Kamboh et al. (1984)
Punjab	146	0.15	0.53	0.31	<0.01	Papiha et al. (1982a)
Sangla, Himachal	97	0.16	0.65	0.18	–	Papiha et al. (1983)
Pub, Himachal	139	0.17	0.55	0.28	–	Papiha et al. (1983)
Nachar, Himachal	93	0.12	0.59	0.29	–	Papiha et al. (1983)
Pondicherry (Tamil)	112	0.14	0.63	0.23	–	Constans et al. (1985)
Bharmour	70	0.16	0.54	0.30	–	Papiha et al. (1983)
Chuwari	62	0.12	0.58	0.30	–	Papiha et al. (1983)
Chuwari	145	0.13	0.59	0.28	–	Papiha et al. (1983)
Churah	118	0.11	0.61	0.28	–	Papiha et al. (1983)
Palampur	141	0.17	0.53	0.30	–	Papiha et al. (1983)
Nepal	144	0.24	0.48	0.27	–	Yuasa et al. (1983a)
Nepal	195	0.25	0.52	0.22	<0.01	Constans et al. (1985)
Iran						
Zoroastrians	236	0.14	0.62	0.22	–	Papiha et al. (1982b)

Table 2 (continued)

Population	Number tested	1F	1S	2	Others	Reference
Asia						
Tibet	230	0.36	0.37	0.24	0.01	Constans et al. (1979b)
Japan						
Mie	510	0.46	0.24	0.26	0.04	Ishimoto et al. (1979)
Tokyo	531	0.48	0.24	0.24	0.02	Ishimoto et al. (1979)
Tokyo	305	0.47	0.26	0.25	0.02	Omoto and Miyake (1978)
Tokyo	100	0.50	0.22	0.27	0.01	Kamboh et al. (1984)
San-in District	173	0.44	0.28	0.26	0.01	Yuasa et al. (1983b)
Osaka	342	0.45	0.25	0.25	0.03	Shibata (1983)
Western Area	1000	0.44	0.24	0.27	0.03	Yuasa et al. (1984)
Osaka	316	0.42	0.30	0.25	0.02	Matsumoto et al. (1980)
Okinawa	502	0.47	0.20	0.31	<0.01	Matsumoto et al. (1980)
Hokkaido – Ainu	271	0.58	0.20	0.21	0.01	Matsumoto et al. (1980)
Hong Kong						
Chinese	362	0.49	0.25	0.24	–	Kwok and Lewis (1981)
Thailand						
Bangkok	199	0.40	0.35	0.24	<0.01	Constans et al. (1985)
Bangkok	59	0.45	0.33	0.22	–	Kamboh et al. (1984)
South Vietnam	186	0.49	0.27	0.23	<0.01	Constans et al. (1985)
Laos	293	0.47	0.38	0.15	–	Constans et al. (1985)
China						
Beijing	113	0.48	0.25	0.26	<0.01	Kamboh et al. (1984)
Korea						
Chonju	303	0.43	0.23	0.30	0.03	Matsumoto et al. (1980)
Taiwan						
Atyal	354	0.58	0.29	0.11	0.01	Matsumoto et al. (1980)
Chinese	373	0.39	0.27	0.30	0.02	Matsumoto et al. (1980)
Indonesia						
Java	176	0.53	0.28	0.17	0.01	Matsumoto et al. (1980)
Borneo	260	0.60	0.26	0.12	<0.01	Matsumoto et al. (1980)
Batak	232	0.62	0.23	0.15	–	Tan et al. (1981)
Java	47	0.58	0.25	0.16	–	Tan et al. (1981)
Minang Kabau	56	0.60	0.25	0.14	–	Tan et al. (1981)
Timore	131	0.55	0.24	0.16	0.04	Kamboh et al. (1984)
Flores	72	0.49	0.31	0.19	<0.01	Kamboh et al. (1984)
Roti	59	0.56	0.29	0.13	0.02	Kamboh et al. (1984)
Sumbawa	100	0.50	0.35	0.15	<0.01	Kamboh et al. (1984)
Bali	161	0.53	0.33	0.13	<0.01	Kamboh et al. (1984)
Bali	294	0.68	0.25	0.07	<0.01	Constans et al. (1985)
Northern Halmahera	185	0.57	0.25	0.18	–	Kamboh et al. (1984)
Malaysia						
Malay	134	0.79	0.15	0.05	–	Tan et al. (1981)
Bidayah	207	0.72	0.22	0.06	–	Tan et al. (1981)
Chinese	121	0.68	0.15	0.16	–	Tan et al. (1981)
Iban	108	0.61	0.27	0.12	–	Tan et al. (1981)
Indians	78	0.14	0.60	0.25	–	Tan et al. (1981)
Middle East						
Iraq						
Kurds	58	0.22	0.59	0.17	<0.01	Constans et al. (1980a)

