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Frequency of Prenatal Deaths and Its Relationship to the ABO Blood Groups in Man

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INTRODUCTION

During the past 20 years a number of papers have been published reporting the operation of selection in the human ABO blood group system. Various characters have been examined in these studies, including the frequency of prenatal deaths (natural abortions and stillbirths). Among papers reporting relationships between the frequency of prenatal deaths and ABO selection, one of the most representative might be the work of Matsunaga and Itoh [1]. Analyzing a large set of data comprising more than 1,500 families on Hokkaido, the northernmost island of Japan, they showed that the frequencies of natural abortions among ABO-incompatible mating types were consistently higher than those among compatible mating types. Their results were confirmed later by Haga [2].

In 1962, two independent field studies were carried out on a Brazilian population [3] and on a population living in the city of Ohdate in the northern part of Japan [4]. One of the original purposes of these two studies was to reconfirm the presence of ABO incompatibility effects in modern human populations based upon complete family studies. However, they failed to repeat the results obtained by Matsunaga and Itoh; the effect of incompatibility on fetal death was absent or at most very much reduced.

Several other studies have also been reported which examined the relationships between parental blood types and the frequencies of prenatal deaths. Reed [5] studied the associations between ABO (and other systems) mating types and reproductive performances in Negro and Caucasian families in California. In analyzing the frequencies of abortions, stillbirths, or number of pregnancies, he found 44 statistically significant ($P = .05$) associations with the mating types among 1,008 tests. The expected number of significant results due to Type I errors is 50, and therefore the majority of the observed 44 significant results might be

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simply due to Type I errors. In four of the 44 cases, however, the associations were significant at the .0004 probability level; some of these might indicate real associations. Based on these observations and the results reported in other studies, he concluded that strong, consistent effects of ABO blood groups on reproductive performance have yet to be demonstrated.

Cohen and Sayre [6] examined the relationships between maternal blood types and fetal wastage in both whites and Negroes using the live-birth and fetal-death records from New York City. They found that type O white mothers showed significantly higher frequencies of fetal losses than other types, and they attributed this to ABO incompatibility effects. The relationship of fetal loss to maternal ABO type in Negroes did not mirror that for whites, however, and no clear pattern emerged.

The purpose of the present study is to show that selection in the ABO blood groups is operating in Japanese populations resulting in differential viabilities (mortalities) but is unrelated to ABO incompatibility among filial genotypes.

SUBJECTS AND METHODS

The two sets of data analyzed included the Ohdate study performed in 1962 and the Akita study completed in 1971. Both cities are located in Akita Prefecture in the northern part of the Japanese mainland. The method of collecting family data was identical for both studies and is described in [4].

Briefly, family records maintained in the city offices were examined and families chosen at random from among those in which the wife was between 30 and 40 years of age. The ABO typing for the parents and offspring was performed mainly by experienced professional technicians in the public health centers. The reproductive history of each family was obtained through interview with well-trained nurses who were residents of the communities and were acquainted with the families. A sample of 2,441 families was studied in Ohdate and 2,731 in Akita. As shown in our previous report [7], the frequency of ABO misclassifications appeared negligibly small.

RESULTS

It must be noted that family planning was in widespread use among these families and one of the methods used was induced abortions. The frequency of induced abortions among all pregnancies was 24.1% (about 1.0 per family) in Ohdate and 16.9% (about 0.5 per family) in Akita. Information about the nature of abortions, whether induced or natural, was obtained from each wife through interviews by trained nurses experienced in family-planning consultation. Although there might be a small fraction of misclassifications, the accuracy of such information is generally good. Data on induced abortions were excluded from tabulations.

A summary of the reproductive performances of each mating type in the two studies is given in table 1.

Because of the widespread use of family planning (especially in the Akita study), neither the average number of pregnancies nor the number of children born is useful for studying natural selection and therefore will not be discussed in the present study.

