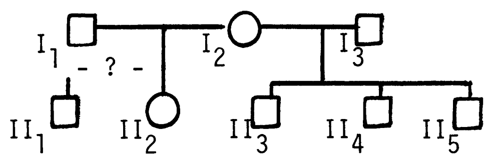
PARENTAGE TESTING FOR THE DETERMINATION OF SIBSHIP. Chantal R. Harrison and Sherrie L. Warner, Dept. of Pathology, Univ. of TX Health Science Center, San Antonio, TX 78284, USA.

INTRODUCTION

Genetic markers in blood have been used for paternity investigation and methods to quantify the genetic data into a paternity index or a probability of paternity have been described (1,2,3,4,5). We report here a case where the genetic investigation was attempted to determine whether two adults were biological siblings. A method to quantitate the genetic data and calculate a fraternity index using logic similar to that used to calculate a paternity index was devised for this particular situation. We also report a general method to calculate a fraternity index for a biallelic codominant genetic system.

CASE REPORT

Two adults (II_1 and II_2), North American Caucasians, a male and a female, had been adopted in the same family. Their adoptive parents are now deceased and they wish to know whether they are biological siblings. They now have children and there is a possibility that their children want to intermarry. Records of who the biological parents (I_1 and I_2) of the woman are available. Unfortunately they are also deceased. However, her mother had three additional children from a different man (I_3). Two are available for testing (II_3, II_4). These relationships are better described in the following pedigree.



The ABO, Rh, MNS, Kell, Duffy, Kidd, and HLA type of II_1, II_2, and II_3, and II_4 were determined with the following results.

II_1: A_1B, cDEe, Ns, K-, Fy^aFy^b, Jk^aJk^b, A1A2B3B27

II_2: A_1B, cde, Ms, K+, Fy^b, Jk^aJk^b, A2A29B12

II_3: B, cde, MSs, K-, Fy^aFy^b, Jk^a, A1A29B8B12

II_4: O, cde, MSs, K-, Fy^b, Jk^aJk^b, A1A29B8B12

II_5: Was not available for testing.

LOGIC OF CALCULATION

The following logic was used to determine a fraternity index in this particular situation:

1) Identify what possible genotypes I_2 must have had to sire her 3 known children (II_2, II_3, and II_4).
2) Identify which possible corresponding genotypes I_3 must have had to sire II_3 and II_4.
3) Calculate the frequency of such matings in the general population.
4) Calculate the frequency of the combination of each particular mating and 2 children of II_3 and II_4 genotypes.
5) Calculate the relative frequency of such combination.
6) Deduce the probability of each genotype for I_2.
7) Identify which possible genotypes I_1 must have had to sire II_2.
8) Calculate the frequency of the possible I_1 and I_2 matings.
9) Calculate the frequency of the combination of each particular mating and one child of II_2 genotype.

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10) Calculate the relative frequency of such combination.
11) Calculate the probability that such combination could result in a second child of II_1 genotype: This is the X value (probability that II_1 and II_2 are sibs).
12) Calculate the frequency of II_2 phenotype in the random population: This is the Y value (probability that II_1 is a random unrelated child).
13) X/Y (fraternity index) is calculated for each blood group and the final result is the total product of each X/Y.

RESULTS OF CALCULATIONS

Below is an example of the calculation method for the ABO blood group using the genetic frequencies for U.S. whites published by the American Association of Blood Banks in 1977(5).

To have sired an A_1B, a B, and an O child I_2 has only two possible genotypes, A_1O and BO. If she is A_1O then I_3 must be BO; if she is BO then I_3 may be OO, AO, or AB (here A is $A_1 + A_2$). First we calculated the probability that I_2 is A_1O or BO.

