

Are there true ABO and Rh segregation distortions?

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ABSTRACT

Reports on ABO and Rh segregation distortions found in mother-child or sib-sib pair analyses have been contested (Fonseca and Krieger, *Rev. Bras. Genet.* 17: 109-112, 1994), because multiple observations from the same family could inflate type I statistical error. The present study has assumed this criticism as a hypothesis and reanalyzed the aforementioned data with a new biological design. The distortions remained significant even in groups with only one child. Also, significant distortions were found when samples were analyzed according to sex or birth order of newborns. Thus, the hypothesis of type I statistical error inflation was shown to be false. Also, the probability distribution determined in Fonseca and Krieger (1994) does not agree with the hypothesis of type I error inflation.

INTRODUCTION

Published ABO and Rh segregation distortions (Valenzuela *et al.*, 1982; Valenzuela and Harb, 1982; Valenzuela and Walton, 1985) have been contested. The reduced number of Rh(+)-Rh(-) mother-newborn pairs we found in Santiago (Chile) was explained by Nath *et al.* (1992) as a bias due to preferential admission of Rh(-) mothers to maternity services. They proposed a model that requires a rate of admission of Rh(+) mothers of less than 85% of Rh(-) ones. However, in Santiago (Chile), admission to maternities was over 98% of all delivering mothers and models based on the selective lack of Rh(-) newborns from Rh(+) mothers fitted the data better than those based on biased admission (Valenzuela and Harb, 1993). More recently, Fonseca and Krieger (1994) did not find significant deviations of segregation in pairs of relatives taken as single observations, but they did among multiple observations. They concluded that traditional segregation analyses are less prone to biases and should be preferred in studies of population dynamics, because these analyses take into account the

within-family phenotypic distribution, regardless of family size or of heterogeneity of size among families. For this same reason, segregation analyses are blind for counterbalanced selective processes, for dynamic population processes where reproductive time is the critical variable or for selective processes where family size is involved. As a result, epistemic and statistical type II errors are huge. Mathematical and statistical models all have advantages and disadvantages; so, it would be better to concentrate on developing sharper biological designs, instead of complicating the mathematical analysis. The more complex the mathematical algorithm we apply to the biotic process, the less biological information the analysis could give us (Valenzuela, 1985a, 1994). The present study intends to show that technical or clerical errors, mother-infant blood admixture, inflation of observed proportions of type I errors, wrongly assigned paternity, and in general, non-biotic causes cannot explain segregation distortions for ABO and Rh systems that we and other authors have described. Also it intends to show that traditional analyses have severe restrictions in finding evident distortions. We use biological designs and reduce mathematics or statistics to a minimum.

MATERIAL AND METHODS

Data

Published data were used: i) Mother-newborn pairs typed for ABO, attended in a maternity service, from Melbourne, Australia (Kirk *et al.*, 1955); ii) Mother-newborn pairs typed for ABO, including the sex of the newborn, from Melbourne, Perth (Shield *et al.*, 1958) and Subiaco (kindly sent by Drs. Kirk and Vos and published in Valenzuela, 1985b; it included single births and it excluded mothers with Rh antibodies); iii) Mother-newborn pairs from Santiago (Chile) where Rh, ABO and sex were studied (Valenzuela and Walton, 1985); iv) Mother-newborn pairs from Leipzig (Krauss and Zimmermann, 1970) where ABO, Rh and sex of newborns were considered; v) Probabilities from tests on segregation distortions published by Fonseca and Krieger (1994). ITO matrices were used to test the observed-expected proportions of mother-newborn pairs (Li, 1976). This method gives maximum likelihood estimates of gene frequencies: p for the A allele; q for B; r for O; and their respective standard errors, with which z tests of proportions can be obtained. With these estimates expected numbers of mother-newborn pairs can be calculated to test the observed ones by a χ^2_1 with one degree of freedom for each pair alone or with a χ^2_{11} with eleven degrees of freedom for the total matrix of pairs.

