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A Two-Generation Study of Human Sex-Ratio Variation

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SUMMARY

We report here the first vertical population study of human sex-ratio variation. Sex-ratio data for 2 generations from Akita, Japan, have been analyzed. Parental age, birth order, sequences of the sexes at birth, and generations have no statistically significant effect on sex ratio. There is a slight excess of males at birth, as is typical for human sex-ratio studies. There is evidence of sex-ratio-dependent family planning. An analysis of vertical transmission of sex-ratio modifying factors that excludes effects of birth order in both the parental and offspring generations has detected a marginally significant paternal effect. Genetic variability of the sex ratio, if present at all, is of a very minor magnitude.

INTRODUCTION

Human sex-ratio variation has been the subject of many investigations, reviewed by Gini [1] and Edwards [2, 3]. It is well established that the number of males regularly exceeds the number of females at birth, and that the magnitude of the excess varies among populations [4–6]. Some sex-ratio modification is caused by interaction between Hepatitis B virus and male-associated antigens [7]. Birth order and paternal age might effect progeny sex ratio [8–11], but statistical complications render the data analyses equivocal [6]. Positive correlations between the sexes of successive births have been detected [12, 13] but are not general [14].

The possible genetic basis of human sex-ratio variation has been of particular interest, even though convincing evidence of such variability is lacking [3]. Variation among populations is not sufficient to demonstrate genetic variability.

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Edwards [2] cites two well-known family trees that exhibited a marked excess of one sex, one case involving 72 female births and no male births. Morton et al. [5] found that the unusually high male sex ratio of Koreans persists in interracial crosses in Hawaii that involve Korean males. This exceptional observation is consistent with a primary segregation disturbance or gametic selection. Because heterogeneity among families is a prerequisite for genetic variability, much effort has been devoted to analysis of family sex ratios within single populations and single generations. The statistical problems are complex; between-family heterogeneity is confounded with binomial sampling error, and with temporal changes in families (parental age, birth order, sex-ratio-dependent family planning). Edwards [12] developed and applied a statistical method of sex-ratio analysis that detects parity effects and is independent of family limitation. The method has so far revealed only a "remarkable" absence of heterogeneity [3].

We report here a new approach to the search for genetic variability of human sex ratio. We test for the transmission of sex-ratio modifying factors by analyzing 2-generation family data that include sequences of the sexes in both generations. It is, to our knowledge, the first vertical population study of human sex-ratio variation. We also present horizontal analyses that provide information about the excess of males at birth, the correlations between successive births, birth order and parental age, and family planning effects on sex ratio.

SUBJECTS AND METHODS

The data analyzed here are part of a larger study of ABO blood groups, prenatal mortality, and birth-order-dependent ABO segregation conducted by Hiraizumi et al. [15, 16]. The study population is from the city of Akita, Akita Prefecture, Japan. Data collection was completed in 1972 using the methods described by Hiraizumi [17]. Briefly, family records maintained in city offices were examined and families were chosen at random from among those in which the wife was between ages 30 and 40. The reproductive history of each family was recorded through interviews conducted by well-trained nurses. Nurses were residents of the community and were acquainted with the families. Data recorded included the following: birth dates of the wife (proband) and her spouse; the number and sequence of sexes of the wife's sibs and the husband's sibs; birth dates of their live-born offspring; and sequences of the sexes among all of the probands' pregnancies, where known, including live births, stillbirths, and clinical abortions.

Statistical methods for the horizontal analyses are based on techniques developed by Edwards ([3] and references therein). The statistical technique for vertical analysis presented here is new. It is designed to test for the transmission of sex-ratio modifying factors from generation to generation. The technique is nonparametric, applicable to the male and female lines separately, and is independent of birth order. It is described below under the title of "position-by-position" analysis.

RESULTS

Parental and Offspring Sibships

Distributions of sibship sizes based on live births are shown in table 1. For the parental generation data, 2,511 maternal sibships and an equal number of paternal sibships have been pooled. Parental sibship counts include probands, husbands of probands, and incidences of infant mortality among sibs of known or unknown sex. Parental sibships are complete. Offspring sibships are reported separately for live births and for pregnancies. The latter includes live births, stillbirths, and clinical abortions of known or unknown sex. Offspring sibships are not necessarily complete.