Table 2 (continued)

Population	Number tested	1F	1S	2	Others	Reference
Middle East						
Israel						
Druze	195	0.22	0.54	0.23	<0.01	Constans et al. (1980a)
Muslims	342	0.21	0.60	0.18	–	Nevo and Cleve (1983)
North Yemen						
Bedouins	135	0.27	0.59	0.14	<0.01	Nevo and Cleve (1983)
Oceania						
Cook Islands	200	0.49	0.25	0.26	–	Kamboh et al. (1984)
American Samoa	153	0.27	0.35	0.38	<0.01	Kamboh et al. (1984)
Western Samoa	192	0.35	0.36	0.29	–	Kamboh et al. (1984)
Wallis Island	205	0.32	0.27	0.40	<0.01	Kamboh et al. (1984)
Kiribati	204	0.49	0.26	0.25	–	Kamboh et al. (1984)
Nauru	201	0.36	0.39	0.24	–	Kamboh et al. (1984)
New Caledonia	77	0.40	0.39	0.21	–	Kamboh et al. (1984)
Fiji	200	0.36	0.34	0.26	0.03	Kamboh et al. (1984)
Papua New Guinea						
Port Moresby	193	0.46	0.23	0.24	0.07	Kamboh et al. (1984)
Sepik River	196	0.37	0.31	0.27	0.05	Kamboh et al. (1984)
Eastern Highlands	173	0.22	0.27	0.33	0.18	Kamboh et al. (1984)
Fore	80	0.24	0.25	0.34	0.16	Constans et al. (1985)
Irian Jaya						
Moni	66	0.38	0.36	0.23	0.03	Constans et al. (1985)
New Hebrides	141	0.29	0.39	0.28	0.04	Constans et al. (1985)
Solomon Islands	66	0.39	0.30	0.31	–	Constans et al. (1985)
Mariana Islands	88	0.38	0.36	0.25	0.01	Constans et al. (1985)
Marquesas Islands	166	0.44	0.30	0.26	–	Constans et al. (1985)
Australia						
Aborigines						
Central Desert	216	0.39	0.43	0.10	0.08	Kamboh et al. (1984)
Mowanjum	143	0.27	0.40	0.23	0.10	Kamboh et al. (1984)
Bathurst Island	37	0.38	0.43	0.04	0.15	Kamboh et al. (1984)
Adelaide (White)	400	0.14	0.56	0.30	–	Nicholls and Mulley (1982)

gists and population geneticists since its discovery two decades ago, is the GC Ab or GC 1A1 (according to the new nomenclature). This variant is widely distributed in Pacific and Australian Aboriginal populations (Cleve 1973; Kirk 1980). The highest frequency, about 17%, is observed in Eastern Highlanders from Papua New Guinea. In Australia the incidence of this allelic variant varies from 0.4% to 6%. The *GC*1A1* is present sporadically in Polynesians and Melanesians and exists at a polymorphic level in some Melanesian groups and the Lesser Sunda Islanders from Indonesia (Kamboh et al. 1984). The patchy distribution of the *GC*1A1* allele in Indonesia and a pattern of increasing frequency in the population of the Pacific and Australia correspond broadly with the distribution of the transferrin D1 (TF D1) variant in these populations (Kirk 1980; Kamboh and Kirk 1983), suggesting that peopling of the Pacific occurs through Southeast Asia.

In addition to this variant, IEF has permitted in the delineation of additional anthropologic relationships using unique GC alleles in the Australian-Asian area (Kamboh et al. 1984). Of these new alleles *GC*1C24* provides ancestral links between aboriginal populations of Australia and Indonesia. This allele is present with a frequency of 13% in an aboriginal population on the West Arnhem Land coast of Australia. The *GC*1C24* allele is also polymorphic in several of the Lesser Sunda Islands of Indonesia. Probably the flow of this allele between these populations began about 10,000 years ago due to the movement of Indonesian fishing fleets. Another unique allele, *GC*1C35,* has been detected independently by Yuasa et