There were some differences between the present data and those reported for Akita Prefecture for the corresponding years in the vital statistics in Japan. The

TABLE 1

SUMMARY OF REPRODUCTIVE PERFORMANCES OF FAMILIES IN EACH MATING TYPE IN OHDATE AND AKITA STUDIES

Mating Type and Study (♀ × ♂)	No. Families	No. Fertile Families	Prenatal Deaths*	Live Births	Early Postnatal Deaths*	Total No. Pregnancies†
O × O:						
Ohdate	275	270	105 (.1185)	781	16 (.0205)	886 (3.222)
Akita	291	281	60 (.0920)	592	4 (.0068)	652 (2.241)
O × A:						
Ohdate	275	269	73 (.0865)	771	19 (.0246)	844 (3.069)
Akita	339	329	72 (.0916)	714	7 (.0098)	786 (2.319)
O × B:						
Ohdate	215	209	80 (.1178)	599	18 (.0301)	679 (3.158)
Akita	198	193	55 (.1276)	376	3 (.0080)	431 (2.177)
O × AB:						
Ohdate	78	76	23 (.0970)	214	3 (.0140)	237 (3.038)
Akita	67	66	10 (.0641)	146	0 (.0000)	156 (2.328)
A × O:						
Ohdate	287	277	103 (.1159)	786	20 (.0254)	889 (3.098)
Akita	323	314	62 (.0886)	638	10 (.0157)	700 (2.167)
A × A:						
Ohdate	254	247	52 (.0688)	704	12 (.0170)	756 (2.976)
Akita	318	304	52 (.0794)	603	4 (.0066)	655 (2.060)
A × B:						
Ohdate	200	193	63 (.0983)	578	7 (.0121)	641 (3.205)
Akita	234	225	42 (.0909)	420	2 (.0048)	462 (1.974)
A × AB:						
Ohdate	79	73	23 (.0891)	235	9 (.0383)	258 (3.266)
Akita	86	85	15 (.0794)	174	0 (.0000)	189 (2.198)
B × O:						
Ohdate	203	198	72 (.1104)	580	19 (.0328)	652 (3.212)
Akita	208	204	53 (.1079)	438	12 (.0274)	491 (2.361)
B × A:						
Ohdate	161	159	55 (.1093)	448	8 (.0179)	503 (3.124)
Akita	218	214	53 (.1069)	443	1 (.0023)	496 (2.275)
B × B:						
Ohdate	159	158	61 (.1180)	456	14 (.0307)	517 (3.252)
Akita	143	139	38 (.1138)	296	1 (.0034)	334 (2.336)
B × AB:						
Ohdate	46	44	10 (.0741)	125	2 (.0160)	135 (2.935)
Akita	55	54	10 (.0862)	106	0 (.0000)	116 (2.109)
AB × O:						
Ohdate	75	74	33 (.1231)	235	8 (.0340)	268 (3.573)
Akita	81	77	14 (.0828)	155	0 (.0000)	169 (2.086)
AB × A:						
Ohdate	67	65	16 (.0755)	196	2 (.0102)	212 (3.164)
Akita	82	78	14 (.0809)	159	1 (.0063)	173 (2.110)
AB × B:						
Ohdate	48	48	17 (.1049)	145	3 (.0207)	162 (3.375)
Akita	64	60	7 (.0551)	120	3 (.0250)	127 (1.984)
AB × AB:						
Ohdate	19	19	3 (.0508)	56	3 (.0536)	59 (3.105)
Akita	24	22	4 (.0784)	47	3 (.0638)	51 (2.125)
Total:						
Ohdate	2,441	2,379	789 (.1025)	6,909	163 (.0236)	7,698 (3.154)
Akita	2,731	2,645	561 (.0937)	5,427	51 (.0094)	5,988 (2.193)

* Frequency shown in parentheses.
† Average shown in parentheses.

frequencies of early postnatal deaths (death within 1 month after birth) in the present study agreed fairly well with those reported in the vital statistics. However, the present study showed much higher frequencies of prenatal deaths and much lower frequencies of infertile couples.

Presumably these differences can be partly accounted for by the following. First, it seems likely that the higher frequency of prenatal deaths in the present study was due to the inclusion of a larger fraction of abortions, especially those occurring at the early stages of gestation, which might not have been reported in the vital statistics. Second, the couples in the present study with no live births but who experienced induced or natural abortions were classified as fertile couples. In the vital statistics, some of these might be classified as infertile couples, especially when the abortions occurred at relatively early stages of gestation. We feel that the present data are more exhaustive than those reported in the vital statistics.

