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Population genetics of human glyoxalases

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The gene for glyoxalase I (E.C. 4.4.1.5), *Glo*, has two alleles, Glo^1 and Glo^2, which are autosomally inherited in a co-dominant manner. Glo^1 allele-frequency is highest in native Alaskan-Eskimo and Indian populations and decreases geographically south and east, to minimum levels in Aboriginal-Australian populations and native tribes in Papua New Guinea. There was no correlation between Glo^1 frequency and incidence of insulin-dependent diabetes mellitus (IDDM). The frequencies of GLO phenotypes, *Glo* 1–1, *Glo* 1–2 and *Glo* 2–2, are disturbed in IDDM and there is a suggestion that IDDM patients with or without chronic, clinical complications have characteristic phenotype frequencies.

Keywords: diabetes, diabetic complications, glyoxalase.

Introduction

The glyoxalase system catalyses the conversion of methylglyoxal to D-lactic acid, via the intermediate S-D-lactoylglutathione (Racker, 1951). There are two constituent enzymes: glyoxalase I (E.C. 4.4.1.5), a dimeric protein which catalyses the formation of S-D-lactoylglutathione from methylglyoxal and reduced glutathione

$$MeCOCHO + GSH \xrightarrow{\text{Glyoxalase I}} MeCH(OH)CO\text{-}SG$$

and glyoxalase II (E.C. 3.1.2.6), a monomeric protein that catalyses the hydrolysis of S-D-lactoylglutathione to D-lactate, regenerating reduced glutathione

$$MeCH(OH)CO\text{-}SG + H_2O \xrightarrow{\text{Glyoxalase II}} MeCH(OH)CO_2H + GSH$$

Recent investigations of the glyoxalase system have suggested that there may be characteristic activities of glyoxalase enzymes associated with the development of clinical complications in insulin-dependent diabetes mellitus (Thornalley *et al.*, 1989), and glyoxalase activity may be a predisposition factor for developing complications should an individual develop the disease (Thornalley, 1990). The genetics and polymorphism of glyoxalase have also been investigated in diabetes mellitus and associated clinical complications. There is considerable variation in the population genetics of glyoxalase with geographical location. This provides an opportunity to investigate the correlation of glyoxalase allele and phenotype frequencies with the incidence of diabetes mellitus and its susceptibility to complications.

This report describes the genetic characteristics of glyoxalase I and II, surveys the variation of allele frequency with geographical location and assesses the association of glyoxalase with the incidence of diabetes mellitus and associated complications.

Genetics of glyoxalase I

Human glyoxalase I was found to exhibit genetic polymorpism originally in red blood-cells (Kompf *et al.*, 1975a). There were three phenotypes *Glo* 1–1, *Glo* 1–2 and *Glo* 2–2, representing the homozygous and heterozygous expression of a two allelic gene, Glo^1 and Glo^2 (Kompf *et al.*, 1975b). An analogous phenotypic expression was found in 23 different human tissues in each of 49 autopsies (Stohlmacher & Haferland, 1980). The *Glo* alleles are inherited autosomally in a co-dominant manner. The *Glo* locus has been assigned to chromosome 6 by somatic-cell hybridization (Bender & Grzeschik, 1976), and to the major histocompatibility complex by linkage analysis (Kompf *et al.*, 1976). *Glo* lies between the centromere and HLA-DR; the meiotic distance between HLA-DR is ~6 cM (Bakker *et al.*, 1979; Leach *et al.*, 1986).

The allele frequencies of *Glo* in geographically classified human-populations are presented in Fig. 1. The Glo^1 allele-frequency is highest in native tribes in Alaska (Inpiat, Aleuts, Tlingits, Yupik and Athabaskan), 0.6663–0.8529, and is lowest in the Aboriginal population of Australia, 0–0.1008, Papua New Guinea, 0–0.1558 and island of the Western Pacific–E. Carolines, 0.0455 (Fig. 1).