Rationale

In the present analyses, biological designs are preferred to test distortions; for example, sex or birth order of newborns are expected to be randomly distributed among blood groups or genetic markers or vice versa. Systematic or structured behavior of environment is used to test environmental factors, such as technical or clerical errors, and mother-newborn blood admixture. For example, blood admixture implies that recessive homozygotes O (OO) or Rh(-) (dd) could appear as A or B, or Rh(+), respectively. Blood admixture for Rh should correlate with more A, B and AB newborns; and these excesses can be tested. If no A, B, or AB excesses are found, the hypothesis of blood admixture is refuted. Blood admixture should occur equally in both sexes. If there is heterogeneity for distortions between both sexes, then, the simple hypothesis of blood admixture (as the cause of distortions) should be considered false. Weak or mixed sera produce systematic deviations and should be randomly distributed in sexes or among infants distributed according to their birth order. Also, the ITO

matrix applied to mother-newborn pairs where newborns are considered separately according to birth order can show distortions, hardly explained by non-biotic factors. A study of mother-newborn pairs in a fixed period shows the velocity of production of pairs. This design includes reproduction time, while segregation analyses do not. The number of children is insufficient to study selection or distortions. In an ITO matrix within a fixed period, parents that produce children faster will show more observed than expected pairs (Cifuentes *et al.*, 1991). In summary, the logical procedure we propose is to test hypotheses on the cause or factors of distortions by the biological implications these factors have on another biological feature, different from the one under study.

Semantics

Segregation distortions are usually understood as deviations from Mendelian distortions within families. Also, it can be understood as the deviations from Mendelian proportions in populational crosses. For example, if AA individuals produce more children when mating with AB individuals, then AA individuals are going to produce more AA and AB individuals than expected from simple random mating. This is the meaning we shall use.

RESULTS AND DISCUSSION

Table I shows data of mother-infant pairs from Australia (Melbourne 1952-53) by birth order. There was a significant excess of AB-B pairs and lack of A-AB and O-A pairs. Since only two years were considered for the analysis and newborns were taken separately (birth order), no sib-sib pairs were included. Nevertheless, significant deviations were seen in the first and second infant. Thus, it is impossible to explain these segregation distortions as dependent observations. Furthermore, wrongly assigned paternity does not alter these results. Undertyping of AB individuals could explain these deviations. However, undertyping should occur either because of weak anti-A or anti-B antisera, or mixture of anti-A and anti-B. Weak anti-B cannot be the reason for the excess of AB-B pairs. Weak anti-A cannot be the reason either, because of the excess of A-A, AB-A, A-B, B-A, and A-O pairs. Contamination of anti-A with anti-B would yield a highly significant lack of A-A and excess of AB-AB pairs. There was an excess of A-A and lack of AB-AB pairs instead. The B gene frequency was higher in the

second newborn than in any other. The comparisons by a z test of proportions between q(B) of the second and the third or the fourth infant were significant ($P < 0.0125$; $P < 0.0154$). Five groups yield 10 possible comparisons for each of the three gene frequencies. In 30 tests no significant comparison is expected at the 0.0154 level, yet two were found. Thus, there is a highly significant segregation distortion in these Australian data, that cannot be explained by dependence of observations, wrongly assigned paternity or technical errors. Segregational analysis is blind for this kind of distortion because it works with an average q(B) and no difference among groups could be found.

Table II shows the analysis of three mother-newborn pair samples from Melbourne, Perth and Subiaco (Australia), divided according to the sex of the newborn. Samples from Melbourne and Perth were taken in 1953-54-55 and 1955-56 periods, respectively; thus, a few cases of sib-sib pairs could be included in these samples. The sample from Subiaco was taken in the 1955-62 period; it may include an indeterminate proportion of sib-sib pairs. The high degree of segregational distortion found in Melbourne cannot be explained by dependence of observations; so, one could postulate that technical errors are present in this analysis. But the significant disagreement of distortions between male and female is powerful evidence in favor of biotic causes. The excess of B-A pairs was present only in females, significantly in Melbourne and non-significantly in Perth; males had a lack of B-A pairs. In Subiaco, males and females had a significant excess of B-A pairs; this was more significant in females. Again, this evident disagreement of results from different cities, obtained by applying the same methodology, indicates that a biotic factor should be operating. A similar case occurred with O-B pairs: a significant lack was found in males from Subiaco while females showed an excess. Significant heterogeneity of the sex ratio among mother-newborn pairs was found in Melbourne (Shield *et al.*, 1958), a fact very difficult to explain by non-biotic processes. Technical errors or the lack of independence of pairs should produce a high correlation of the direction of deviations between sexes; however, 8, 7 and 8 signs coincided in both sexes in Melbourne, Perth and Subiaco, respectively. Seven coincidences are expected to occur at random in 14

Table I - ITO analysis of ABO mother-infant pairs from Melbourne 1952-53 according to the newborn birth order (Kirk *et al.*, 1955).

