

GENETIC ASSOCIATION IN INFERTILITY: ABO, Rh (Subtypes), Le^a BLOOD GROUPS, G6PD DEFICIENCY AND HAEMOGLOBIN TYPES

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SYNOPSIS

Three hundred and eight Chinese and seventy four Indian infertile (primary) females were investigated for the distribution of ABO blood groups, G6PD deficiency and abnormal haemoglobins. A subsample of the smaller size was investigated for Rhesus blood groups (subtypes) and Le^a blood group. There was a relative excess of blood group A among infertile Chinese women compared to normal controls. Further a relative excess of Le^a negative A blood group was observed in the infertile groups compared to fertile women. R₁R₁ Rhesus gene complex was deficient in the infertile groups compared to fertile groups with lack of homozygotes in general. There was no significant difference in the distribution of G6PD deficiency and haemoglobin types between the infertile and control groups.

INTRODUCTION

Differential fertility and mortality are two of the important factors for selection and for the maintenance of the genetic polymorphism in a population. Infertility is at the lowest end of the scale of the former and is expected to exert a selective influence to maintain such a polymorphism. There has been a considerable amount of work on differential fertility in relation to ABO blood groups in different populations. The most commonly cited series with positive relationships are those of Waterhouse and Hogben, 1947; Allan, 1953; Kirk *et al*, 1953 and 1955; and Matsunaga and Itoh, 1958. Similarly there are series reported in which no association of fertility with ABO blood groups was observed (Johnstone, 1954; Haga, 1959; Reed *et al*, 1964).

There has been relatively less work on the association of blood genetic markers in infertility. This is also limited primarily to ABO incompatibility between husband and wife in infertile and fertile couples. (Behrman *et al*, 1960; Solish and Gershowitz, 1969 and Nag and Banerjee, 1970). Behrman *et al*, (1960) observed an excess of ABO incompatibility among the infertile couples compared to fertile ones. Solish and Gershowitz (1969) however in extensive investigations in America and Nag and Banerjee (1970) in India did not observe any such difference of ABO incompatibility between fertile and infertile or subfertile couples. No doubt

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that the sperm-antibody or antigenicity of uterine secretion may be one of the important factors for infertility (Morgan *et al*, 1977), the underlying mechanism of action is far from being clear.

Very little work has been reported in the literature on other polymorphism in relation to fertility or infertility excepting ABO and Rhesus blood groups (Reed *et al*, 1964; Cohen, 1970; Nag and Banerjee, 1970). In this study we have investigated the question of genetic association in infertility from a different angle, that is how far infertility has acted as a selective force in the maintenance of genetic polymorphism in the population. We examined the distribution of ABO, Rhesus subtypes and Le^a blood groups, G6PD (glucose-6-phosphate dehydrogenase) deficiency and haemoglobin types in a group of infertile women compared with controls.

MATERIALS AND METHODS

Patients

Three hundred and eighty two women of primary infertility comprised of 308 Chinese and 74 Indians formed the sample of this study. These were attending the Infertility Clinic under the supervision of one of us (S.S.R.), at the Kandang Kerbau Hospital, Singapore between January and December, 1971. They were all confirmed cases of primary infertility as established by clinical and laboratory investigations. It was not possible to collect samples of blood from the husbands for technical reasons. However they were examined clinically and their semen was examined microscopically. All of them were considered to be non-sterile.

All subjects were investigated for the distribution of ABO blood groups, G6PD deficiency and abnormal haemoglobins. A subsample of 190 Chinese and 47 Indian women were tested for distribution of Le^a blood group; and 117 Chinese and 20 Indians were investigated for Rhesus subtypes.

Controls

For ABO blood groups the published data based on blood donors of the Singapore Blood Transfusion Service (Chan, 1962) was taken as a control. For Rhesus blood groups 254 Chinese and 35 Indian fertile women attending the same hospital were investigated. For Le^a blood grouping the published series of Saha (1973) was taken as a control for the Chinese and 97 Indian fertile women of Indian origin were investigated for the Le^a control series (unpublished). For the control series of G6PD deficiency and abnormal haemoglobins 254 Chinese and 35 Indian fertile women attending the same hospital were investigated.

METHODS

5 ml of venous blood was collected from each individual using heparin as anti-coagulant. Blood was stored at 4°C and tested within 48 hours of collection. Routine blood grouping was carried out by slide test

using commercial antisera (Anti-A, B, D, C, E, c, e and Le^a) purchased from Biotest, USA. The details of the methods for G6PD deficiency and abnormal haemoglobins were the same as reported previously (Saha *et al*, 1973).

RESULTS AND DISCUSSION

ABO And Le^a Blood Groups.

Table I shows the distribution of ABO blood groups in infertile Chinese and Indian females compared to the control series based on the blood donor sample. There was an excess of individuals having blood group A (34.42%) in the infertile group compared to control series (25.99%) in the case of the Chinese. The difference is significant for A-O comparison ($\chi^2_1 = 8.21$) and A-B comparison ($\chi^2_1 = 7.17$). The fertility in relation to ABO types has been reported to be maximum in case of A group mothers (Waterhouse and Hogben, 1947; Kirk *et al*, 1953; Ford, 1961). The present finding is contrary to the above reports. However, this lends support to the A-type heterozygous disadvantage and B-type heterozygous advantage for selection suggested by Peritz (1967).