I_2		I_3	Frequency of Mating	Frequency of O Child	Frequency of B Child	Frequency of Combination	Relative Frequency of Combination
A_1O	X	BO	.0261663248	.25	.25	.0016353953	.0980099502
BO	X	OO	.0438983267	.5	.5	.0109745817	.6577114428
BO	X	AO	.0349327078	.25	.25	.0021832942	.1308457711
BO	X	BO	.0100946228	.25	.75	.0018927418	.1134328358
					Total	.016686013	1.0000000000

Probability that I_2 is A_1O: .0980099502

I_2 is BO: .9019900492

Then we identify the possible genotypes of I_1:
if I_2 is A_1O then I_1 may be BB, BO, or AB,
if I_2 is BO then I_1 may be A_1A_1, A_1A_2, A_1O or A_1B

I_2		I_3	Frequency of Mating	Frequency A_1 B Child	Frequency of Combination	Relative Frequency of Combination
A_1O	X	BB	.0005661055	.5	.0002830527	.0030577025
A_1O	X	BO	.0137653015	.25	.0034413254	.037175225
A_1O	X	AB		.25		
BO	X	A_1A_1	.0350053318	.5	.0175026659	.1890741133
BO	X	A_1A_2		.25		
BO	X	A_1O	.2853734159	.25	.071343354	.7706929592
BO	X	A_1B		.25		
				Total	.092570398	

The probability that the combination have another A_1B child is

X = .2980329539

Y = .029944

Thus X/Y for the ABO is 9.953010752

Similar calculations for all genetic systems tested give the following results.

Blood Group		X/Y
ABO		9.953010752
Rh		.6684571344
MNS		.0927939075
Kell		.5224660397
Duffy		.5235727762
Kidd		1.16241347
HLA		.29831395
	Total Product	.0585733327

Thus the final X/Y or FI (fraternity index) is .0587 or $\frac{1}{FI} = 17.1$

It is 17.1 times more likely that they are not biological brother and sister. A probability of fraternity (PF) could be calculated as $\frac{FI}{1 + FI} = .055$ or 5.5%.

Of interest is the MNS blood group system. II_1 is homozygous for $N\bar{s}$ and II_2 is homozygous for Ms. The two half-brothers are $MS\bar{s}$. If the third one was homozygous for either MS or NS that would completely exclude II_1 as a brother of II_2, since it would exclude the possibility that I_2 possesses $N\bar{s}$. The HLA system could also bring out an exclusion if the third untested half-brother would turn out to be entirely different from II_1, II_3, and II_4. Thus testing this person might bring out a certitude instead of a probability in this case.

GENERAL CALCULATIONS FOR A BIALLELIC CODOMINANT SYSTEM

Let the system have two genes A, B with frequencies of p, q. The X value is the probability of the same parents siring both children. The Y value is the product of the phenotypic frequencies of the two children. Example: Child #1 is AA, child #2 is AB.

Possible phenotypes of parents of both children	Frequency of Mating	Frequency of Child #1	Frequency of Child #2	Frequency of Combination
AB X AA	$4p^3q$	.5	.5	p^3q
AB X AB	$4p^2q^2$	.25	.5	$.5p^2q^2$

X = probability of same parents siring both children = $p^2q\,(p+.5q)$

Y = product of phenotypic frequencies = $2p^3q$

$$\frac{X}{Y} = \frac{2p+q}{4p} = \frac{1}{2} + \frac{q}{4p} = \frac{1}{4} + \frac{1}{4p}$$

Thus when the two children share one antigen $\frac{X}{Y}$ for that system is >1, when the frequency of the shared antigen is <.33. By applying the same logic to all possible phenotypic combinations the following formulas are obtained.

child 1 / child 2	AA	AB	BB
AA	$1 + \frac{q}{p} + \frac{q^2}{4p^2}$ or $\frac{1}{4} + \frac{1 + 2p}{4p^2}$ always >1		.25
AB	$\frac{1}{2} + \frac{q}{4p}$ or $\frac{1}{4} + \frac{1}{4p}$ always >.5	$\frac{1 + pq}{4\ pq}$ or $\frac{(p-q)^2 + pq}{4\ pq}$ always >1	$\frac{1}{2} + \frac{p}{4q}$ or $\frac{1}{4} + \frac{1}{4p}$ always >.5
BB	.25		$1 + \frac{p}{q} + \frac{p^2}{4q^2}$ or $\frac{1}{4} + \frac{1 + 2q}{4q^2}$ always >1

This shows that when the two subjects share two antigens the FI is always greater than 1; if they share one antigen it is always greater than .5 and if they do not share any antigen the FI is .25 and independent from the frequency of the genes.

CONCLUSION

A logic similar to that used to calculate a paternity index can be applied to the determination of a paternity index to quantitate the possibility that two individuals may be biological siblings. In this particular instance a calculation similar to the power of exclusion cannot be used since the power of exclusion will always be 0.

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