Pair	Birth order					Total
	1°	2°	3°	4°	5°, > 5°	
AB-AB	+	-	-	-	-	-
AB-A	+*	-	+	+	+	+
AB-B	+	+***	+	+	+	+****
A-AB	-	-	.*	-	-	-****
A-A	+	+	+	-	+	+
A-B	+	+	+	+	+	+
A-O	-	+	+	-	+	+
B-AB	-	-	-	+	-	-
B-A	+*	-	-	+	+	+
B-B	-	+	+	+	+	+
B-O	-	+	+	-	-	+
O-A	-	.*	.*	-	-	-**
O-B	-	-	-	-	-	-
O-O	+	+	-	+	-	+
Total	2601*	2366*	1454	784	850	8055****
Gene frequencies						
p(A)	0.2397	0.2428	0.2472	0.2446	0.2440	0.2429
(SE)	0.0053	0.0056	0.0072	0.0098	0.0094	0.0030
q(B)	0.0680	0.0743	0.0632	0.0613	0.0655	0.0680
(SE)	0.0029	0.0032	0.0038	0.0051	0.0050	0.0017
r(O)	0.6923	0.6829	0.6896	0.6941	0.6905	0.6891
(SE)	0.0057	0.0060	0.0077	0.0104	0.0100	0.0033

+ = More observed than expected pairs; - = less observed than expected pairs; *, **, ***, **** = probability less than 0.05, 0.025, 0.01 and 0.005, respectively. SE = Standard error.

pairs. Kirk and Vos (1957) were conscious of possible technical errors; they improved their typing techniques and performed a check on the accuracy of ABO typing by studying the secretor state of the newborn. They did not find typing errors.

The following analysis deals with the study of ABO, Rh and sex simultaneously. Mother-newborn pairs published by Valenzuela and Walton (1985) showed great ABO, Rh and sex ratio distortions. This study included 25501 pairs collected from 1975 to 1983 in a single maternity service. There were 927 Rh(+)-Rh(-) and 1240 Rh(-)-Rh(+) pairs. Both kind of pairs should be equal under Mendelian segregation and Hardy-Weinberg equilibrium. There was a 25.24% lack of Rh(+)-Rh(-) pairs. These data have been contested because they included sib pairs and statistical dependence could explain those deviations. However, there were only $2227/25501 = 8.73\%$ sib pairs (Cifuentes and Valenzuela, 1986). This cannot explain a 25.24% lack of Rh(+)-Rh(-) mother-newborn pairs. Moreover, the expected proportion of identical sib-sib pairs is 1/4,

Table II - ITO analysis of ABO mother-infant pairs from Melbourne 1953-54-55, Perth 1955-56 (Shield *et al.*, 1958), and Subiaco 1955-62 (Valenzuela, 1985b) according to the sex of the newborn.

Pair	Melbourne		Perth		Subiaco	
	Male	Female	Male	Female	Male	Female
AB-AB	-	-	+	+	-	..**
AB-A	+**	+	+	-	-	-
AB-B	+	-	+	-	+****	+****
A-AB	-	..****	-	-	+	-
A-A	+	+	-	+	-	-
A-B	+	+	+	+*	-	+
A-O	+	-	+	-	-	+
B-AB	-	-	+	+	-	-
B-A	-	+**	-	+	+**	+****
B-B	+	+	-	-	+	-
B-O	-	+	-	+	..*	-
O-A	..****	..*	-	-	+	+
O-B	-	+	-	-	..*	+
O-O	+	-	+	-	+	-
Total	6073****	5435****	1856	1856	10739****	9836****

Gene frequencies						
p(A)	0.2417	0.2439	0.2456	0.2446	0.2510	0.2497
(SE)	0.0035	0.0037	0.0060	0.0098	0.0027	0.0028
q(B)	0.0719	0.0704	0.0723	0.0613	0.0688	0.0680
(SE)	0.0020	0.0021	0.0034	0.0051	0.0015	0.0015
r(O)	0.6865	0.6857	0.6820	0.6941	0.6802	0.6822
(SE)	0.0038	0.0040	0.0064	0.0104	0.0029	0.0030

+ = More observed than expected pairs; - = less observed than expected pairs; *, **, ***, **** = probability less than 0.05, 0.025, 0.01 and 0.005, respectively. SE = Standard error.

so, only 2.2% of mother-infant deviations could be attributed to correlation between sib-sib phenotypes.

