Ann. Hum. Genet., Lond. (1962), **26**, 39
Printed in Great Britain

Haptoglobin frequencies in Jewish communities*

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The variation of the haptoglobins of human plasma was shown by Smithies (1955) and Smithies & Walker (1955, 1956) to be a Mendelian trait controlled by two alleles. These two alleles, Hp^1 and Hp^2, co-exist generally in human populations, and their relative proportions exhibit geographic variation. Additional haptoglobin variants have been detected, but their genetic relationships to the first two alleles are not clearly established.

The discovery of this polymorphic system added yet another tool to the battery of biochemical tests available to the anthropologist and hence was followed up by a series of extensive studies, in which the haptoglobin frequencies in most of the major ethnic groups were mapped (see Sutton, Matson, Robinson & Koucky, 1959, for earlier references; Allison & Barnicot, 1960; Baitsch, Meier, Schoeller & Kahlich-Koenner, 1960; Lange, 1961; Moullec, Fine & Linhard, 1960*a*, *b*; Baitsch, Liebrich, Pinkerton & Mermod, 1961*a*, *b*; Blumberg & Gentile, 1961; Bennett, Auricht, Gray, Kirk & Lai, 1961; Parker & Bearn, 1961).

While the haptoglobins of the three common phenotypes are capable of forming complexes with haemoglobin, the plasma of types 1–1 and 2–1 appears to bind more haemoglobin per unit volume than that of the 2–2 homozygote (Nyman, 1958). It has been suggested that this reaction may fulfil a physiological function in various acquired and inherited haemolytic conditions, and it is plausible that the Hp^1 allele, because of its higher Hb-absorptive capacity may be selectively favoured in populations where such conditions are common (cf. Sutton *et al.* 1959).

The different Jewish groups, which have been scattered for at least 80 to 90 generations over numerous countries in three continents were doubtlessly exposed to different selective agents by their diverse environments. From time to time these Jewish groups must have experienced admixtures of various types and amounts of genes from the autochthonous populations surrounding them. However, the strict observance over long periods of a religious code forbidding intermarriage with gentiles and granting proselytism only as a comparatively rare favour appears to have ensured a large measure of reproductive isolation to each one of these communities. Wherever population size dwindled, gene frequencies may have responded with rapid drift, and inbreeding tendencies (Goldschmidt, Ronen & Ronen, 1960) may have created an 'isolate effect' in large congregations. The differences as well as the affinities between the Jewish groups have aroused considerable interest (Gurevitch and collaborators, 1951–56; Margolis, Gurevitch & Hasson, 1957; Sachs & Bat-Miriam, 1957; Mourant, 1954, 1959; Szeinberg & Sheba, 1958;

* This research was supported by Research Grant RG-6892 from the National Institutes of Health, U.S.Public Health Service and by a Research Grant from Ford Foundation.

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Szeinberg, Sheba & Adam, 1958; Kalmus, Amir, Levine, Barak & Goldschmidt, 1961). The present study of the haptoglobin frequencies in some of the Jewish communities may add further material to this discussion.

METHODS

The blood samples were all collected in Israel, mainly from voluntary blood donors among healthy male army recruits, most of whom were in the age range 18–20 years. The subjects were questioned about the countries of origin of both their parents and also about their community affiliation in cases where geographic origin alone is insufficient for classification. Nearly all the bloods of Kurdish Jews were collected in an immigrant village which was studied simultaneously for the incidence of 'glutathione instability' (deficiency of the enzyme glucose-6-phosphate dehydrogenase) and of thalassaemia (Cohen, Goldschmidt, Adam, Theodor & Szabo, 1959; Cohen, Bloch, Goldschmidt, Matoth & Adam, 1962). These bloods came from males and females of all ages. This was a family study and the majority of the subjects investigated were therefore lost for the gene count and only a minority chosen for this purpose appear in Table 1 (4d). The subjects included are the oldest investigated of their kinships. Sibs, children and grandchildren of these subjects were excluded from the gene count, but the high consanguinity rate of this community made the elimination of first cousins unfeasible.

Venous blood was collected in oxalate and centrifuged and deep-frozen in Jerusalem. The frozen samples were packed in ice and shipped by air to Ann Arbor where they were subjected to electrophoresis according to the vertical starch-gel method of Smithies (1959) for ascertainment of the haptoglobin and transferrin types. When necessary, cyanmethaemoglobin was added to ensure complete saturation of the haptoglobins. After the gels were sliced, one half of each was stained for protein with amido black, the other half was stained for peroxidase activity (haemoglobin) with dianisidine (Owen, Silverman & Got, 1958).