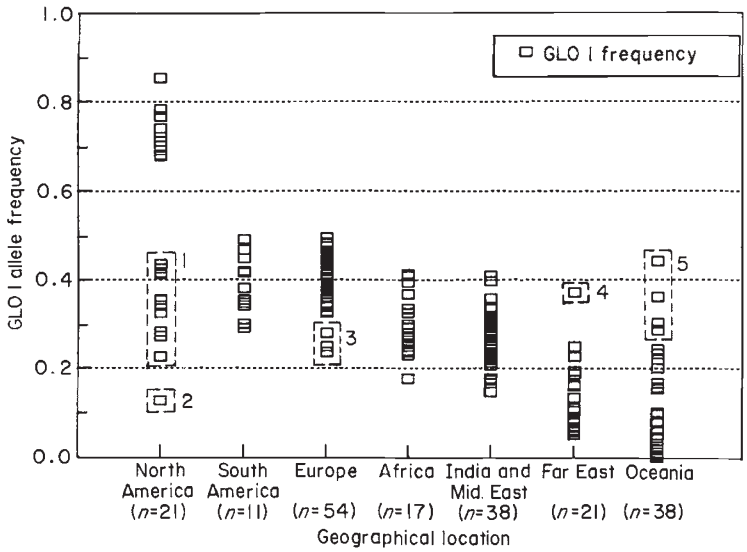

Fig. 1 Variation in *Glo*^{1} allele-frequency with geographic location. Data taken from 202 reports (16 other reports rejected for failure of the Hardy–Weinberg Principle). A full list of data and references is avilable on request. Data are shown in subcontinental classification. Where immigrant populations with *Glo*^{1} allele-frequencies significantly different from the native population were defined, the immigrant class is identified:

(1) European and African immigrants in USA;
(2) Native Dogrib tribe (Canada, NW Territories);
(3) Indian and African immigrants in UK;
(4) European immigrants in Siberia;
(5) European and Indian immigrants in Australia, Tokelau and Malaya.

The *Glo*^{1} allele-frequency decreases geographically south and east from Alaska, to Europe or South America, through Africa, the Middle East and India, to the very low *Glo*^{1} allele-frequencies of the Far East (Japan and China) and Oceania (Australian Aboriginals, Papua New Guinea). Where there is extreme diversity of *Glo*^{1} allele-frequency within a region, this can be assigned to an immigrant population–Europeans and Africans in the USA (North America), Indians and Africans in the United Kingdom (Europe), European immigrants in Eastern Siberia (Far East), Australia and other Pacific island (Oceania). One exception to this trend was the report for the native Dogrib tribe, Northwest Territories of Canada which gave an anomalously low *Glo*^{1} allele-frequency (0.1266).

Glyoxalase I is not polymorphic in closely-related hominoid species, e.g. *Pan troglodytes* — the chimpanzee (Payne *et al.*, 1982). The electrophoretic mobility of glyoxalase I in the chimpanzee was found to be identical to the human *Glo* 2–2 phenotype. The *Glo*^{2} allele has been proposed to be the ancestral allele with the *Glo*^{1} allele arising by mutation. The geographical distribution of *Glo*^{1} allele-frequency is consistent with this mutation occurring in North America or there being some environmental advantage for the *Glo*^{1} allele in North American and West European population.

Polymorphism of glyoxalase I in diabetes mellitus

Polymorphism of glyoxalase I has been described in five independent surveys of diabetic patients and normal, healthy controls. There was no significant difference in *Glo*^{1} allele-frequency between these two groups. The distribution, however, of GLO phenotypes was disturbed.

For insulin-dependent diabetes mellitus (IDDM) there was a significant disturbance in GLO phenotype distribution: an increase in *Glo* 1–1 homozygote (McCann *et al.*, 1981; Cambdon de Mouzon *et al.*, 1982) or an increase in *Glo* 1–2 heterozygote (Kirk *et al.*, 1985). Other surveys (Allannic *et al.*, 1985; Kirk *et al.*, 1979) found no significant difference between IDDM patients and controls. The present paper reports an investigation of the relationship between geographical variation in glyoxalase I genotype and the incidence of IDDM for 10 countries, using the recently collated data of LaPorte *et al.* (1985), and the corresponding *Glo*^{1}-genotype data obeying the Hardy–Weinberg principle. No significant correlation was found using the Kendall Rank-correlation-coefficient analysis between the incidence of IDDM and *Glo*^{1} allele-frequency or *Glo*-genotype distribution ($Z = 0.447$, Fig. 2).

For non-insulin-dependent diabetes mellitus (NIDDM), a disturbance in the GLO-phenotype distribution has also been reported (Kirk *et al.*, 1979), associated with an increase in the *Glo* 2–2 phenotype, but this was not confirmed (Kirk *et al.*, 1985; McCann *et al.*, 1981).

