

The percentages of concordance in twins and mode of inheritance

by

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In about 20-25% of a random sample of human twins the partners show a more or less impressive resemblance. These twins are always of the same sex and are considered to have developed from the same zygote.

The formal genesis of these so-called *monozygous* human twins is deduced from observations on zoological material, with the exception of the monochorial-diamnial twins of which human embryological preparations are known (Corner, 1955).

The development from the same cell material implies that both partners of a monozygous pair will possess the same genetic make-up: as far as their genes are concerned they are identical. It is known, however, that the presence of a certain combination of genes does not necessarily result in the presence of a certain manifestation in the phenotype of the individual. Apparently, this applies to each of both partners of a pair of monozygous twins: although they do possess the same genotype, they may and will sometimes differ phenotypically in characters for which the genetic basis is well established.

It is generally accepted, that the phenomenon of discordance in monozygous twins results from the influence of environmental factors. These factors may interfere with the genetically determined development in one (or in both) of the twins. It should be added, that it has been found that also other genes may influence the phenotypical manifestation of certain genes.

In the following considerations only concordance (or discordance) in monomeric characters is discussed: one pair of alleles, a_1 and a_2 , is involved.

It is supposed in our theory that a homozygous condition, be it a_1a_1 or a_2a_2 , always results in a certain observable. Thus, homozygosity in monozygous twins implies that the partners are concordant.

In current terminology complete dominance is said to be present, when the heterozygous condition a_1a_2 always results in the effect of the gene studied. Examination of a large number of heterozygotes, however, will often reveal that the effect of the heterozygous condition occurs only in a certain fraction of the possessors of this condition. Hence, the penetrance of the gene in heterozygotes will frequently be found to be incomplete, i.e. less than 1 (= 100%).

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It follows, that discordance in monozygous twins may occur in case the character studied results from the heterozygous condition of an incomplete penetrant gene. One partner may show the effect; in the other partner the development may have been led along other paths.

Some genes have a very low penetrance. In case this value is found to be as low as zero, the gene is called a recessive. None of the heterozygotes, but only the carriers of the homozygous condition of these genes will show the effect.

Unlike the monozygous twins, a so-called *dizygous pair* is the consequence of the fertilization of two mature eggs, each by its own spermatozoon. Hence, dizygous twins are genetically the non-identical pairs. This does not mean that both partners never would possess identical genes; the 'identity' refers to all the genes as a whole: the genome. In half of the cases of dizygous pairs the partners are of the same sex. On the average, the partners do not resemble each other more than do two sibs. The impression of a greater resemblance than that found in sibs, is mainly due to the fact that the twins are of the same age.

The assumptions made above lead to the conclusion that also in dizygous pairs concordance will always be present, when both partners possess the gene studied in homozygous condition. It may be present in case both partners are heterozygotes.

However, if one partner of a monozygous pair is a homozygote, the other partner *must* be a homozygote too. If one partner of a dizygous pair is a homozygote, the second *may* be a homozygote. This is one of the reasons why the percentage of concordance in a number of dizygous twins will always be found to be smaller than that in a number of monozygous pairs for the same genetically determined character. As a matter of fact, the use of twins in genetic research is based upon this line of reasoning. In case the percentages of concordance are found not to differ significantly in the two types of twins, the chance that the character, for which the concordance was established, has a genetic basis, is negligibly low.

At this point we may remark that the study of the significance of percentages of concordance should be based on the examination of a non-selected material. In material gathered from literature and comprising many case reports, the relative number of concordant pairs is often too great and thus unreliable.

A representative series of twins consists of both types of twins in the same relative quantities as are present in the population from which the series is drawn. One may start to register, within a certain limited period, if possible, all living patients suffering from the disease to be studied in twins, i.e. the character under study. In this way Idelberger (1951) succeeded in collecting 22,004 cases of congenital luxation of the hip joint in Germany. The next step to be taken is to note, which of these patients belong to a pair of twins. Idelberger found this to be the case in 236 patients ('first' partners). Of course a certain amount of the 'second' partners will have deceased. Generally, in about 30-50% the partners of the patients belonging to a twin pair can not be examined. In Idelberger's case the relevant medical history of 138 pairs of twins could be traced.