RESULTS

Among the 929 individuals investigated, no transferrins other than C were found.

The frequencies of the haptoglobin phenotypes and of the Hp^1 gene are listed in Table 1, while Table 2 summarizes the homogeneity tests for the combined results as well as for various groupings of the communities according to their presumed affinities.

The Hp^1 frequencies of the Jewish communities are lower, on the whole, than those reported for West Europeans (Harris, Robson & Siniscalco, 1959; Galatius-Jensen, 1960). The Oriental Jews from different countries range close to the Hp^1 frequency of 0·25 reported by Harris *et al.* (1959) for a small sample of autochthonous Persians. All European Jews (Ashkenazim) originating from different areas of Central and Eastern Europe do not differ significantly in this respect from all Oriental Jews (Table 2 (5)).

It is somewhat surprising to find the Ashkenazic Jews, who are expected to exhibit some 'Mediterranean features' (Mourant, 1959), possessing slightly *lower* Hp^1 rates than the various Italian and Sardinian groups reported in the literature (Harris *et al.* 1959). As seen in Fig. 1, the haptoglobin frequencies of gentiles in Middle and Western Europe resemble the Italian pattern, but there is a tendency to higher Hp^1 rates, especially in Switzerland, Austria, Germany and France. While the data on Slavic groups are extremely scanty, it is of interest to note that the Polish Jews have significantly less Hp^1 ($\chi^2 = 5{\cdot}61$; $P = 0{\cdot}02$–$0{\cdot}01$) than the 0·36 found in Polish gentiles by Murawski & Miszczak (1961).

Table 1. *Haptoglobin frequencies in Jewish communities*

Community	No.	Phenotypes: 0	2–1 mod.	1–1 (o)	1–1 (e)†	2–1 (o)	2–1 (e)†	2–2 (o)	2–2 (e)†	Hp^1 frequency	± S.E.
(1) Ashkenazim											
*(*a*) Austria	37	1	—	4	3·7	15	15·7	17	16·6	0·32	0·06
(*b*) Germany	27	—	—	1	1·1	9	8·7	17	17·1	0·20	0·05
*(*c*) Poland	181	1	—	12	14·0	77	72·9	91	93·1	0·28	0·02
(*d*) Roumania	41	—	—	3	4·1	20	17·8	18	19·1	0·32	0·05
(*e*) Russia	92	1	—	11	8·3	33	38·4	47	44·3	0·30	0·03
(*f*) Others	121	—	—	12	10·8	48	50·6	61	59·6	0·30	0·03
All Ashkenazim	499	3	—	43	41·7	202	204·4	251	250·0	0·29	0·01
(2) Sephardim	44	—	—	5	6·2	23	20·6	16	17·2	0·38	0·05
(3) Inter-ethnic and unclassified	41	—	—	7	6·2	18	19·5	16	15·2	0·39	0·05
(4) Orientals											
*(*a*) North Africa	119	2	—	9	9·0	47	47·0	61	61·0	0·28	0·03
*(*b*) Near East	48	—	—	2	3·3	21	18·4	25	26·3	0·26	0·04
(*c*) Baghdad	79	—	1	5	4·8	29	29·3	44	43·8	0·25	0·04
(*d*) Kurdistan	42	—	—	1	2·6	19	15·8	22	23·6	0·25	0·05
*(*e*) Persia	16	—	—	1	1·9	9	7·2	6	6·9	0·34	0·08
(*f*) Yemen	41	1	—	2	2·5	16	15·0	22	22·5	0·25	0·05
All Orientals	345	3	1	20	23·9	141	133·0	180	184·1	0·26	0·02

* Further specification of groupings: (1) (*a*) Austria: includes Czechoslovakia and Hungary. (1) (*c*) Poland: includes Balticum. (4) (*a*) N. Africa: includes Algeria, Morocco, Tunisia, Tripolitania. (4) (*b*) Near East: includes Turkey, Syria, Lebanon and Egypt. (4) (*e*) Persia: includes Afghanistan.

† (e) = expected zygote frequencies calculated from observed gene frequencies on assumption of equilibrium. Phenotypes o and 2–1 mod. were excluded from the calculations.

