Distribution of Genetically Determined Deficient Variants of Glucose-6-Phosphate Dehydrogenase (G6PD) in Southern Italy.

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INTRODUCTION

The genetic locus coding for G6PD (Gd) is located at the tip of the long arm (q28) of the human X chromosome leading to the typical "sex linked" pattern of inheritance of G6PD genetic variants. Thus variants are fully expressed, and therefore easily recognized, in hemizygous male subjects. Gd locus is highly polymorphic in human populations living in countries lying between 45° N and 35° S Latitude. Genetic polymorphism is mostly due to the occurrence within a given population of one or more variants associated with a reduced level of enzyme activity in red blood cells, together with the common G6PD B form (Luzzatto and Battistuzzi 1985).

MATERIALS AND METHODS

Blood specimens were collected by venepuncture from 15,000 unrelated male donors, representative of the various populations of Southern Italy. G6PD phenotype was determined on red blood cells lysates according to Betke et al. (1967) on cellulose acetate strips. Subjects showing a variant phenotype were further characterized in terms of enzyme activity level, electrophoretic mobility, and biochemical characteristics (Modiano et al. 1979).

RESULTS AND DISCUSSION

Distribution of G6PD Deficiency

The highest proportion of G6PD deficient subjects was found in the island of Sardinia, where 13% of the male population carry a G6PD variant with reduced enzyme activity (Fig. 1). A much lower frequency of G6PD deficiency is found in the Sicilian and peninsular population (2.5% and 2.2%). A detailed analysis of the distribution of G6PD deficiency within each area showed a considerable amount of variation. In Sardinia, the highest frequency is found in the province of Oristano (18%) while only approximately one third of this frequency (6.7%) is found in the nearby area of Sassari. An even more striking example of geographic variation of G6PD(-) frequency is shown by the populations of Sicily and of the Matera area. In the former case, the highest frequency is found in the "Val di Noto", the southernmost corner of the island, specifically in Ragusa (6.3%) and Siracusa (4.5%). From this level, the frequency of G6PD deficiency smoothly decreases along

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the Southern and Eastern coasts of the island.

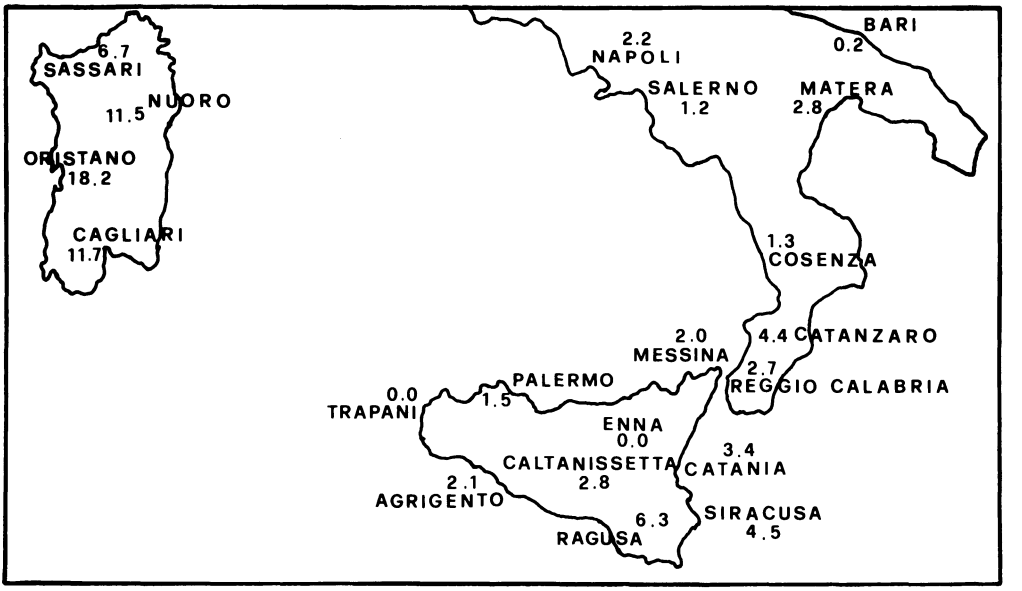

Fig. 1. Distribution of the frequency of G6PD deficiency in Southern Italy.

In the Matera province, the frequency of G6PD deficiency appears to be inversely related to the distance of each examined town from the Ionian coast, the greater the distance the lower the frequency. In both cases the pattern of variation of G6PD(-) frequency appears to be related to the population origin and migrational pattern and to the altitude, which in turn is known to be correlated with past malarial endemia (Siniscalco et al. 1966).

Type of Deficiency

The analysis of the enzyme activity level evidences a further element of variation within and between populations. At least two types of deficiency can be easily recognized in each population. A class of subjects is characterized by an extremely low level of G6PD activity in red blood cells ($< 5\%$) while others show an activity level ranging from 15 to 50% of normal G6PD B activity.

The relative proportions of these two classes of individuals vary considerably according to the population examined. In Sardinia as far as 92% of deficient subjects are included in the severe deficiency class. However, in Napoli severe deficiency accounts for only 30% of the total frequency (Table 1).

Table 1. Relative frequency of severe and moderate G6PD deficency in various Italian populations.

Origin	Mild	Severe	Total
Sardinia general	0.010	0.120	0.130
Bari	-	0.002	0.002
Napoli	0.015	0.007	0.022
Matera	0.008	0.020	0.028
Southern Italy general	0.015	0.007	0.022
Agrigento	0.021	-	0.021
Caltanissetta	0.007	0.021	0.028
Catania	0.028	0.006	0.034
Messina	0.015	0.005	0.020
Palermo	0.010	0.005	0.015
Ragusa	0.047	0.016	0.063
Siracusa	0.034	0.011	0.045
Sicily general	0.018	0.007	0.025

Genetic Basis of Deficiency

On the basis of electrophoretic analysis and enzyme activity assay on red blood cells lysates and of biochemical analysis on partially purified enzyme preparations it has been possible to identify the number and type of protein variants which account for G6PD deficiency in various populations of Southern Italy (Table 2).

Table 2. Minimum number of common genetic variants in Italian populations and associated degree of deficiency.

Origin	Total	Number of variants associated with enzyme deficiency	
		Mild	Severe
Sardinia	4	1	3
Sicily	5	4	1
Southern Italy	11	10	1

For each variant the familiar segregation has been demonstrated. On the basis of this analysis we have established that the minimum number of common Gd genetic variants segregating in the Italian population is fifteen, eleven of which had been already described (Testa et al. 1980; Fenu et al. 1982; Colonna Romano et al. 1985). The four new variants have different than normal electrophoretic mobility (namely 90, 93, and 110% of normal), with two variants showing the same mobility (90%) but easily distinguishable on the basis of enzyme activity ($< 15\%$ and $> 25\%$ respectively). Moreover these variants show normal kinetic parameters. Among the fifteen variants only

three appear to be associated with a severe degree of deficiency (< 5%), the previously described G6PD Cagliari, G6PD Sassari, and G6PD Mediterranean variants (Testa et al. 1980; Fenu et al. 1982). The remaining twelve are associated with a mild to moderate level of G6PD deficiency.

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