It may be found, that the frequency of the character (the affection studied) is

higher in twins than in single births. In that case, twinning per se is to be listed among the aetiological (environmental) factors. This finding does not affect the significance of studying twins in search of the possible presence of hereditary factors as well.

In this phase we have at our disposal twins, *of which at least one of the partners (the 'first' one) shows the character under study*. The most important step in investigations of this kind is the differentiation of the pairs collected into mono- and dizygous twins. Among the pairs of the same sex a number of dizygous twins are to be traced. This number is the same as that of the number of (dizygous) twins of unlike sex. As many genetically determined characters as possible should be included in the attempt to differentiate the like-sexed pairs, with the exception of the character under study. The representative series collected in this unbiased way is representative as far as the distribution among twins of the character under study is concerned.

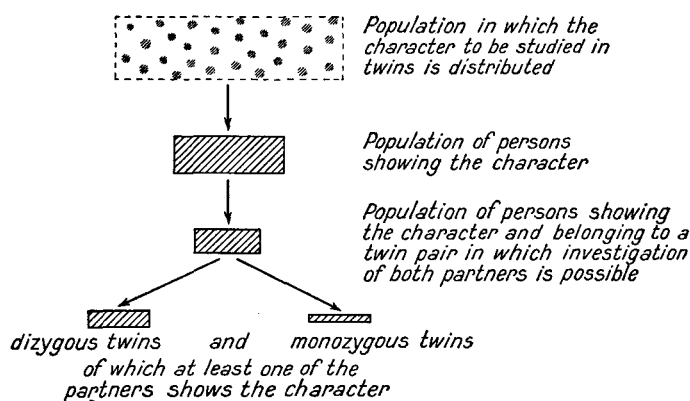


Fig. 1. The sampling of a representative series of twins to be studied for a certain character

Suppose the effect of the gene a_1 is studied.

It is to be seen, that the percentage of concordance is related to both the frequency of this gene in the population (p) and to its penetrance (φ).

A high gene frequency results in many homo- and heterozygotes, the first ones showing the character in any case, on the basis of our assumptions. On the other hand, the number of heterozygotes presenting the character depends on the penetrance.

The significance of these factors (gene frequency and penetrance) in the study of twins may be elucidated by the following line of thought:

The 'first' partners of the twins collected possess the character.

a) In case the gene a_1 is rare, we may presume for the moment that both partners of the *monozygous* twins will be heterozygotes (a_1a_2), as the chance of being homo-

zygous for this rare gene (a_1a_1) is considerably low. In this case, the presence of concordance depends on whether or not the gene a_1 finds expression in the 'second' partner as well. This chance is given by the penetrance; a low penetrance will result in an equally low frequency of concordance in this case.

Example: a character based on a rare gene with a frequency $p = 0.001$ and a penetrance φ amounting to $0.3 (= 30\%)$, will theoretically be found in both partners in a fraction $0.3012 (= 30.12\%)$ of a number of non-selected monozygous twins (see below).

b) In case of *dizygous* twins one may reason as follows: Here too, in case of a rare gene, it may be presumed that the 'first' partner is a heterozygote. Unlike the case of monozygous twins this does not imply that the 'second' partner is a heterozygote too. This depends on the genetic composition of the parents. The chance that the rare gene under consideration will be present in both parents may be assumed to be negligible. It may be expected, that the marriage has been of the type $a_1a_2 \times a_2a_2$. On the average, half of the children resulting from this marriage will possess the heterozygous condition. Thus, the chance that the 'second' partner will possess the gene studied, equals $\frac{1}{2}$. Independent of this chance, the chance of showing the character is given by the penetrance of the gene. Thus: complete penetrance and a very low frequency of the gene concerned will result in concordance in 50% of the cases.

Example: a character based on a rare gene, with a frequency $p = 0.001$ and a penetrance φ amounting to $0.3 (= 30\%)$, will theoretically be found in both partners in a fraction $0.1507 (= 15.07\%)$ of a number of non-selected dizygous twins (see below).