Total sex ratio (percent males) in the parental generation is 50.48, based on 21,760 pooled maternal and paternal sibs, but not including probands and their husbands. Because the sample was selected from married couples, inclusion of probands and husbands would bias the sex ratio toward 50.0; that is, inclusion of probands and husbands increases the sample size by 5,022 individuals, exactly half of whom are female. The biased sex ratio in the parental generation is 50.39. Sex ratio in the offspring generation is 50.67, based on 5,038 pooled live births, or 50.99, based on 6,724 pooled pregnancies. There are no statistically significant differences in sex ratio between generations or between live births and stillbirths in the offspring generation. In table 1 and below, sex-ratio means and variances were computed by pooling individuals without weighting by family size.

Birth-order Effects

Sex ratios classified according to birth order are shown, for both generations, in the second part of table 1. There is a consistent excess of males particularly evident in the early births and pregnancies. The linear regression of sex ratio on birth order in the parental generation is not statistically significant [regression coefficient (b) = 0.0008, standard error of the regression coefficient (se) = 0.0019]. Similar regression analyses for the offspring generation show no statistically significant trends in birth order (for live births, b = −0.0180, se = 0.0133; for pregnancies, b = 0.0114, se = 0.0122). Regressions include birth orders with 10 or more individuals of known sex. The regression analyses test only for overall interaction; sex-ratio distortion at particular birth positions and statistical associations between births will be considered in a later section.

Sibship Size and Sex Ratio

The third part of table 1 shows mean sibship sex ratios classified by total sibship size for the parental generation data. The linear regression of sex ratio on size is not statistically significant (b = 0.0010, se = 0.0015). The standard deviations of sex ratios reported in the third part of table 1 are very close to that expected on the basis of binomial sampling. There is no consistent trend of over or under dispersion of sibship sex ratios.

While no overall interaction is indicated, it is possible that family planning has been practiced, based on a desire to end reproduction with one male and one female birth [13, 18, 19]. Such family planning would cause an excess of sibships with the last two sibs of different sexes, compared to the numbers of sibships ending with two births of the same sex. Appropriate data are presented in the fourth part of table 1, which include all sibships of the parental generation for which the sexes of the last two births are known. The total number of families ending with different sexes is not significantly different from the number of families ending with the same sex. In pairwise contrasts classified by sibship size, the differences between numbers of the two types of families are negative in five cases, positive in five cases, and zero in two cases. From the data presented,

TABLE 1

SUMMARY OF SEX RATIO DATA

1. Distribution of sibship sizes

	SIBSHIP SIZE													
	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Generation:														
Parental	0	152	292	488	771	925	890	722	430	204	104	33	9	2
Offspring (live births)	92	434	1,486	398	79	16	1	3	2	0	0	0	0	0
Offspring (pregnancies)	92	295	861	680	363	143	51	17	8	0	0	1	0	0

2. Sex ratio by birth order

		BIRTH ORDER												
		1	2	3	4	5	6	7	8	9	10	11	12	13
Generation:														
Parental	F*	2,370	2,404	2,238	2,013	1,685	1,135	769	408	173	65	20	5	2
	M*	2,578	2,407	2,288	2,029	1,596	1,246	718	357	170	78	23	5	0
	%M	52.1	50.0	50.6	50.2	48.6	52.3	48.3	46.7	49.6	54.5	53.5	50.0	0.0
Offspring (live births)	F	1,185	987	247	48	13	2	2	1	0	0	0	0	0
	M	1,234	998	251	53	9	4	3	1	0	0	0	0	0
	%M	51.0	50.3	50.4	52.5	40.9	66.7	60.0	50.0	...	...	...	...	...
Offspring (pregnancies)	F	1,056	856	376	162	43	9	5	1	0	0	0	0	0
	M	1,146	806	463	129	40	16	6	1	0	0	0	0	0
	%M	52.0	48.5	55.2	44.3	48.2	64.0	54.6	50.0	...	...	...	...	...

