Investigations on the distribution pattern of haptoglobin subtype allele frequencies in European populations
- Preliminary report -

K.Wendt and H.Walter

Dept.of Human Biology, University of Bremen, 28334 Bremen, Germany

Introduction

Human haptoglobin (HP) is a polymorphic serum glycoprotein with various biological activities (Lange,1992). It consists of two types of polypeptide chains, α and ß, covalently linked through disulfide bridges. The genetic polymorphism is essentialy based on variations in the aminoacid sequence of the α-chains. Today the most common codominant HPα-alleles are HP*1S and HP*1F (subtype alleles of HP*1) and HP*2FS, HP*2SS, HP*2FF (subtype alleles of HP*2), controlling 15 different phenotypes, respectively genotypes. In addition, several rare α- and ß-variants have been observed. The distribution of HP alleles indicates a high diversity in the different populations of the world (Roychoudhury and Nei,1988). Within European populations the HP*1 allele frequencies show a marked geographical distribution pattern of decline from Northwest to Southeast Europe (De Stefano et al.,1987).

In this paper some new HP subtype data for European populations are given. Furthermore the distribution pattern of HP subtype allele frequencies within Europe will be analyzed statistically.

Material and Methods

EDTA serum of unrelated individuals (blood donors) from three European population samples (Hannover, n=260, Thuringia, n=199, Tyrol, n=264) has been subtyped.
They were collected in 1991 in coopération with Prof.Dr.W.Stangel (Hannover), Dr.J. Schimmel (Jena), Dr.U.Jaeger (Jena), Prof.Dr.R.Uhlig (Erfurt) and Prof.Dr.H.Reissigl (Innsbruck,Austria). HP subtyping was carried out according to the method proposed by Patzelt (1984) and Bertrams et al.(1988). The gel was prepared with a modified ampholyte mixture (LKB): 0,28ml pH 3,5-10, 0,46ml pH 5-7, 0,18ml pH 6-8 in 18,5ml total gel volume. If samples turned out to be only weakly stained by the classical Coomassie staining, destaining and drying, this process was followed by a rapid silver staining excepted stop-reagent according to Willoughby and Lambert (Westermeier,1990). For the statistical analysis the relations between the degree of longitude/HP*, the degree of latitude/ HP* and the degree of longitude-latitude/HP* were examined for 37 hitherto HP subtyped European population samples by means of Spearman's correlation analysis as well as by simple and multiple linear regression analysis (Sachs,1984).

Results and Discussion

After PAGIEF, each HPα-polypeptide chain is visible as a single major band corresponding with a characteristic minor band. By the modified ampholyte composition the discrimination of the HP 2FS and HP 1F allele products could be improved. Formerly we frequently had to control the results adding an HP typing by means of vertical PAGE. The addition of silver staining optimizes the visualisation of weak bands which can be observed by this subtyping method in some instances (low HP serum concentration, low HPα output, intense destaining etc.).
The distribution of HP phenotype and allele frequencies in the three population samples under study is shown in Table 1. Genetic equilibrium can be assumed for all of them. All possible 5 HP subtype allele products including HP 2FF were observed. The investigated allele frequencies are in good accordance with those obtained from other European population studies. In general there is a relatively high interregional HP subtype variability within European populations (Fig.1). In Europe the most frequently occuring HP*1 subtype allele is HP*1S (0,1573-0,3110) and concerning the HP*2 subtype allele HP*2FS (0,4630-0,6653).

The correlation and regression analysis verify the results of De Stefano et al.(1987) with respect to the HP subtype data. R-, F- and p-values (Table 2) indicate that the HP system shows a clear Northwest to Southeast distribution gradient in Europe with the most prominent gradient from West to East. This pertains to the conventional haptoglobin polymorphism as well as to the subtyped one. The decrease frequency of the HP*1 mainly reflects a decrease in HP*1F. The parallele increase frequency of HP*2 cannot be attributed to a specific HP*2

Table 1: HP phenotypes and allele frequencies in three European population samples (Hannover, Thuringia, Tyrol)

	Hannover		Thuringia		Tyrol	
Phenotypes	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.
HP 1S	16	21,06	13	13,07	19	16,25
HP 1S-1F	26	22,78	13	14,61	18	16,62
HP 1F	7	6,16	4	4,08	2	4,25
HP 2FS	73	74,84	60	60,81	97	93,97
HP 2FS-1S	87	79,40	58	56,39	69	78,15
HP 2FS-1F	38	42,94	32	31,51	44	39,97
HP 2SS	--	0,14	--	0,45	--	0,11
HP 2SS-1S	2	3,42	5	4,87	5	2,73
HP 2SS-1F	2	1,85	4	2,72	--	1,39
HP 2FS-2SS	8	6,44	10	10,50	6	6,55
HP 2FF	--	0,00	--	--	--	0,02
HP 2FF-1S	1	0,28	--	--	1	1,00
HP 2FF-1F	--	0,15	--	--	1	0,51
HP 2FS-2FF	--	0,53	--	--	2	2,39
HP 2SS-2FF	--	0,02	--	--	--	0,08
Total	260	260,01	199	199,01	264	263,99
	$X^2_{(10)} = 6,797$ $p > 0,70$		$X^2_{(6)} = 1,323$ $p > 0,95$		$X^2_{(10)} = 7,415$ $p > 0,50$	