Here we may discuss the line of argument advised to Idelberger (1951; p. 64-65) by Lenz. In this reasoning it is thought, that in case of complete dominance (i.e. complete penetrance in our terminology) a percentage of concordance of 33.3% is to be expected when a number of dizygous pairs is investigated. Apparently, Lenz also starts from the assumption that marriages, from which a 'patient' results, are of the type $a_1a_2 \times a_2a_2$. We want to stress that this supposition is only valid in case the frequency of the gene a_1 is very low. Anyhow, the chance of a child being 'affected' ($= a_1a_2$) equals $\frac{1}{2}$. It follows, that the chance that two consecutive fertilizations (a dizygous pair of twins) result in a concordant pair of 'affected' children amounts to $\frac{1}{4}$. The chance of the pair being discordant amounts to $\frac{2}{4}$. Lenz argues: this fraction $\frac{3}{4}$ of the total amount of dizygous twins is at our disposal, as at least one of the partners is 'affected'. $\frac{1}{4}$ of this fraction consists of concordant pairs, i.e. the percentage of concordance to be expected in this case amounts to 33.3% ($\frac{1}{3}$).

It will be clear that this line of reasoning does not apply to the material collected in the way mentioned above; consequently, not to the material collected by Idelberger either. Indeed, the dizygous pairs are collected because at least one of the partners shows the character under study. The chance, that the 'second' partner is also 'affected', is the same as the chance that this partner possesses the genotype a_1a_2 , i.e., in those circumstances, 50%.

The following scheme applies to a random mating population, in which the effect of the gene a_1 is studied. The gene frequency p and its penetrance φ are the symbols used. The effect may be a certain affection.

The arrow indicates, that a fraction φ of heterozygotes will show the character that is always present in the possessors of the homozygous condition a_1a_1 .

Scheme			
Possible genotypes:	a_1a_1	a_1a_2	a_2a_2
Frequencies:	p^2	$2 pq$	q^2
Penetrance:		φ	
		←	
Frequencies phenotypes:	$p^2 + 2 pq\varphi$		$q_2 + 2 pq(1 - \varphi)$
	affected		not affected

It is to be seen, that in this population the chance of being affected depends on p and φ .

We suppose the chance of a 'first' partner of a twin pair being affected, to be the same as that of an individual taken at random, i.e. $p_2 + 2 pq\varphi$.

a) Monozygous twins

We start from the fact, that the 'first' partner shows the character studied. This may be due to the fact, that the genotype a_1a_1 is present, as this always leads to manifestation of the effect. However, he may also possess the genotype a_1a_2 , as a fraction φ of the possessors of this condition will show the character as well.

The chance of being homozygous amounts in the part of the population affected, to $\frac{p^2}{p^2 + 2pq\varphi} = \frac{p}{p + 2q\varphi}$.

The chance of being heterozygous, amounts to $\frac{2pq\varphi}{p^2 + 2pq\varphi} = \frac{2q\varphi}{p + 2q\varphi}$.

If the 'first' partner is affected as a consequence of the genotype a_1a_1 , the 'second partner' will also be affected. Hence, the contribution to the expected frequency of concordance from this source amounts to $\frac{p}{p + 2q\varphi}$.

If the 'first' partner has been a heterozygote (chance expectation $\frac{2q\varphi}{p + 2q\varphi}$ the second partner will also be a heterozygote. *This does not mean, however, that this partner will show the character!* For only the fraction φ of the heterozygotes will be affected. Thus, the chance that the 'second' partner will be a heterozygote and affected, amounts to $\frac{2q\varphi^2}{p + 2q\varphi}$.

Hence, the total chance expectation of partners of a monozygous pair being concordant, is to be expressed as

$$C_1 = \frac{p + 2q\varphi^2}{p + 2q\varphi}$$

Some conclusions can easily be drawn from this formula. A complete dominant gene ($\varphi = 1$) results in 100% of the cases in concordance, independent of the gene frequency. The same applies to a recessive gene ($\varphi = 0$). However, one does not need a formula to come to these conclusions. In table 1 a survey is given of C_1 -values,

for several values of p and φ .