3. Sibship sex ratio by size

	Parental sibship size												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Mean sex ratio	47.4	48.8	53.3	50.3	49.9	50.1	51.0	49.8	51.1	50.7	49.3	54.8	45.3
Standard deviation	50.1	34.0	30.4	25.1	22.6	20.7	20.1	17.3	15.4	16.6	18.6	15.7	1.2

4. Sex ratio and family planning

	Parental sibship size											
	2	3	4	5	6	7	8	9	10	11	12	13
Sex of last two offspring:												
Same	131	250	394	445	430	339	221	99	54	14	5	1
Different	157	228	369	472	451	375	201	98	48	26	5	1

*F = female, M = male.

it is possible to construct 11 two-by-two contingency tables, one for each sibship size 2–12, to test the hypothesis that stopping or continuing reproduction is independent of the similarity or difference of the sexes of the last two sibs. The test for sibship size 2 is statistically significant ($\chi^2 = 5.80$, df = 1, $P < .025$). For the other sibship sizes, there is no significant or marginally significant chi-square. Comparable tests for the offspring generation would not be informative because sibships are not necessarily complete.

Effect of Parental Age

Table 2 presents data for testing the effect of parental age on progeny sex ratio. Offspring are classified according to birth order and sex. For each classification, the mean paternal and maternal ages are shown. A paternal effect on progeny sex ratio would be manifest as a difference between mean ages of fathers of males and fathers of females for a given birth order. All mean differences are less than 10 months, and are much smaller than the standard deviations of the mean parental ages. It can be concluded that there is no significant parental-age effect on progeny sex ratio independent of birth order. A similar analysis based on pregnancies rather than on live births gives the same result.

Sequences of the Sexes

Edwards [20] described a unified method of analysis of sex-ratio data based on factorial experimentation. A 2^N factorial design tests for the effect of N factors corresponding to the presence or absence of a male birth among each of N offspring in a family. Main effects indicate the deviation of sex ratio from 50.0 for each birth order, while two-factor and higher-order interactions test for statistical associations between births. Interaction terms can be divided into consecutive and nonconsecutive interactions to test the effects of successive births and nonsuccessive births. A complete description is contained in [20], and computational notes are contained in the appendix to Edwards [18].

TABLE 2

PARENTAL AGE AND PROGENY SEX RATIO

			PATERNAL AGE		MATERNAL AGE	
BIRTH ORDER	SEX	N*	Mean	SE*	Mean	SE
1	F*	1,179	28.6	0.09	25.1	0.09
	M*	1,230	28.5	0.10	24.9	0.09
2	F	980	31.2	0.11	27.5	0.11
	M	993	31.5	0.12	27.7	0.10
3	F	247	32.5	0.29	28.6	0.20
	M	249	32.6	0.23	28.4	0.22
4	F	47	32.6	0.47	29.3	0.39
	M	52	33.6	0.53	30.1	0.50
All	F	2,466	30.2	0.08	26.5	0.07
	M	2,531	30.2	0.08	26.5	0.07

*N = no. individuals of given birth order and sex, SE = standard error of the mean, F = female, M = male.

TABLE 3

FACTORIAL ANALYSIS OF THE SEQUENCES OF SEXES, PARENTAL GENERATION

	N* = 2		N = 3		N = 4		N = 5	
	X^2	df	X^2	df	X^2	df	X^2	df
Main effects	1.51	2	9.84†	3	1.03	4	11.68	5
Consecutive two-factor interactions	2.35	1	3.36	2	1.27	3	5.94	4
Nonconsecutive two-factor interactions	...	...	1.21	1	1.28	3	6.11	6
Higher-order interactions	...	...	0.13	1	4.86	5	9.53	16
Total	3.86	3	14.54†	7	8.44	15	33.26	31

*N = sibship size.
†$P < .05$.

Results of a factorial analysis of the parental generation in the Akita study are shown in table 3, where N is sibship size. The only statistically significant term is for main effects in sibship size 3, attributable to the excess of male births in the first-birth position. A similar analysis of the offspring generation is summarized in table 4, showing statistically significant interaction between birth orders 1 and 3. There are insufficient data to analyze the N = 5 case. The analysis-of-offspring data must be interpreted cautiously, because sibships are not necessarily complete. The factorial analysis can be modified to a logarithmic factorial analysis to achieve independence from the effects of family limitation, as shown by Edwards [12]. The logarithmic factorial analysis of the Akita data shows no statistically significant terms, conforming to simple binomial expectations both with respect to the sex ratio at each birth and the sequences of sexes among births. It follows that the horizontal analyses give no evidence for between-family heterogeneity of the sex ratio which could be of genetic origin.