The frequencies of ABO types which can be tabulated from table 1 were homogeneous between male and female parents ($\chi^2_3 = 5.27$, $.20 > P > .10$ for Ohdate; $\chi^2_3 = 0.97$, $.90 > P > .80$ for Akita), and the frequencies of mating types agreed with the expectations. Based upon the assumption of random combinations of parental types, the χ^2 values were: $\chi^2_9 = 6.55$, $.70 > P > .50$ for Ohdate; $\chi^2_9 = 7.02$, $.70 > P > .50$ for Akita.

Frequency of Infertile Couples

The frequency of sterile couples was very low in the two studies (2%–3%), and therefore the information associated with them is limited. Analysis was performed by computing frequencies of sterile matings for each mating type in each study and then subjecting them to the arcsin transformation. Variance analysis was performed following the method described by Steel and Torrie [8]. Results are shown in table 2.

Clearly, there is no detectable difference in the frequencies of infertile couples among mating types, and no further analysis was performed.

Frequency of Prenatal Deaths

There was an apparent tendency for the frequency of prenatal deaths to increase with increasing pregnancy order. However, the pregnancy order $\times$ mating-type interaction was not significant in either of the two studies, the studies being pooled for all pregnancy orders in each mating type. Since the average number of pregnancies was smaller in the Akita study (see table 1), a reduced frequency of prenatal deaths for this city would be expected. In fact, the frequency in Akita (.0937) was slightly smaller than in Ohdate (.1025). This difference, however, is not large and may be due to the "pregnancy-order effect."

Variance analysis was performed as before; there was no overall difference in the frequency of prenatal deaths between Ohdate and Akita ($\chi^2_1 = 2.14$, $.20 > P > .10$), and the study $\times$ mating-type interaction was not significant ($\chi^2_{15} = 11.35$, $.80 > P > .70$). There were, however, highly significant differences among the 16 mating types ($\chi^2_{15} = 33.87$, $P < .01$). To examine this more specifically, a 4×4

TABLE 2

FREQUENCY OF INFERTILE COUPLES IN EACH MATING TYPE IN THE TWO STUDIES AND RESULT OF VARIANCE ANALYSIS

MATING TYPE ♀ × ♂	AKITA Freq.	AKITA *N*	OHDATE Freq.	OHDATE *N*	TOTAL Freq.	TOTAL *N*
O × O	.034	291	.018	275	.027	566
O × A	.027	339	.022	275	.024	614
O × B	.025	198	.028	215	.027	413
O × AB	.015	67	.026	78	.021	145
A × O	.025	323	.035	287	.030	610
A × A	.044	318	.028	254	.037	572
A × B	.034	234	.035	200	.035	434
A × AB	.012	86	.076	79	.042	165
B × O	.019	208	.025	203	.022	411
B × A	.018	218	.012	161	.016	379
B × B	.028	143	.006	159	.017	302
B × AB	.018	55	.043	46	.030	101
AB × O	.049	81	.013	75	.032	156
AB × A	.049	82	.030	67	.040	149
AB × B	.063	64	.000	48	.036	112
AB × AB	.083	24	.000	19	.047	43
Total	.023	2,731	.034	2,441	.028	5,172

ANALYSIS OF VARIANCE

Source	χ^2	df	Probability
Between studies	1.31	1	$.30 > P > .20$
Among mating types	17.70	15	$.30 > P > .20$
Study × mating-type interaction	9.65	15	$.90 > P > .80$

NOTE.—*N* = no. families.

contingency table was constructed as shown in table 3. Since the Ohdate and Akita studies showed homogeneous percentages of prenatal deaths, they were pooled. The result of variance analysis is also shown in this table.

The frequency of prenatal deaths was heterogeneous among paternal as well as maternal genotypes. Interaction was not significant. The type A and AB parents (both fathers and mothers) showed a reduced frequency of prenatal deaths. The fact that this effect was observed in both mothers and fathers suggests that the frequency of prenatal deaths depends not upon parental genotype but upon the genotype of the fetus itself. Note that the average frequencies of prenatal deaths for type A and for type AB parents are practically identical as are those for type O and for type B parents. The fetus with the *A* gene (or genes) presumably shows higher viability and thus demonstrates a reduced frequency of prenatal deaths.