It is clear, that the figures may be used for the drawing of graphs, such as those demonstrated in fig. 2: the relation between C_1 and p is given for each of certain constant values of φ . More curves would have impaired the surveyability of this figure heavily. It is to be seen, however, that a certain value of C_1 may result from a great number of (p, φ)-combinations, i.e. an observed value of C_1 gives no clue whatever as to the frequency of the gene concerned, or to the mode of inheritance ($= \varphi$). To solve these two unknowns we need another independent equation in p and φ .

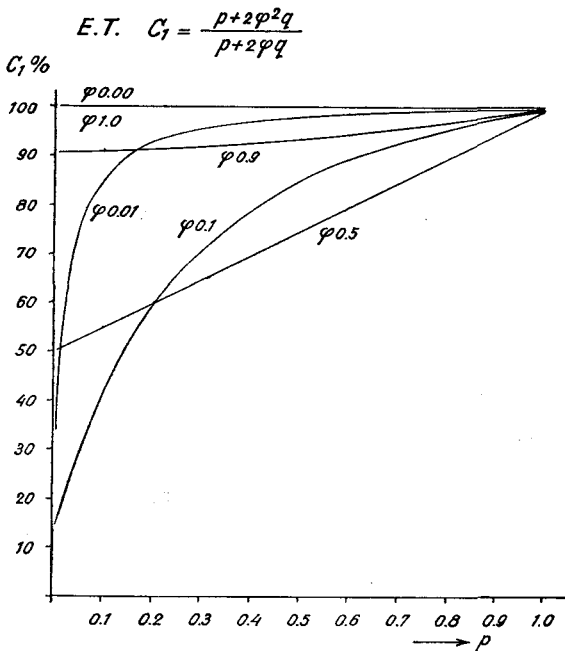


Fig. 2. The relation between C_1 and p for some values of φ

Two cases are to be considered: the 'first' partner, showing the character, may possess the genotype a_1a_1 or the combination a_1a_2 .

1. THE 'FIRST' PARTNER POSSESSES THE GENETIC CONSTITUTION a_1a_1

It follows, that both parents of this patient should carry the gene a_1 . Several types of marriages may be present in which this condition is fulfilled. The expectancy of those marriages in which a child, known to possess the genotype a_1a_1 may have been born is given in the following table.

The genetic constitution of these parents allow that the 'second' partner may be a_1a_1 or a_1a_2 genotypically. The genotype a_1a_1 results in a case of concordance; the heterozygote a_1a_2 has a chance φ of being affected.

b) Dizygous twins

As was already stated above, the chance that partners of a dizygous pair are identical for a certain genotype depends on the genetic composition of the parents.

No	Father	Mother	Expectancy
1	a_1a_1	a_1a_1	p^4
2	a_1a_1	a_1a_2	$2 p^3 q \cdot \frac{1}{2}$
3	a_1a_2	a_1a_1	$2 p^3 q \cdot \frac{1}{2}$
4	a_1a_2	a_1a_2	$4 p^2 q^2 \cdot \frac{1}{4}$
Total			p^2

Within this limited constellation of marriages, the chance of a child being a_1a_1 as a consequence of type of marriage 1, amounts to $\frac{p^4 \cdot 1}{p^2}$; etc. (nr 2, 3, 4).

The possibilities of a child being a_1a_2 and affected start with type of marriage 2. The chance, that this type of marriage results in an affected child with the genotype a_1a_2 , amounts to $\frac{p^3 q \cdot 1/2 \cdot \varphi}{p^2}$; etc. (nr 3, 4). Adding these 7 chances of the 'second' partner for being affected in case the 'first' one is a homozygote a_1a_1 , the chance of being a concordant pair of twins appears to be $(\frac{1+P}{2})^2 + \varphi q (\frac{1+P}{2})$.

2. THE 'FIRST' PARTNER POSSESSES THE GENETIC CONSTITUTION a_1a_2

In this case at least one of the parents carries the gene a_1 . Again, several types of marriages may result in a child with this genotype. The expectancy of those marriages in which an affected heterozygous child may have been born is given in the next table.