According to our rationale we can test technical or non-biotic distortions by the simultaneous analysis of Rh, ABO and sex. The next analysis considers together Rh, ABO and sex of newborns from the Valenzuela and Walton (1985) and Krauss and Zimmermann (1970) data, which are presented in Table III. The ABO classes have been reduced to AB, A and B or non-O (NO), and O (O). The maximum likelihood estimate of the O frequency (r) with its standard error is included for comparisons [$r(O)$].

The symmetry of these matrices facilitates observation of distortions. NO-O should equal O-NO pairs. In the Valenzuela and Walton (1985) data, significant deviations were found in males of the groups Rh(+)-Rh(-) and Rh(-)-Rh(-) ($P = 0.0387$ and $P = 0.0121$, respectively), due to a lack of NO-O pairs. Females deviated significantly in the Rh(-)-Rh(+) group ($P = 0.0349$) due to an excess of O-NO pairs, and in the

Rh(-)-Rh(-) group ($P = 0.0157$) due to a lack of O-NO pairs. These significant and different distortions cannot be explained by multiple tests (eight), technical errors, dependence of observations, fetomaternal blood admixture or non-biotic reasons. Moreover, $r(O)$ differed significantly between males and females in Rh(+)-Rh(+) and Rh(-)-Rh(+) pairs ($P < 0.0294$ and $P < 0.0436$). In the Krauss and Zimmermann (1970) data, only males Rh(-)-Rh(+) deviated at the limit of significance ($P < 0.051$) due to an excess of NO-O pairs. However, the sexes showed quite different $r(O)$ frequencies in Rh(+)-Rh(-), Rh(-)-Rh(+) and Rh(-)-Rh(-) pairs ($P < 0.0262$, $P < 0.0188$ and $P < 0.0188$, respectively). In both samples, $r(O)$ differed among Rh mother-newborn pairs within each sex. In the Valenzuela and Walton (1985) data, the highest $r(O)$ was found in Rh(-)-Rh(-) males; it was significantly higher than those of Rh(+)-Rh(-), Rh(+)-Rh(+) and Rh(-)-Rh(+) pairs ($P < 0.002$, $P < 0.006$, $P < 0.046$). Females did not show significant differences among Rh groups. In the Krauss and Zimmermann (1970) data Rh(-)-Rh(-) males showed the lowest $r(O)$; it was significantly lower than those of Rh(-)-Rh(+) and Rh(+)-Rh(+) pairs ($P < 0.015$ and $P < 0.025$). The lowest $r(O)$ in females was that of Rh(-)-Rh(+) pairs. It was significantly lower than those of Rh(-)-Rh(-) and Rh(+)-Rh(-) pairs ($P < 0.027$ and $P < 0.032$).

Next, we studied the distribution of probabilities yielded by analyses performed by Fonseca and Krieger (1994) on 18 genetic systems and six types of pairs of relatives: "All sib-pairs"; "One pair of sibships"; "Pairs of sibships with < 3 years" of difference in age; "Between sex"; "Mother-all children"; "Mother-one child". The Rh-D system in "One pair of sibships" appears with a χ^2 with two degrees of freedom equal to 22.28, but it is not marked as a highly significant result. If this result was true, the conclusion had to be that their data showed a large distortion and there would not be disagreement with the conclusion of Valenzuela and Walton (1985) and Cifuentes and Valenzuela (1986); but it could be a misprint error, thus, in the present analysis this result was omitted. When several tests are performed, it is possible to study the distribution of the probabilities they yield, under the expected uniform distribution within the interval (0.0-1.0). Three tests were chosen. i) The number of probabilities under 0.5

must equal the number of probabilities over 0.5; since we have 18 systems, the expected number of probabilities under and over 0.5 is 9 and a χ^2 test can be applied. ii) Probability holes; some probability intervals may have a lack of cases; the probability that an interval of length "s" is lacking in all cases is $(1-s)^{18}$. iii) Probability excesses; some probability intervals may have an excess of cases; the probability of this excess can be calculated according to a Poisson or a χ^2 with one degree of freedom distribution. Figure 1 shows the probability of the six kinds of pairs and the 18 tests for each gene locus. The "One pair of sibships" probabilities were united through a line with the corresponding probability for the same genetic system of the "All sib-pairs". The same procedure was performed between probabilities of "Mother-one child" and "Mother-all children". This procedure allows to test the hypothesis that dependent information produced by the inclusion of several relatives should reduce the probability of the test, because random segregation deviations in one child should be increased when considering the complete sibships.