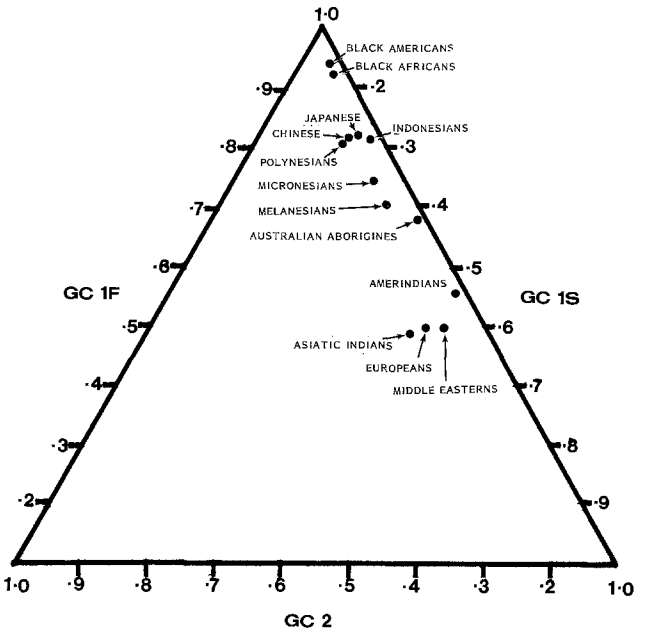

Fig. 3. Triangular display of selected population groups using three common GC allele frequencies data from Table 2. Allele frequencies are measured by the perpendicular distance to the sides of the triangle

al. (1984) in Japanese and by Kamboh et al. (1984) in Australian Aborigines. The frequency distribution indicates that this allele is rare in Japanese but polymorphic in several Australian populations. On IEF the banding patterns of these two variants are indistinguishable. The virtual absence of *GC*1C35* in other Pacific populations may represent independent mutations. Alternatively, the low incidence of *GC*1C35* in Japanese may represent the remnants of genes of early populations who moved through Southeast Asia down to Australia. If the latter assumption is true, then it is possible that this allele is present in at least some Pacific populations but has not been detected so far. Further screening of populations in the Pacific area would be of great interest in clarifying this issue.

Several GC variants have been recognized in East and Southeast Asians, and in Mongoloid-derived populations in North and South America. The first unique variant, GC 1A3, (GC N) was found at high frequency (21%) in Negritos living in remote areas of the Philippines (Omoto et al. 1978). Subsequently GC 1A3 has been observed at a low frequency in Chinese, Japanese, Koreans, and Indonesians (Matsumoto et al. 1980; Kamboh et al. 1984). The sporadic occurrence of this variant has also been reported in Alaskan Eskimo and Machiguenga and Quechuan Indians from Peru (Matsumoto et al. 1980). The high frequency of GC 1A3 in Negritos may indicate its origin by mutation in these people and subsequent spread to neighboring populations or the effects of genetic drift in small populations. This variant seems to have been incorporated into the Mongoloid gene pool at an early date and to have been present in the Asian ancestors of Eskimos and Amerindians.

Two other variants which are markers of Mongoloid populations are GC 1A2 (GC J) and GC 1A9 (GC TK1). These are fairly common in Japanese and Chinese and are present at low frequencies in Eskimos (Kuwata et al. 1978; Matsumoto et al. 1980). Another variant GC 1A4 (GC ESK) which seems to have a localized distribution, is polymorphic in Eskimos and rare in Quechuan Indians from Peru. The GC 1A10 (GC Chippewa) variant which was first detected in North American Indians (Cleve et al. 1963) has not yet been observed in other Amerindian population groups. A further characterization of aboriginal American populations with respect to GC, using IEF, would aid in resolving questions regarding the genetic relationships among American aboriginals and between them and their Asian ancestors.

The third set of populations which are characterized by having unique GC variants are Blacks from Africa and America. Like Australian–Pacific populations, there is a widespread distribution of the GC 1A1 variant in these groups. However, unlike the former, the frequency of GC 1A1 in Blacks is relatively low and variable. On the African continent the *GC*1A1* frequency is higher in South and West Africans (2–4%) than in North and East Africans (less than 1%). The sporadic occurrence of GC 1A1 in North Africa and the Middle East suggests the introduction of the GC 1A1 variant from the Sub-Sahara through long established contact between these populations. Another example which provides evidence of physical contact between Saharan and Northeast Africans is that of GC 1C3. This variant is spread from Northeast Africa in the Republic of Djibouti through North Africa into Algeria and Mali to West Africa in Senegal. However, no example has been observed in Pygmies from the Sub-Sahara (Constans et al. 1980a). A Negroid marker GC 2A3 is present at about 9% frequency in Pygmies and further detection of few examples in North and South Africans gives additional support of gene flow in the African continent (Constans et al. 1985). In addition to GC 1A1, Black Americans have another polymorphic variant, GC 1C10, which has not been detected outside America (Dykes and Polesky 1984). Because of admixture in American Blacks, the exact origin of this variant is uncertain. The historical views about African ancestary of American Blacks is further strengthened by the detection of GC 2A3 and 2A5 variants in these groups. Several GC mutants have been recognized in Europeans but none of them achieve polymorphic proportions and their distribution is also restricted.