Vertical Analyses

Data for detecting vertical transmission of sex-ratio factors are presented in table 5. Offspring are classified according to birth order and sex. For each classification, the mean sex ratio among corresponding paternal and maternal families

TABLE 4

FACTORIAL ANALYSIS OF THE SEQUENCES OF SEXES, OFFSPRING GENERATION

	N* = 2		N = 3		N = 4	
	X^2	df	X^2	df	X^2	df
Main effects	1.66	2	1.15	3	4.32	4
Consecutive two-factor interactions	0.15	1	0.33	2	1.08	3
Nonconsecutive two-factor interactions	...	...	5.15†	1	1.80	3
Higher-order interactions	...	...	0.21	1	1.90	5
Total	1.81	3	6.84	7	9.10	15

*N = sibship size.
†$P < .05$.

TABLE 5

MEAN SEX RATIO IN PARENTAL SIBSHIP GIVEN SEX AND BIRTH ORDER OF OFFSPRING

BIRTH ORDER OF OFFSPRING	SEX OF OFFSPRING	SEX RATIO OF PATERNAL SIBSHIP Mean	SE*	N*	SEX RATIO OF MATERNAL SIBSHIP Mean	SE	N
1.............	F*	51.26	0.81	1,141	49.97	0.82	1,138
	M*	50.95	0.78	1,189	51.13	0.79	1,182
2.............	F	51.39	0.87	955	50.03	0.89	947
	M	50.29	0.90	957	51.59	0.88	954
3.............	F	49.22	1.74	237	51.45	1.73	237
	M	50.26	1.69	239	52.50	1.72	239
4.............	F	47.00	4.42	46	43.40	3.72	46
	M	53.82	3.73	52	50.82	3.26	52
All............	F	51.04	0.38	2,711	50.22	0.39	5,022
	M	50.86	0.38	2,698	51.43	0.38	5,143

*SE = standard error of the mean, N = no. individuals of given birth order and sex, F = female, M = male.

is shown, excluding probands and husbands. Transmission of sex-ratio modifying factors independent of birth-order effects would be manifest as a difference between the mean paternal or maternal sibship sex ratios for male and female offspring of a particular birth order. Pairwise contrasts fall well within the range of variation of paternal and maternal sex ratios, and are in no cases statistically significant. Numbers of maternal and paternal families considered differ slightly because of the exclusion of families with one or more sibs of unknown sex.

By pooling of the parental generation in the above vertical analysis, the possible effects of a transmissible sex-ratio factor are confounded with grandparental age and birth-order effects in the parental generation. This complication can be overcome, with some loss of information, by considering a "position-by-position" vertical analysis. The test involves comparison of the sex of the *i*th sib in the maternal or paternal family with the sex of the *i*th birth among the offspring. Data are shown in table 6, where the parameters a–d are defined. Probands and husbands are included. Following the statistical method of Morton and Chung [21], we define $\theta = E\ (ad/bc)$, where θ is a parameter expressing the degree of association between sexes of the *i*th parental sib and the *i*th offspring. On the hypothesis of no association, $\theta = 1$ and the maximum likelihood score $U = (ad - bc)/N$, with variance $K = (a + b)(c + d)(a + c)(b + d)/N^3$. For each birth order i, X^2 is computed as U^2/K. There are no statistically significant associations for either paternal or maternal transmission, although the deviation X^2 for paternal effects is marginally significant ($P = .057$). Further, for all five birth orders in the paternal analysis for which $N \geqslant 10$, U is positive, indicating a tendency toward positive correlation between the sexes of the *i*th paternal sib and the *i*th offspring. There is no indication of possible maternal transmission of sex-ratio modifying factors.

DISCUSSION

The analysis of 2 generations of sex-ratio data from Akita shows, for the most part, a close fit to the expectations of simple Mendelian segregation and binomial sampling. There are only a few significant deviations.