No	Father	Mother	Expectancy
1	a_1a_1	a_1a_2	$2 p^3 q \cdot \frac{1}{2} \cdot \varphi$
2	a_1a_1	a_2a_2	$p^2 q^2 \cdot \varphi$
3	a_1a_2	a_1a_1	$2 p^3 q \cdot \frac{1}{2} \cdot \varphi$
4	a_1a_2	a_1a_2	$4 p^2 q^2 \cdot \frac{1}{2} \cdot \varphi$
5	a_1a_2	a_2a_2	$2 p q^3 \cdot \frac{1}{2} \cdot \varphi$
6	a_2a_2	a_1a_1	$p^2 q^2 \cdot \varphi$
7	a_2a_2	a_1a_2	$2 p q^3 \cdot \frac{1}{2} \cdot \varphi$
Total			$2 p q \varphi$

Here too, the types of marriages allow that the 'second' partner may be a_1a_1 or a_1a_2 genotypically. Within this limited constellation of marriages the chance of a child being a_1a_1 as a consequence of type of marriage 1, amounts to $\frac{p^2q\varphi \cdot I/2}{2pq\varphi}$; etc. (nr 3, 4).

The chance, that a child will be affected as a consequence of the genotype being a_1a_2 is, in type of marriage 1: $\frac{p^2q\varphi \cdot I/2 \cdot \varphi}{2pq\varphi}$; etc. (nr. 2, 3, 4, 5, 6, 7).

As a result of adding these 10 chances, the chance of being a concordant pair of twins, in case the 'first' partner is an affected heterozygote appears to be $\frac{p}{2} \left(\frac{I+p}{2} \right) + \varphi \left(\frac{I+pq}{2} \right)$.

In this phase we know the probabilities of being a concordant pair of dizygous twins within each of the two situations 1 and 2.

The ultimate expression of the expected frequency of concordance should imply the chances that the situations 1 and 2 occur.

The probability of the 'first' partner being homozygous a_1a_1 is p^2

The probability of the 'first' partner being heterozygous a_1a_2

and affected is $2pq\varphi$

Total $p^2 + 2pq$

Thus, the expression for the probability of concordance in dizygous twins runs as follows:

$$C_2 = \frac{p}{p + 2pq} \left\{ \left(\frac{I+p}{2} \right)^2 + \varphi q \left(\frac{I+p}{2} \right) \right\} + \frac{2pq\varphi}{p + 2pq} \left\{ \frac{p}{2} \left(\frac{I+p}{2} \right) + \varphi \left(\frac{I+pq}{2} \right) \right\}$$

In table 2 a survey is given of C_2 -values for several values of p and φ . Fig. 3 shows some of the curves, which can easily be drawn with the aid of the figures from table 2.

Comparison of table 1 and 2 reveals (as was to be expected), that for the same combination of p - and φ -values the frequency of concordance to be found in monozygous twins is always higher than that to be observed in a number of dizygous pairs.

Now we have at our disposal two equations, in which the same symbols p and φ occur as the two unknowns. C_1 and C_2 respectively are the values to be observed in a non-selected material of twins.

It may be questioned, however, whether the symbols p and φ really have the same meaning and the same value in the component parts of the twin-population, i.e. in mono- and dizygous twins respectively. As far as p is concerned, this may be brought back to the question, whether a certain monomeric character (here: the character studied) is always the effect of the same gene, i.e. a gene situated on the same locus (here: the gene a_1). Some investigators have pointed out, that it may not be excluded that a certain character is not always the effect of the same gene. This may be revealed in some instances by studies of pedigrees (crossings). In that case such a character would literally be heterogenous, and p would not stand for the frequency of a certain gene.

In the majority of cases, however, this warning is only of rather academic value. Unless the opposite is true (and this is not easily to be proved by investigation of twins), we deal as if the monomeric character studied is always the effect of the same gene a_1 .