Conclusion and synthesis

The significance of IEF in the measurement of population structure of various racial groups is becoming more apparent as its application is widening to additional blood genetic markers. The detection of new alleles in the GC system increases the estimated heterozygosity level and also makes it one of the most highly polymorphic loci. There is almost a two-fold increase in the average heterozygosity using IEF as compared to conventional electrophoresis (Table 3).

The synthesis of existing IEF data reveals a remarkable variation in the distribution of two GC sub-alleles. There is a geographical cline from Southeast Asia, through Europe and the Middle East and down to Africa in the *GC*1F* and *GC*1S* allele frequencies. The cline in GC frequencies in these geographical areas could be explained by gene flow through migration. However, the wide range variation observed in populations from different geographical areas may be due to some selective forces acting on the GC locus to maintain the variation. In this connection a correlation though not universal, between low *GC*2* frequency and incident ultraviolet light was reported (Kirk et al. 1963; Mourant et al. 1976; Daiger and Cavalli-Sforza 1977).

Table 3. Comparison of heterozygosity obtained by conventional electrophoresis and IEF in selected populations at the GC locus

Population	Conventional	IEF
Chinese	0.39	0.64
Japanese	0.41	0.63
Indonesians	0.30	0.60
Polynesians	0.44	0.65
Micronesians	0.38	0.64
Melanesians	0.35	0.66
Australian Aborigines	0.34	0.67
Asiatic Indians	0.43	0.58
Europeans	0.40	0.57
Amerindians	0.21	0.58
Black Americans	0.22	0.46
Black Africans	0.27	0.48
Mean	0.34	0.60

The primary function of GC is to bind and transport vitamin D3 from its site of synthesis in the skin in response to ultraviolet exposure (Loomis 1967; Holick et al. 1980). However, the rate of vitamin D synthesis in skin is regulated by pigmentation and keratinization of stratum corneum. In pigmented (black) and keratinized (yellowish) skin types the rate of UV light penetration is lower compared to nonpigmented and nonkeratinized white skin. It is important to note here that populations with black and yellowish skin have much higher frequencies of the IF allele compared to white populations. Although pigmented skin provides protection against excessive UV radiation, dark skinned individuals are more susceptible to rickets. It is suggested therefore that during the course of evolution GC 1F allele products having a greater affinity for vitamin D3 might be selectively favored in dark skinned peoples by more efficiently transporting vitamin D3 from the skin to target tissues. This idea is further supported by in vitro experiments in which the IF allele products have been found to show greater affinity for its ligand as compared to 1S and 2 allele products (Constans et al. 1980b).

One of the most promising and neglected areas of research is on the interaction of GC with target tissues. To date most research has focused on the interaction of the different GC isoproteins with various vitamin D metabolites. Less attention has been paid to the interaction of the holoprotein with target tissues. Constans et al. (1981a) have reported that GC binds to the plasma membrane and cytoplasm of lymphocytes and that the different holo forms differ with respect to binding to the lymphocyte membrane. It is known that GC from a variety of species forms a tight 1:2 molar complex with actin (Van Baelen et al. 1980), and the same authors suggest that the cytoplasmic vitamin D binding protein is a complex between serum vitamin D binding protein (GC) and a cytoplasmic protein. These findings suggest that actin may act as a cell surface receptor for the vitamin D-GC complex, and participate in the internalization of vitamin D in target tissues. Comparative studies of the affinity of various GC allele products for actin, and assays of more distal physiologic effects may give additional insight into forces maintaining the GC polymorphism in human populations.

For anthropologic studies GC is a useful marker providing ancestral links between populations through its unique variants. The most important example is that of GC 1A1 variant. Its widespread distribution in Pacific populations and Blacks from Africa and America pose interesting questions about the origin of the 1A1 mutant in these populations. Whether this variant resulted from a single mutation or multiple independent mutations is still to be determined. Electrophoretically these variants are indistinguishable. However, two avenues of further research are: (i) to determine the exact amino acid substitution involved, and (ii) to look at variation at the DNA level in the region of the GC structural gene and its flanking sequences. The recent cloning of the GC gene provides the opportunity to explore the latter avenue of research.

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