First, there is evidence in these data, as in other human sex-ratio data, of a slight excess of males at birth. The sex ratio falls within the range of variation observed in other human populations.

Second, while there is no overall interaction between family size and the mixture of the sexes among offspring, families of two like-sexed offspring are more likely to continue reproduction than are families of two different-sexed offspring. This can be explained by sex-ratio-dependent family planning, as has been observed in several other studies [13, 18, 19].

Third, the position-by-position analysis (table 6) gives marginally significant evidence for vertical transmission of sex-ratio modifying factors through the paternal line, but not through the maternal line. In classifying individuals of the

TABLE 6

POSITION-BY-POSITION VERTICAL ANALYSIS

Test for paternal transmission:

	Paternal sib *i*							
	F Offspring *i*		M Offspring *i*					
	F (*a*)	M (*b*)	F (*c*)	M (*d*)	*N*	*U*	*K*	X^2
i = 1	419	429	733	782	2,363	+5.59	135.84	0.23
2	395	358	552	585	1,890	+17.70	113.25	2.77
3	89	74	135	150	448	+7.50	25.92	2.17
4	15	15	22	26	78	+0.77	4.60	0.13
5	6	1	4	2	13	+0.62	0.57	0.66
Sum						+32.16	280.18	

Heterogeneity X^2 = 2.27, df = 4
Deviation X^2 = 3.69, df = 1
Total X^2 = 5.96, df = 5

Test for maternal transmission:

	Maternal sib *i*							
	F Offspring *i*		M Offspring *i*					
	F (*a*)	M (*b*)	F (*c*)	M (*d*)	*N*	*U*	*K*	X^2
i = 1	704	717	464	493	2,378	+6.05	142.92	0.26
2	561	563	381	386	1,891	+1.08	113.97	0.01
3	144	137	87	83	451	+0.07	26.46	0.00
4	23	28	18	18	87	−1.03	5.26	0.20
5	5	4	2	2	13	+0.15	0.69	0.03
Sum						+6.32	289.30	0.50

Heterogeneity X^2 = 0.36, df = 4
Deviation X^2 = 0.14, df = 1
Total X^2 = 0.50, df = 5

NOTE: Parameters *a*–*d* indicate the no. of the four possible combinations of the sexes of two individuals: the *i*th-born in the offspring generation and the *i*th-born in the parental generation. The individuals of the parental generation are considered separately for the paternal and maternal lines. *N* = the no. sex combinations considered for a given birth order "*i*." Computation of the parameters *U*, *K*, and X^2 is described in the text.

offspring generation according to birth order and sex, it appears that there is no transmission: mean sex ratios among maternal and paternal sibs are the same for male and female offspring, as shown in table 5. However, pooling parental sibs confounds effects of birth order and grandparental age in the parental generation, so an alternative test has been devised. We compared the sex of the *i*th paternal or maternal sib with the sex of the *i*th offspring, as shown in table 6. There is a consistent trend toward positive association between the sexes of those individuals through the paternal line; the deviation X^2 is marginally significant ($P = .057$). The direction of the deviation is consistent with modification of the segregation of the sex chromosomes in males, but the influence of cultural factors or sex-dependent viability cannot be ruled out.

No statistically significant effects of birth order, parental age, sequence of sexes, or generations have been detected. There are striking differences in family size between generations, due in part to sampling bias. The sampling method excluded families of the parental generation with zero progeny, while the offspring-generation families are not necessarily complete.

It must be concluded that the genetic variability of the sex ratio, if present at all, is of a very minor magnitude. Considering the many biological factors by which sex ratio could be modified, including production and motility of X- and Y-bearing sperm, and the relative viabilities of the sexes, the absence of heterogeneity is remarkable. Models of the adaptive evolution of population sex ratio do not preclude heterogeneity of family sex ratios within populations [3, 22]. As Williams [22] has argued, the physiological advantages of adjusting offspring sex to maternal capabilities and the demographic advantages of decreasing competition for mates ought to have led to adaptive evolution of sex-ratio control. Instead, the evidence from vertebrates, further documented in this study, suggests that sex ratio is almost indistinguishable from a simple process of binomial sampling. The apparent absence of genetic variation and adaptive evolution in vertebrate sex ratio remains a serious problem in evolutionary theory.

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