Table 2. *Homogeneity tests of haptoglobin frequencies*

Groups compared	χ^2	D.F.	*P*
(1) All Ashkenazim (1*a–f*)	3·11	5	0·7–0·5
(2) Germany (1*b*) versus all other Ashkenazim	2·08	1	0·2–0·1
(3) All Orientals (4*a–f*)	1·74	5	0·9–0·8
(4) Four major groups (1–4)	9·09	3	0·05–0·02
(5) All Ashkenazim (1) versus all Orientals (4)	0·87	1	0·5–0·3
(6) All Ashkenazim (1) versus 2046 gentile Europeans*	38·46	1	$\ll$0·001

* Based on Hp^1 = 0·40 (Galatius-Jensen 1960).

Only two small groups in the present sample show excellent agreement with non-Jews from Italy and from some Central European countries. These are the Sephardim ('Spanish Jews') and the mixed group (3) 'Inter-ethnic and unclassified'. The Spanish Jews of our sample were mostly settled in Bulgaria, Greece, Italy and Jugoslavia before their immigration into Israel and it so happens that the inter-ethnic group includes many subjects related to this community through one parent. The higher Hp^1 values of these two samples are responsible for the

heterogeneity between the four major groups Table 2 (3). But since this heterogeneity is significant only at the 5% level, it hardly justifies any far-reaching conclusions.

The modified 2–1 phenotype appears to be very rare among Jews and was found only once in a subject from Iraq. Ahaptoglobinaemia is likewise very uncommon, in both Ashkenazim and