Table 4 shows the frequencies of abortions for three groups of matings classified

TABLE 3

FREQUENCY OF PRENATAL DEATHS IN A 4 × 4 CONTINGENCY TABLE, AND RESULT OF VARIANCE ANALYSIS

MATERNAL ABO TYPE	PATERNAL ABO TYPE									
	O		A		B		AB		Total	
	Freq.	N	Freq.	N	Freq.	N	Freq.	N	Freq.	N
O	.107	1,538	.089	1,630	.122	1,110	.084	393	.102	4,671
A	.104	1,589	.074	1,411	.095	1,103	.085	447	.091	4,550
B	.109	1,143	.108	999	.116	851	.080	251	.109	3,244
AB	.108	437	.078	385	.083	289	.064	110	.088	1,221
Total	.107	4,707	.088	4,425	.108	3,353	.082	1,201	.099	13,686

ANALYSIS OF VARIANCE

Source	χ^2	df	Probability
Between male genotypes	17.76	3	$P < .001$
Between female genotypes	9.08	3	$P \doteqdot .025$
Male × female interaction	7.68	9	$.70 > P > .50$

NOTE.—N = total no. pregnancies.

according to the probabilities of producing a fetus with the A gene. The probability zero group includes mating types O × O, O × B, and B × B; the probability .5–.6 group includes O × AB, B × AB, B × A, and O × A matings; and the .75–.83 probability group includes AB × AB, A × AB, and A × A.

The correlation between the frequencies of prenatal deaths and the probabilities of having an A-bearing fetus is clearly seen. Note that the relationship seems to deviate from linearity; the last group shows a reduction in the frequency of prenatal deaths greater than would be expected based upon the difference between the first two groups. This may suggest that the viability of the A homozygote is greater than that of the heterozygote, although this question is open for future studies.

TABLE 4

RELATIONSHIP BETWEEN FREQUENCY OF PRENATAL DEATHS AND PROBABILITY OF PRODUCING A-CARRYING FETUS

	PROBABILITY		
	0	.5–.6	.75–.83
Frequency of prenatal deaths	.1129	.0967	.0761
No. pregnancies	4,642	6,691	2,353

As mentioned at the beginning of this section, the frequency of prenatal deaths seems to increase with increasing pregnancy order. The figures shown in table 4 were retabulated for each pregnancy order (fourth and later were pooled together) separately and are shown in table 5. The tendency was consistent in each pregnancy order.

TABLE 5

RELATIONSHIP BETWEEN FREQUENCY OF PRENATAL DEATHS IN EACH PREGNANCY ORDER AND PROBABILITY OF PRODUCING *A*-CARRYING FETUS

	Probability							
	0		.5–.6		.75–.83		Total	
Pregnancy Order and Study	Freq.	*N*	Freq.	*N*	Freq.	*N*	Freq.	*N*
1:								
Ohdate	.0739	812	.0660	1,121	.0687	393	.0692	2,326
Akita	.0814	786	.0704	1,293	.0571	473	.0713	2,552
Total	.0776	1,598	.0684	2,414	.0624	866	.0703	4,878
2:								
Ohdate	.0860	709	.0810	963	.0570	351	.0786	2,023
Akita	.1127	612	.0899	1,001	.0720	361	.0937	1,974
Total	.0984	1,321	.0855	1,964	.0646	712	.0861	3,997
3:								
Ohdate	.1188	564	.1207	729	.0639	266	.1103	1,559
Akita	.1424	330	.1149	470	.1267	150	.1263	950
Total	.1275	894	.1184	1,199	.0865	416	.1164	2,509
4:								
Ohdate	.1972	649	.1536	866	.1055	275	.1642	1,790
Akita	.1469	177	.1793	251	.1548	84	.1641	512
Total	.1864	826	.1594	1,117	.1170	359	.1642	2,302

NOTE.—N = no. pregnancies.

A comparison between ABO-incompatible and compatible mating types was also made; no difference was found between the two groups ($\chi^2_1 < 1$).

Frequency of Early Postnatal Deaths among Live Births

The postnatal deaths discussed here are those which occurred from natural causes within 1 month after birth. As seen in table 1, the frequency of postnatal deaths is generally low, especially in the Akita study. Since the frequency was too low (less than 1%) in the Akita study to obtain any meaningful information, variance analysis was performed only for the Ohdate study by constructing a 4×4 contingency table as before. No significant difference was found either among maternal genotypes ($\chi^2_3 = 1.74$, $.70 > P > .50$) or among paternal genotypes ($\chi^2_3 = 2.63$,

$.50 > P > .30$). Interaction between paternal and maternal genotypes was not significant ($\chi^2_9 = 14.11$, $.20 > P > .10$).