"All sib-pairs" showed excess of points below 0.5 ($P = 0.018$); two significant holes, between 0.3088 and 0.1056 ($P = 0.015$) and 0.8850 and 0.6795 ($P = 0.016$); and a highly significant excess below 0.04 ($P < 10^{-6}$). "One pair of sibships" had a significant excess of probabilities under 0.5 ($P = 0.029$); three significant holes, between 0.1880 and 0.0034 ($P = 0.031$), 0.6771 and 0.4966 ($P = 0.034$), and between 0.9113 and 0.7047 ($P = 0.020$). "Pairs of sibships with > 3 years" showed probabilities equally distributed below or over 0.5 ($P = 0.346$); one hole between 0.8650 and 0.6856 ($P = 0.029$); and an excess under 0.08 ($P = 0.016$). "Between sex" probabilities distributed equally below and above 0.5 ($P = 0.157$); showed one hole between 0.3929 and 0.1890 ($P = 0.017$); and an excess over 0.789 (Poisson $P = 0.040$, $\chi^2 P = 0.015$). "Mother-all children" probabilities were in excess under 0.5 ($P = 0.005$); one significant hole was observed between 0.6477 and 0.4404 ($P = 0.015$); and had a high proportion of probabilities below 0.03 ($P < 10^{-6}$). "Mother-one child" probabilities accumulated significantly over 0.5 ($P = 0.018$); presented a very significant hole between 0.2236 and 0.0000 ($P = 0.011$);

Table III - Distribution of mother-newborn segregation distortions of ABO and Rh systems according to the sex of the newborn.

Newborn	Valenzuela and Walton, 1985				Krauss and Zimmermann, 1970			
	Male		Female		Male		Female	
	NO	O	NO	O	NO	O	NO	O
Mother								
Rh(+)-Rh(+) pairs								
NO	3173	1573	3004	1552	813	217	783	214
O	1633	5440	1608	4938	221	402	206	352
r(O)	0.77200		0.76530		0.61401		0.60186	
SE	0.00245		0.00256		0.00805		0.00839	
Rh(+)-Rh(-) pairs								
NO	156	50	126	44	123	31	99	35
O	65	215	58	213	27	43	27	54
r(O)	0.75273		0.77749		0.56744		0.62901	
SE	0.01250		0.01253		0.02269		0.02202	
Rh(-)-Rh(+) pairs								
NO	156	99	188	88	109	51	127	34
O	82	300	60	267	42	59	29	45
r(O)	0.78123		0.75508		0.63282		0.57086	
SE	0.01035		0.01117		0.01992		0.02210	
Rh(-)-Rh(-) pairs								
NO	55	13	49	30	99	32	79	24
O	28	121	21	96	28	30	27	45
r(O)	0.81416		0.78767		0.56248		0.63485	
SE	0.01649		0.01842		0.02479		0.02427	

NO = A + B + AB phenotypes. r(O) = The allele O frequency. SE = Standard error of r(O).

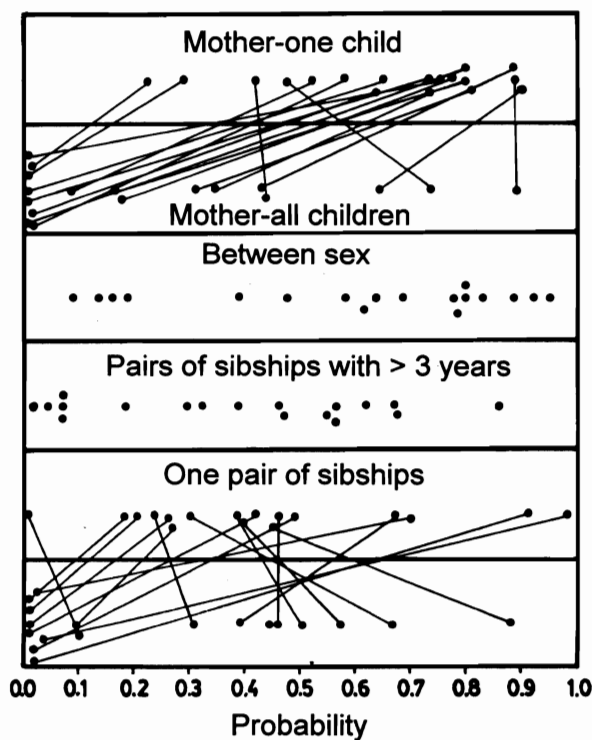


Figure 1 - Probability distributions of Fonseca and Krieger (1994)'s tests.