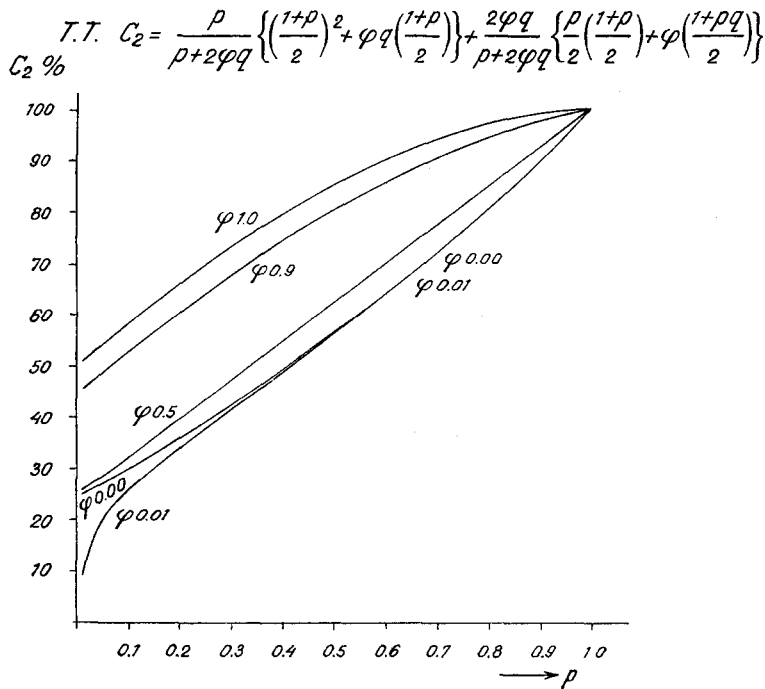


Fig. 3. The relation between C_2 and p for some values of φ

The question, whether the penetrance φ of a certain gene a_1 in a population of monozygous twins may be presumed to have the same value in another population, is more difficult to answer. It follows from our introduction, that it is generally accepted that the penetrance of a gene is influenced by environmental factors, and in other cases by the presence of other genes as well.

In a previous paper (1954) the possibility was discussed that the penetrance in heterozygotes might be considered to be a function of the heterozygous constitution itself. If this would really be the case, the question whether the value of φ is constant, would no longer exist.

Even a quick survey of the relevant literature will reveal, that in the more extensive investigations of twins, one always compares the frequency of concordance found in monozygous pairs, with that found in the dizygous cases. Also those investigators, who are convinced that environmental factors are mainly responsible for the character

Table 1 - C_1 -values for several (p, φ) -combinations

$p \backslash \varphi$	0	0.001	0.005	0.01	0.05	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0	$\varphi \backslash p$
0.001	1.0	0.3342	0.0955	0.0572	0.0594	0.1045	0.2020	0.3012	0.4007	0.5005	0.6003	0.7002	0.8001	0.9000	1.0	0.001
0.003	1.0	0.6011	0.2351	0.1395	0.0778	0.1133	0.2060	0.3035	0.4022	0.5015	0.6010	0.7006	0.8004	0.9002	1.0	0.003
0.005	1.0	0.7156	0.3378	0.2088	0.0954	0.1221	0.2099	0.3058	0.4037	0.5025	0.6017	0.7011	0.8006	0.9003	1.0	0.005
0.007	1.0	0.7792	0.4164	0.2680	0.1226	0.1306	0.2138	0.3081	0.4052	0.5035	0.6023	0.7015	0.8008	0.9004	1.0	0.007
0.010	1.0	0.8349	0.5050	0.3422	0.1372	0.1433	0.2197	0.3116	0.4075	0.5050	0.6033	0.7021	0.8012	0.9006	1.0	0.010
0.020	1.0	0.9108	0.6728	0.5100	0.2110	0.1833	0.2388	0.3230	0.4149	0.5100	0.6067	0.7043	0.8025	0.9011	1.0	0.020
0.030	1.0	0.9393	0.7569	0.6112	0.2744	0.2205	0.2574	0.3343	0.4223	0.5150	0.6100	0.7065	0.8038	0.9017	1.0	0.030
0.050	1.0	0.9634	0.8411	0.7274	0.3776	0.2875	0.2930	0.3564	0.4370	0.5250	0.6168	0.7109	0.8064	0.9028	1.0	0.050
0.080	1.0	0.9775	0.8974	0.8149	0.4919	0.3727	0.3429	0.3886	0.4588	0.5400	0.6270	0.7175	0.8103	0.9046	1.0	0.080
0.100	1.0	0.9823	0.9178	0.8490	0.5500	0.4214	0.3739	0.4094	0.4732	0.5500	0.6339	0.7221	0.8130	0.9058	1.0	0.100
0.200	1.0	0.9921	0.9617	0.9267	0.7286	0.6000	0.5077	0.5058	0.5429	0.6000	0.6690	0.7454	0.8270	0.9122	1.0	0.200
0.300	1.0	0.9953	0.9773	0.9558	0.8203	0.7136	0.6138	0.5916	0.6093	0.6500	0.7053	0.7703	0.8423	0.9192	1.0	0.300
0.400	1.0	0.9970	0.9853	0.9712	0.8761	0.7923	0.7000	0.6684	0.6727	0.7000	0.7429	0.7967	0.8588	0.9270	1.0	0.400
0.500	1.0	0.9980	0.9901	0.9806	0.9136	0.8500	0.7714	0.7375	0.7333	0.7500	0.7818	0.8250	0.8769	0.9357	1.0	0.500
0.600	1.0	0.9987	0.9934	0.9870	0.9406	0.8941	0.8316	0.8000	0.7913	0.8000	0.8222	0.8552	0.8968	0.9454	1.0	0.600
0.700	1.0	0.9992	0.9957	0.9916	0.9610	0.9290	0.8829	0.8568	0.8468	0.8500	0.8642	0.8875	0.9186	0.9564	1.0	0.700
0.800	1.0	0.9995	0.9975	0.9951	0.9768	0.9571	0.9273	0.9087	0.9000	0.9000	0.9077	0.9222	0.9429	0.9690	1.0	0.800
0.900	1.0	0.9998	0.9989	0.9978	0.9896	0.9804	0.9660	0.9562	0.9510	0.9500	0.9529	0.9597	0.9698	0.9833	1.0	0.900
1.000	1.0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1.000