Although no significant difference was found among mating types, it is interesting to examine whether the frequencies of early postnatal deaths tend to correlate to differential mortalities of genotypes of the children with or without the *A* gene, as was the case in prenatal deaths. The 16 mating types were grouped into three classes according to the probabilities of producing *A*-carrying zygotes, as done before. These are shown in table 6.

TABLE 6

RELATIONSHIP BETWEEN FREQUENCY OF EARLY POSTNATAL DEATHS AND PROBABILITY OF PRODUCING *A*-CARRYING FETUS

	Probability					
	0		.5–.6		.75–.83	
Study	Freq.	*N*	Freq.	*N*	Freq.	*N*
Ohdate	.0277	2,416	.0212	3,302	.0219	1,191
Akita	.0118	1,702	.0084	2,742	.0081	983

NOTE.—*N* = no. live births.

The tendency is not so clear, but it is noted that the non-*A* producing group showed the highest frequency of postnatal deaths in both studies. Probably the relative viabilities of genotypes are parallel between pre- and postnatal deaths, but the difference is much smaller for the postnatal deaths.

Again, no difference was found between ABO-compatible and incompatible mating groups.

DISCUSSION

This study failed to confirm the results obtained by Matsunaga and Itoh [1] and Haga [2]; no difference was detected in the frequency of prenatal deaths between ABO-incompatible and compatible mating groups.

There was, however, clear evidence that the frequency of prenatal deaths was dependent upon the genotype of the fetus; the fetus bearing the *A* gene seems to show lower mortality. Although the differences are very small, a similar tendency is also found in the frequency of postnatal deaths.

The present results are not in good agreement with those obtained by Cohen and Sayre [6]. They compared the frequencies of fetal losses between type O and type AB (or "non-O" as a group) white mothers and found that the frequency was higher for type O mothers. They attributed this to ABO incompatibility effects. In their study, however, type B mothers also showed as low or lower frequency of fetal loss as that of type AB mothers, and it seems difficult to conclude that these results were due to incompatibility effects. Their data could be interpreted to mean that type B and type AB, or *B*-carrying, white mothers experienced reduced frequency of prenatal deaths. Whether the difference in results between Cohen and Sayre's and our studies are due to selective forces which operate in different directions between Japanese and Caucasian populations is yet unknown.

Finally, it should be mentioned that the present observation, differential mortalities among genotypes, does not necessarily imply the existence of distorted segregation frequencies among children. Segregation frequencies would certainly be affected by differential viabilities, but by other factors as well.

In our previous paper [7], we reported that the segregation frequencies among children agreed fairly well with those expected based upon the Hardy-Weinberg distribution. A similar result was reported by Sing et al. [9]. The simplest interpretation of these results is that natural selection in the ABO system is nearly absent among modern human populations. However, the rough agreement between observed and expected frequencies could be the result of two or more selective forces operating in the opposite directions at different stages of the life cycle in such a way that their effects on segregation frequencies are somehow balanced. A simple model for this would be the balance in selective forces between pre- and postzygotic stages, such that the postzygotic stage selects for while the prezygotic stage selects against the *A* gene. A complete description of the selective mechanisms operating in the ABO system is still open for future studies but on the strength of the observations reported in the present paper (see the consistent results shown in table 5) we conclude that natural selection (differential viability) is operating in favor of *A*-carrying zygotes. Perhaps other selective forces, such as prezygotic selection against the *A* gene, may also be operating in this system.

SUMMARY

Two large sets of family data collected from the cities of Ohdate (1962) and Akita (1971) in Akita Prefecture, northern Japan, were analyzed to study the relationships between the ABO blood types and the frequencies of infertile couples and pre- and postnatal deaths.

The frequency of deaths for fetuses bearing the *A* gene (or genes) appeared lower than that for fetuses without it. This relationship may also be true for early postnatal deaths, but the data were less clear. The frequency of infertile couples appears independent of ABO blood type. There was no evidence to support any effect of ABO incompatibility.

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