Atti Accademia Nazionale dei Lincei

Classe Scienze Fisiche Matematiche Naturali

Rendiconti

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- Population studies on Caeruloplasmin polymorphism

Atti della Accademia Nazionale dei Lincei. Classe di Scienze Fisiche, Matematiche e Naturali. Rendiconti, Serie 8, Vol. **62** (1977), n.1, p. 93–96.

Accademia Nazionale dei Lincei

<http://www.bdim.eu/item?id=RLINA_1977_8_62_1_93_0>

Atti della Accademia Nazionale dei Lincei. Classe di Scienze Fisiche, Matematiche e Naturali. Rendiconti, Accademia Nazionale dei Lincei, 1977.

Genetica. — *Population studies on Caeruloplasmin polymorphism.* Nota di GIORGIO BATTISTUZZI (*), MAURO SERAFINI (*) e ROMANO PETRUCCI (*), presentata (**) dal Socio G. MONTALENTI.

RIASSUNTO. — È stato studiato il polimorfismo della ceruloplasmina sierica in due campioni di individui, uno della popolazione italiana ed uno della popolazione nepalese. Il campione italiano è stato suddiviso per zone d'origine (Lazio, Sicilia, Sardegna) allo scopo di controllare l'eventuale esistenza di una qualche relazione tra endemia malarica e frequenza dell'allele Cp^A della ceruloplasmina. Era stato infatti precedentemente suggerito che questo allele in eterozigosi conferisse un qualche vantaggio selettivo in condizioni malariche tale da causarne una maggiore diffusione.

I nostri dati sono in accordo con quelli già ottenuti per popolazioni caucasoidi e per popolazioni della regione indiana e non sembrano avvalorare l'ipotesi di selezione malarica diretta.

INTRODUCTION

Caeruloplasmin is an $\alpha - 2$ serum globulin containing 90 % of serum copper. Though its physiological function still remains unknown it has been proposed by Shokeir and Shreffler (1969) and Marceau *et al.* (1970) that it may be involved in the storage of copper and its transfer to copper-containing enzymes such as cytochrome oxidase. An association between hepatolenticular degeneration (Wilson's disease) and caeruloplasmin deficiency has been discovered (Sheiberg and Sternlieb, 1965). Genetically determined structural variants were first described by Martin *et al.* (1961) and later by Shreffler *et al.* (1967). It has been shown, from family studies, that the synthesis of caeruloplasmin, which takes place in the liver, is under the control of an autosomal gene. In the course of population surveys six electrophoretically distinguishable forms have been so far detected and explained as the product of six different codominant alleles: Cp^A, Cp^B, Cp^C, Cp^{NH}, Cp^{Bpt} and Cp^{Th}. The first three are universally distributed, Cp^B being largely the most common one, whereas the others are characteristic of only some populations. On the basis of the high Cp^A allele frequency variability in various populations affected in the past or in the present by malaria there has been proposed a direct (Shokeir and Shreffler, 1974) or Haemoglobin S mediated (Battistuzzi, 1976) selective advantage in these environmental conditions.

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(**) Nella seduta dell'8 gennaio 1977.

THE SAMPLES

We examined 1965 healthy unrelated individuals of both sexes. The composition of the samples was as follows:

Origin		Number of individuals
Italy: Latium:	Rome	754
Sardinia:	North Sorso	80
	Centre: Nuoro	138
	Centre: Ozieri	99
	South: Miscellaneous. .	85
Sicily:	Palermo	403
Nepal:	Sherpas [1]	136

(1) For detailed information on the composition of the Sherpa sample see Morpurgo *et al.* (1972).

Methods

Electrophoretic caeruloplasmin phenotypes have been determined according to the methods of Shreffler *et al.* (1967) and Shokeir and Shreffler (1970) with minor modifications.

RESULTS AND DISCUSSION

The results are shown in Table I. Considering the low frequency of the Cp^C allele, the finding of a subject with a CpC phenotype is intriguing. Since the sera of his parents could not be examined, it is not known if the underlying genotype is Cp^C/Cp^C or Cp^C/Cp^O. The presence of a Cp^O allele in the population, though at very low frequency, cannot be excluded since lack of caeruloplasmin activity has been demonstrated in individuals affected by Wilson's disease.

In the 402 individuals from Sardinia we did not find any variant phenotype. The population examined in this survey has been subjected in the past to such an intense and long lasting malarial selection as to cause drastic genetic effects such as the accumulation of *Th* and Gd^- genes. A similar effect would be expected for the *Cp* gene if caeruloplasmin *per se* played some role in the adaptation toward malaria. Our data do not—at least in this population —confirm the suggestion by Shokeir and Shreffler (1970) that the high fre-

TABLE I.