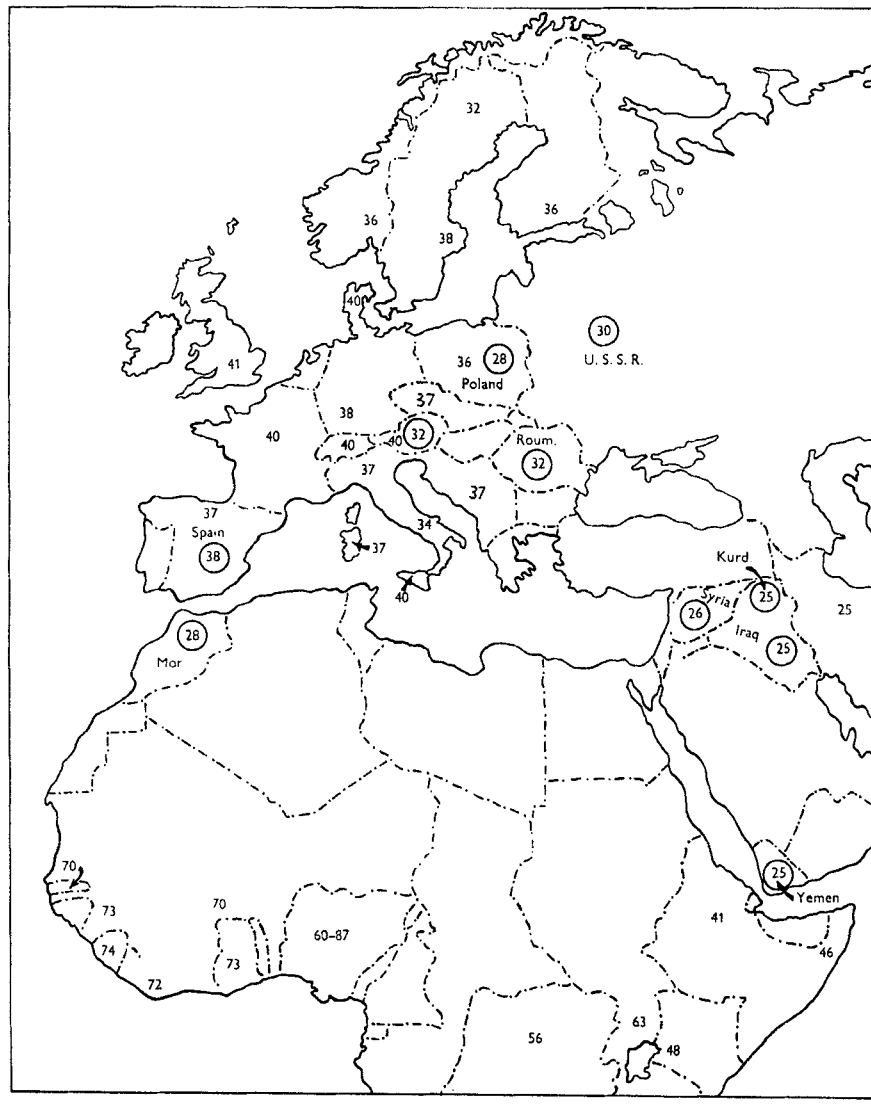

Fig. 1. Map of Hp^1 gene frequencies (in per cent) for Europe, Africa and the Near East. The encircled figures refer to the Jewish populations described in this paper. Figures outside circles are based on the literature dealing with autochthonous populations. Apart from the references quoted by Sutton *et al.* (1960) the following publications were used in the compilation of the map: Adam *et al.* (1961); Allison & Barnicot (1960); Baitsch *et al.* (1960); Baitsch *et al.* (1961, 1962); Murawski & Miszczak (1961).

Orientals. If phenotypic ahaptoglobinaemia may occur as a result of haemolytic conditions, a higher frequency of it might have been expected in the Oriental communities, in many of which the inherited deficiency of glucose-6-phosphate dehydrogenase (G–6–P–D) is very common (Szeinberg *et al.* 1958). It may be argued that the subjects were young army recruits selected

for good physical condition by previous medical examination. Thus although they would possess the trait for enzyme deficiency they would not be likely to suffer from acute haemolysis when voluntarily donating blood.

These considerations do not apply to the family sample of Jews from Kurdistan, who were unselected for physical fitness. Especial interest attaches to the search for ahaptoglobinaemia in this community, which, apart from G–6–P–D deficiency, exhibits also a high frequency of one of the inherited anaemias–thalassaemia (Matoth, Shamir & Freundlich, 1955; Matoth & Pinhas, 1958; Cohen *et al.* 1959; Cohen *et al.* 1962).

The settlers of the village under study stem from the mountains of Kurdistan in Northern Iraq, near the boundaries of Turkey, Syria and Persia. The bloods investigated revealed a high frequency of thalassaemia minor while over 70 % of the males as well as numerous females exhibited the enzyme deficiency.

If ahaptoglobinaemia can be temporarily produced by haemolytic conditions, the two erythrocyte defects might jointly or separately be responsible for such an effect in some individuals of this group. However, in the family sample of ninety-two individuals from the settlement no ahaptoglobinaemia was observed. Seventy-one persons with G–6–P–D deficiency had normal haptoglobin patterns and eight of these were also classified as suffering from thalassaemia minor. Two additional thalassaemic individuals without enzyme deficiency were also not ahaptoglobinaemic.

DISCUSSION

The blood group frequencies of the various Jewish communities have been carefully analysed by Mourant (1954, 1959). The *ABO* system indicates a more marked diversity among the Jews from various countries than do the *Rhesus* chromosomes. It is generally held that *ABO* frequencies change rapidly under the impact of selection while the more conservative *Rhesus* group yields better historical information. Although the Jewish communities differ quite markedly in the concentrations of the *C–D–E*–chromosomes, Mourant has drawn attention to certain characteristics which are shared to some extent by all the Jews including even the Ashkenazim. The high frequencies of both the *CDe* and the *cDE* chromosomes may be interpreted as 'Mediterranean' or 'Asiatic' features. Moreover, in all Jewish groups, including Ashkenazim, the *cDe* chromosome is somewhat more frequent than in gentile Europeans. This characteristic, which is shared by Moslems of the Near East, is taken by Mourant as indicative of some African admixture.

The low Hp^1 frequencies observed by us in Oriental Jews furnish some complementary evidence. By this criterion the Jews resemble other nations of the Near East and are set off more distinctly from the western Mediterranean peoples. The tribes of Western Africa which have been studied have mostly Hp^1 frequencies that are much higher than those of Mediterraneans, but large areas of Africa, including the Nile valley, remain to be studied. It is not impossible that the *cDe* chromosome with its striking gradient from Africa to the Mediterranean may be a much more delicate indicator of ancient African admixture than the haptoglobins. However, the extreme rareness of the modified 2–1 phenotype as well as the absence of any transferrin types other than C in the Jewish groups also testify against African affinities.