No significant difference in the distribution of ABO blood groups has been observed between infertile and control series in the case of Indians. This may be due to the small size of the sample. The present investigation suggests that females with A blood group are at a disadvantage. Further from Table 2 it is seen that there is an excess of blood group A secretors (Le^a-negatives) 31.72% among the infertile Chinese women compared to the control series (22.82%). This suggests that there may be a selection factor operating in case of infertility which may be explained due partly to the A-incompatibility mediated through secretor mechanisms. The results in the case of Indians are not convincing which may be again due to the small size of the sample.

Behrman *et al*, (1960) did not find any significant difference in the incidence of ABO (H) secretors between fertile and infertile couples. In spite of their findings, they suggested that the ABO — incompatibility may work through the secretor mechanism. A more detailed study is indicated to verify this finding.

Rhesus Blood Groups

The distribution of Rhesus phenotypes in infertile and fertile women in Chinese and Indians is presented in Table 3. There is a significant lack of R₁R₁ gene complex and lack of homozygotes in general among infertile women of Chinese origin ($\chi^2_1 = 9.55$ and 10.09 respectively) compared to fertile women. The distribution of Rhesus gene complexes in the present control series is in agreement with other published series from the regions reviewed by Hawkins (1973). A similar trend is also present in the case of Indians, but it has not reached the level of significance probably due to the small size of the sample. The distribution of Rhesus phenotypes in the present Indian control series is in agreement with those published by Kirk *et*

TABLE 1
DISTRIBUTION OF ABO BLOOD GROUPS IN INFERTILE WOMEN AND CONTROLS

Blood Groups	CHINESE				INDIANS			
	Infertility		Controls*		Infertility		Controls*	
	No	%	No	%	No	%	No	%
O	121	39.29	6644	43.53	20	27.03	1951	39.02
A	106	34.42	3967	25.99	17	22.97	1051	21.02
B	67	21.75	3814	24.99	30	40.54	1680	33.60
AB	14	4.55	837	5.48	7	9.46	318	6.36
Total	308	100.01	15262	99.99	74	100.00	5000	100.00

*Chan (1962). χ^2_1 : Chinese O – A = 8.21
O – A + $\frac{1}{2}$ AB = 6.95
A – B = 7.17

TABLE 2
DISTRIBUTION OF Le^a BLOOD GROUPS IN INFERTILE WOMEN AND CONTROLS

ABO blood groups	CHINESE								INDIANS							
	Infertility				Controls*				Infertility				Controls			
	Le ^a (+)		Le ^a (–)		Le ^a (+)		Le ^a (–)		Le ^a (+)		Le ^a (–)		Le ^a (+)		Le ^a (–)	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
O	19	42.22	64	44.14	20	38.46	101	41.91	3	25.00	10	28.57	7	33.33	24	31.58
A	9	20.00	46	31.72	17	32.69	55	22.82	2	16.67	10	28.57	2	9.52	19	25.00
B	12	26.67	30	20.69	12	23.08	59	24.48	7	58.33	11	31.43	11	52.38	28	36.84
AB	5	11.11	5	3.45	3	5.77	26	10.79	0	0.00	4	11.43	1	4.76	5	6.58
All	45	23.68	145	76.32	52	17.75	241	82.25	12	25.53	35	74.47	21	21.65	76	78.35

χ^2_1 : Chinese A Le^a (+) and Le^a (–) = 5.12.

* Saha (1973)

TABLE 3
DISTRIBUTION OF RHESUS BLOOD GROUPS IN INFERTILE WOMEN AND CONTROLS

Rhesus Phenotypes	CHINESE				INDIANS			
	Infertility		Controls		Infertility		Controls	
	No	%	No	%	No	%	No	%
R ₁ R ₂	4	3.42	6	2.36	—	—	—	—
R ₁ R ₁	37	31.62	126	49.61	4	20.00	14	40.00
R ₂ R ₂	2	1.71	3	1.18	—	—	—	—
R ₁ R ₂	45	38.46	84	33.07	4	20.00	6	17.14
R ₂ R ₂	4	3.42	8	3.15	1	5.00	2	5.71
R ₀ r	1	0.85	—	—	—	—	—	—
R ₁ r	21	17.95	22	8.66	7	35.00	12	34.29
R ₂ r	3	2.56	5	1.97	3	15.00	—	—
R''r	—	—	—	—	1	5.00	1	2.86
Total	117	99.99	254	100.00	20	100.00	35	100.00

χ^2_1 : Chinese R₁R₁ and other = 9.55 Homo and Heterozygous = 10.09

al, 1962 and Saha et al, 1976 in the population from southern India.

The above findings suggest a selection factor against heterozygotes at the Rhesus locus which is compatible with the suggestion of Haldane (1942). Further it is possible that the loci of ABO (H) and Rhesus are interdependant in the mechanism of selection as suggested by Cohen (1970).

G6PD Deficiency And Abnormal Haemoglobins.

Only two of 308 Chinese infertile women were deficient of G6PD compared to one in 254 Chinese fertile women. There was no deficient case among 74 infertile and 35 fertile women of Indian origin tested. No case of abnormal haemoglobin was detected in fertile or infertile groups in either race investigated.

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