Diabetic patients suffer chronic complications (retinopathy, cataract, peripheral neuropathy, nephropathy and generalized microangiopathy). No genetic link with the development of complications has yet been established. There has only been one survey relating the development of retinopathy and neuropathy to GLO phenotypes. Here, IDDM patients without complications (retinopathy, neuropathy) had a significant excess of the homozygote *Glo* 1–1 compared to

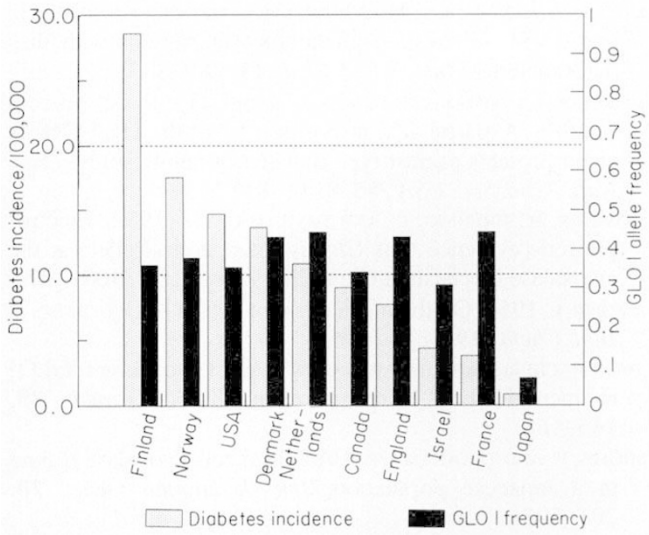

Fig. 2 Geographical population incidence of insulin-dependent diabetes mellitus (IDDM) and *Glo*^{1} allele-frequency. IDDM incidence was taken from LaPorte *et al.* (1985). *Glo*^{1} frequency was calculated from reports of similar ethnic composition to the diabetes incidence data

normal healthy controls (McCann *et al.*, 1981). It was also in IDDM patients that characteristic activities of red-blood-cell glyoxalases were found for patients with or without complications (Thornalley *et al.*, 1989).

International comparisons of *Glo*^{1} allele-frequency and susceptibility to complications are made with caution since the diagnosis and clinical management may vary. Cumulative survival-rates for IDDM patients may give an indication of the severity of complications. Data are available for Finland, USA, Israel and Japan — countries with well developed primary health care services. Survival rates are very similar for Finland, USA and Israel (0.956–0.967) but very much lower in Japan (0.898) (LaPorte, 1990). It is of interest that the *Glo*^{1} frequencies for Finland (0.358), USA (0.379) and Israel (0.306) are also similar, whereas *Glo*^{1} frequency in Japan is very much lower (0.067). Hence, a deficiency in *Glo*^{1} allele may be associated with the occurrence of diabetic complications and high mortality.

Genetics of glyoxalase II

The gene for glyoxalase II humans (HAGH) is on chromosome 16 (Honey & Shows, 1981). There is usually only one phenotype expressed, although a rare second form (frequency 0.016) was found in a Micronesian population (Board, 1980; Sugita & Takahama, 1983). Glyoxalase-II polymorphism occurs in other species. A survey of 10 anthropoid primates indicated a high degree of polymorphism of erythrocyte glyoxalase II (Board *et al.*, 1981). The disturbance of glyoxalase II phenotypes in diabetes has not yet been investigated.

Relevance of glyoxalase genetics to diabetes

Genetic susceptibility markers for IDDM have been suggested (Todd *et al.*, 1987; Morel *et al.*, 1988). The nature of the genetic contribution to the aetiology of NIDDM remains obscure (Jarrett, 1989). There was no correlation between the incidence of IDDM and glyoxalase I allele-frequency, and disturbances in glyoxalase I phenotypes in IDDM and NIDDM have not been generally confirmed. There is a suggestion, however, that IDDM patients with or without chronic clinical complications have characteristic phenotype-frequencies (McCann *et al.*, 1981) and glyoxalase activities (Thornalley *et al.*, 1989). The implication of an involvement of glyoxalases in the development of complications is a novel approach (Thornalley, 1990) and genetic aspects of this require further investigation.

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