Serum caeruloplasmin phenotype and allele frequencies in Italian and Nepalese populations.

Population	*Cp* phenotype frequencies					Allele frequencies		
	N	B	C	AB	CB	Cp^A	Cp^B	Cp^C
Italians:								
Rome	754	748	1	1	4	0.0007	0.9953	0.0040
Sardinia	402	402	—	—	—	—	1	—
Sicily	403	400	—	2	1	0,0025	0.9963	0.0012
Nepalese	136	132	—	3	1	0.0110	0.9853	0.0037

TABLE II.

Cp allele frequencies in European and Oriental populations.

Population [1]	N	Cp^B	Cp^A	Cp^C
Europe:				
Germans	224	0.985	0.013	0.002
Icelanders	106	0.996	0.004	—
Irelanders	240	0.988	0.010	0.002
Greeks (continent)	210	0.960	0.036	0.004
Greeks (Kreta)	155	0.932	0.068	—
Italians	1559	0.997	0.001	0.002
Asia:				
Iranians	198	0.990	0.003	0.007
Pakistani	96	0.995	0.005	—
Indians (Brahamins)	108	0.988	0.012	—
Indians (West Bengal)	978	0.986	0.012	0.002
Koreans	115	0.978	0.009	0.013
Nepalese	136	0.985	0.011	0.004

(1) See for references Kellermann and Walter, 1972.

quency of the Cp^A allele observed in some populations is due to a possible selective advantage provided by the AB phenotype in these environmental conditions.

The highest Cp^A frequency among the Italians examined in the present survey is found in the sample from Sicily, though it is of the same order of magnitude as that found for other Caucasoid populations and cannot be safely assumed to be significantly different from the two above-mentioned groups.

Table II shows the comparisons of the C*p* allele frequencies of European and Oriental populations. Our findings generally confirm the published data, in that allele frequencies reported here can be considered to be in agreement with those reported for Caucasoids (Italian sample) and Orientals (Nepalese sample). The frequencies found in the Nepalese particularly agree with those found in populations living in the Indian region.

A further observation can be made. Whenever we exclude Black populations in which Cp^A allele frequency is highly variable, Cp^A appears more variable in frequency if compared with Cp^C (see for the population not reported here Kellerman and Walter (1972) and Mourant *et al.* (1976).

We thank Prof. Ida Bianco, Centro di Studio per le Microcitemie, Roma for kindly providing the Rome samples, Prof. L. Terrenato, Dr. L. Ulizzi and Prof. G. Modiano for samples from Sardinia, Sicily and Nepal, respectively.

References

BATTISTUZZI G. (1977) – *A connection between the haemoglobin chain and Caeruloplasmin genetic systems* (in press).

KELLERMANN G. and WALTER H. (1972) – *On the population genetics of the Ceruloplasmin polymorphism*, « Humangenetik », *15*, 84.

MARCEAU N. and SASS-KORTSAK, A. (1970) – *The* in vivo *transfer of ceruloplasmin copper to* cytochrome *oxidase*, « Can. Fed. Biol. Soc. Abstr. », *13*, 127.

MARTIN G., MCALISTER R., PELTER W. and BENDITT E. P. (1961) – *Heterogeneity of caeruloplasmin*, « Proc. 2nd Intern. Congr. Hum. Genet. », *2*, 752.

MORPURGO G., BATTAGLIA P., CARTER N. D., MODIANO G. and PASSI S. (1972) – *The Bohr effect and red cell 2–3* DPG *and* Hb *content in Sherpas and Europeans at low and high altitude*, « Experientia », *28*, 1280.

MOURANT A. E., KOPEC A. C. and DOMANIEWSKA-SOBCZAK (1976) – *The distribution of the Human blood groups and other polymorphisms*, 2nd Edition, Oxford University Press, London.

SCHEINBERG I. A. and STERNLIEB I. (1965) – *Wilson's disease*, « Ann. Rev. Med. », *16*, 119.

SHOKEIR M. H. K. and SHREFFLER D. C. (1969) – Cytochrome *oxidase deficiency in Wilson's disease: a suggested ceruloplasmin function*, « Proc. Nat. Acad. Sci. (Wash.) », *62*, 867.

SHOKEIR M. H. K. and SHREFFLER D. C. (1970) – *Two new ceruloplasmin variants in Negroes: data on three populations*, « Biochem. Genet. », *4*, 517.

SHREFFLER D. C., BREWER G. J., GALL I. C. and HONEYMAN M. S. (1967) – *Electrophoretic variation in human serum ceruloplasmin: a new genetic polymorphism*, « Biochem. Genet. », *1*, 101.