The haptoglobin frequencies of the small sample of Sephardic Jews are in good agreement with those of other Mediterraneans. But it came as a surprise to find the Ashkenazim so similar to Oriental Jews with regard to this polymorphic system. In many other respects the Ashkenazim

are rather set apart from the Oriental groups by characters, which they share with the gentile populations of Central and Western Europe. Thus, in a recent survey, Kalmus *et al.* (1961) found the rate of colour blindness in European Jews similar to that of other Europeans and nearly twice as high as that of most other Jewish populations (cf. Fig. 2). The virtual absence in Ashkenazim of G–6–P–D deficiency, which is present with variable frequencies in all the other Jewish communities (Szeinberg & Sheba, 1958; Szeinberg *et al.* 1958), is also regarded as a Central European feature.

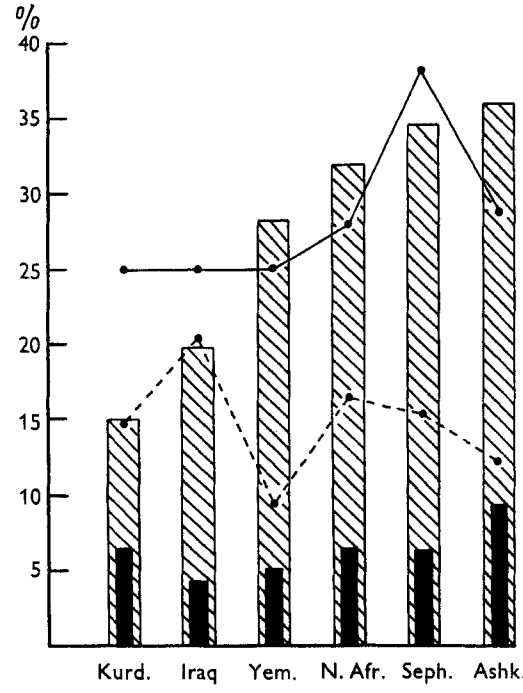

Fig. 2. The frequencies in various Jewish communities of four genes belonging to different polymorphic systems. Frequencies of Hp^1 based on present survey. Frequencies of *B* and *cde* based on Gurevitch and collaborators (1951–56) and on Margolis *et al.* (1957). Frequencies of colour blindness based on Kalmus *et al.* (1961).

% Hp^1, ———; % *B*, – – – –; % *cde*, ▨; % colour blindness, ▮.

While it is plausible that the 'Asiatic' haptoglobin frequencies of European Jews may indeed reflect their origin from the Middle East, the key to their convergence, in this respect, towards the pattern of Oriental Jewry cannot be offered before the completion of the East European map of haptoglobin distributions. The Slavic peoples resemble those of the Near East in the frequency of the *B* antigen. The same may well apply to the haptoglobin concentrations.

In Fig. 2 the Jewish communities are compared for gene frequencies at different loci, each of which reflects rather different affinities among them. Before resorting to the panacea of 'drift' in order to account for all conflicting tendencies, we should weigh carefully how much ethnic information each system can supply in *large* populations. For statistical reasons 'low frequency genes' like colour blindness and *cDe* in Europe may be more informative than 'high frequency genes' like Hp^1 and *CDe*. The haptoglobins do not show much geographic variation from north to south over Western Europe. Their clines in the east of Eurasia remain to be studied.

SUMMARY

Haptoglobin and transferrin types have been determined by starch gel electrophoresis on blood from 929 subjects belonging to various Jewish communities.

The frequency of the Hp^1 gene in 499 Ashkenazic Jews is 0·29 and does not differ significantly from the value of 0·26 found in 345 Jews of Oriental origin. The Hp^1 frequency of Ashkenazic Jews is significantly lower than that reported for the autochthonous populations of Central and Western Europe. Two small samples collected among Sephardic Jews and among the offspring of intercommunity marriages exhibit somewhat higher frequencies of the Hp^1 gene.

The modified 2–1 phenotype was found in a single subject from Baghdad. There were three cases of ahaptoglobinaemia among Ashkenazic Jews and three among the Oriental groups. No ahaptoglobinaemia was discovered in a family sample of ninety-two Jews from Kurdistan among whom thalassaemia minor was common and the majority of whom were affected with G-6-P-D deficiency.

All transferrins were of type C.

We are greatly obliged to Dr Tirzah Cohen for collecting the bloods of the Kurdish family sample. We are also much indebted to Dr J. V. Neel for his encouragement throughout this study and for his criticism during the preparation of the manuscript.

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