and an excess over 0.73 (Poisson $P = 0.027$, $\chi^2 P = 0.006$). The authors presented their analysis as evidence for their belief that the significant results could be explained by the dependence of observations produced when taking all the sib-pairs or children. However, the probabilities calculated from their results are distorted either in analyses of only one relative or taking all of them together. Moreover, the only significant result in "One pair of sibships" was found in the Rh-E locus ($P = 0.003$). This is a large distortion that cannot be explained by the 18 tests performed. Furthermore, it changed to $P = 0.102$ in "All sib-pairs" (non-significant) in direct conflict with the hypothesis that inclusion of all sibs should inflate significance. Thus, it is very probable that a counterbalanced distortion was present in the rest of the sibships that were not included in the "One pair of sibships" group. In the "Mother-one child" sample, probabilities were significantly accumulated towards the fit of the data with the model. Perhaps the random election of mother-child pairs includes deviations in several directions that counterbalance one another, so as to produce a non-significant result. The expected lower probabilities of the whole kinship compared to with only one child randomly taken were not observed between "One pair of sibships" and "All sib-pairs", and there were three exceptions to this expected behavior between "Mother-one child" and "Mother-all children". Thus, the hypothesis that the inclusion of related information should increase significance is untenable with these data. This is explainable with theoretical arguments. If there is a non-significant random distortion in the one sib sample the inclusion of other sibs should correct this distortion, and not increase it, because they are randomly segregating. The expected segregation for one relative is equal for all the relatives, and random deviation should occur in both directions, with similar probabilities. If relatives repeat the deviation systematically, then non-random processes occur. Figure 1 shows very large changes in the value of probabilities between tests with one relative and tests with all relatives. It is improbable that such large changes can be due to sib-sib similarities (0.25), and it is very probable that they have been produced by true segregation distortions.

Finally, we performed a comparison, with the ITO method applied to the ABO system, between familial mother-all children pairs and mother-one newborn pairs attended at a maternity service during a short period (1977-1978) in Visakhapatnam (India). Both mother-newborn (one child) and mother-children pairs showed highly significant distortions ($P < 10^{-8}$ and $P < 10^{-4}$, respectively), but the direction of distortions was different in both samples (Rajani Kumari *et al.*,

1992). Besides that, segregation distortions for ABO, Rh and sex were found in malformed and control newborns from the same maternity service in which the Valenzuela and Walton (1985) study was performed; few or no sib-sib pairs were present in that sample (Cifuentes *et al.*, 1991).

Let us denote as the residual genotype or genome that part of the genome which we are not analyzing (ABO, Rh and sex). If the loci we are analyzing interact in a non-linear way with the residual genotype, environmental or other biotic conditions (parity, age, etc.), distortions should be different in any sample, because it is practically impossible that the environment, residual genotype or the other variables be equal among samples. This could be the explanation for the different or contradictory direction of deviations we have described in some samples in this study. This point was discussed in Valenzuela and Walton (1985) and Valenzuela and Cifuentes (1989). On the other hand, it is important to remember the loss of information, due to epistemic restrictions, that occurs when any mathematical or statistical model is applied to a set of data. In general, the more complicated the algorithm of the model, the greater the epistemic restriction or loss of information on the biological process under study (Valenzuela, 1994). Complex segregation analysis, ITO methods and biological designs should be considered as complementary methods that inform on different aspects of a biotic process, and not as contradictory methods. Unfortunately, positivism gave too much importance to positive results, that is, the fitness of data to the model and not to negative results. However, a positive result does not mean that the model is correct, while a negative one can lead to a conclusion on the incorrectness of the model.

RESUMO

Relatos sobre distorções na segregação ABO e Rh encontradas em análises de pares mãe-filho ou irmão têm sido contestados (Fonseca e Krieger, *Rev. Bras. Genet.* 17: 109-112, 1994), porque múltiplas observações na mesma família poderiam aumentar o erro estatístico tipo I. O presente estudo assumiu essa crítica como uma hipótese e reanalisou os dados acima citados com um novo planejamento biológico. As distorções continuaram significantes mesmo em estudos com apenas uma criança. Além disso, distorções significantes foram encontradas quando se analisaram amostras de acordo com o sexo ou a ordem de nascimento das crianças. Assim, a hipótese de aumento do erro estatístico tipo I mostrou-se falsa. Além disso, a distribuição de probabilidade determinada em Fonseca e Krieger (1994) não está de acordo com a hipótese de aumento do erro tipo I.

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