Alleles	Hannover	Thuringia	Tyrol
HP*1S	0,2846	0,2563	0,2481
HP*1F	0,1539	0,1432	0,1269
HP*2FS	0,5365	0,5528	0,5966
HP*2SS	0,0231	0,0477	0,0208
HP*2FF	0,0019	----	0,0076
	1,0000	1,0000	1,0000

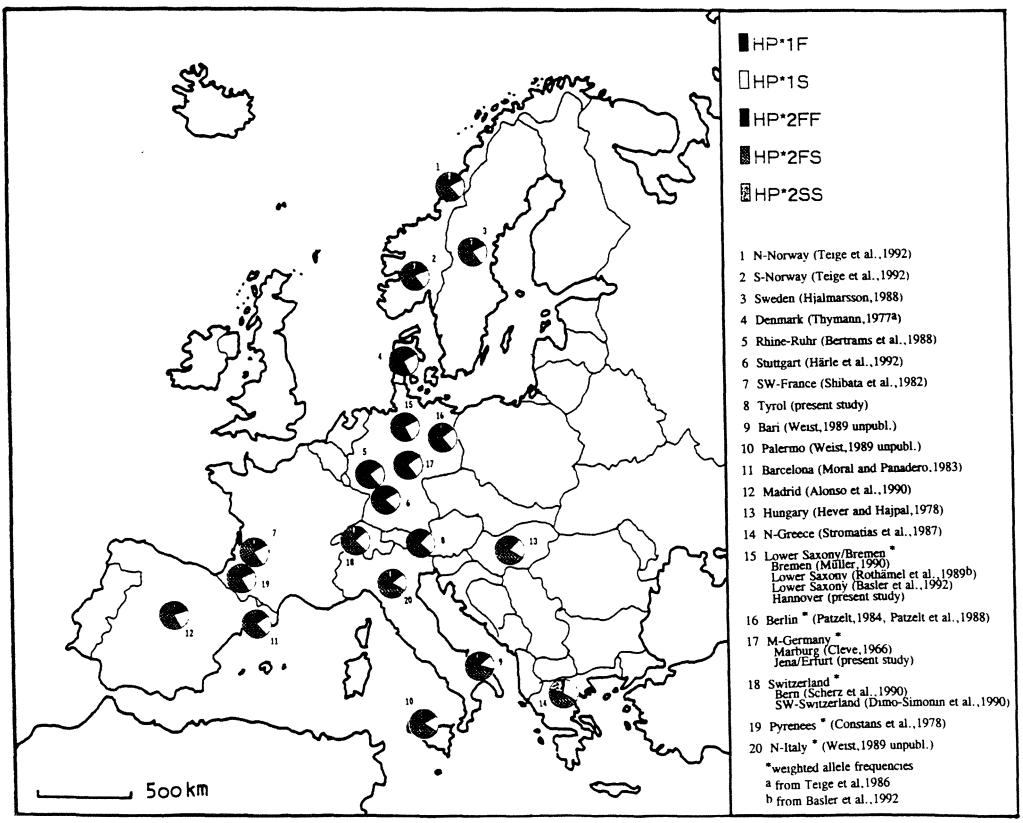

Fig.1: Distribution of HP subtype allele frequencies in European populations

Table 2 : Relations between the degree of longitude/HP*, degree of latitude/HP* and the degree of longitude-latitude/HP* for 37 hitherto HP subtyped European population samples by means of Spearman's correlation analysis (a), simple linear regression analysis (b) and multiple linear regression analysis (c)

	degree of longitude				degree of latitude				degree of longitude-latitude	
HP*	(a) R	mit p<	(b) F	mit p<	(a) R	mit p<	(b) F	mit p<	(c) F	mit p<
HP*1S	-0,239	0,284	0,097	0,759	0,133	0,556	0,053	0,820	0,089	0,915
HP*1F	-0,180	0,422	7,849	0,015	0,092	0,683	1,184	0,290	5,846	0,011
HP*2FS	0,231	0,301	0,135	0,717	-0,212	0,344	0,154	0,699	0,174	0,842
HP*2FF	-0,357	0,102	9,675	0,006	-0,278	0,210	2,887	0,105	5,970	0,010
HP*2SS	0,203	0,365	4,344	0,050	0,214	0,340	0,050	0,826	2,339	0,124
HP*VAR	-0,327	0,138	3,139	0,091	-0,121	0,594	0,377	0,546	1,541	0,240
HP*1	-0,540	0,010	6,726	0,017	0,277	0,211	1,371	0,255	5,896	0,010
HP*2	0,541	0,009	6,679	0,018	-0,278	0,211	1,405	0,250	5,912	0,010

subtype allele. A significant increase is only observed concerning the rare HP*2FF. A mistyping of HP2FF (cathodic drift effect) in some included investigations is not impossible (Zischler,1988). Therefore a check of up-to-date surveys seems advisable in a few years time.

It is of desicive importance that the conventional as well as subtyped HP-system shows a clear geographic distribution pattern in Europe. The observed distribution gradients reveal some paralleles with other known polymorphic blood group systems of man e.g. AB0 and RHESUS. Statements as to what extent physiological factors, evolutionary mechanisms or the history of the European populations contributed to the geographic HP distribution pattern in Europe can be only hypothetic at present.

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