Table 2 - C_2 -values for several (p, ψ) -combinations

$p \setminus \psi$	0	0.001	0.005	0.01	0.05	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0	$\psi \setminus p$
0.001	0.2505	0.6843	0.0256	0.0171	0.0278	0.0514	0.1010	0.1508	0.2007	0.2508	0.3007	0.3508	0.4007	0.4508	0.5008	0.001
0.003	0.2515	0.1518	0.0613	0.0386	0.0331	0.0546	0.1029	0.1524	0.2023	0.2522	0.3022	0.3523	0.4024	0.4525	0.5026	0.003
0.005	0.2525	0.1815	0.0878	0.0567	0.0384	0.0576	0.1049	0.1541	0.2038	0.2538	0.3037	0.3539	0.4040	0.4542	0.5043	0.005
0.007	0.2535	0.1984	0.1084	0.0724	0.0434	0.0606	0.1068	0.1557	0.2054	0.2552	0.3052	0.3554	0.4056	0.4559	0.5061	0.007
0.010	0.2550	0.2138	0.1319	0.0923	0.0509	0.0651	0.1097	0.1582	0.2076	0.2575	0.3076	0.3578	0.4081	0.4584	0.5087	0.010
0.020	0.2601	0.2378	0.1787	0.1389	0.0737	0.0795	0.1194	0.1663	0.2152	0.2650	0.3152	0.3656	0.4160	0.4666	0.5174	0.020
0.030	0.2652	0.2500	0.2048	0.1602	0.0941	0.0935	0.1289	0.1745	0.2228	0.2725	0.3226	0.3732	0.4241	0.4749	0.5260	0.030
0.050	0.2756	0.2665	0.2362	0.2084	0.1294	0.1197	0.1478	0.1908	0.2382	0.2875	0.3378	0.3887	0.4398	0.4913	0.5430	0.050
0.080	0.2916	0.2860	0.2663	0.2462	0.1730	0.1559	0.1758	0.2153	0.2612	0.3100	0.3603	0.4116	0.4632	0.5155	0.5680	0.080
0.100	0.3025	0.2981	0.2823	0.2656	0.1982	0.1784	0.1941	0.2316	0.2766	0.3250	0.3752	0.4266	0.4788	0.5314	0.5843	0.100
0.200	0.3600	0.3581	0.3509	0.3426	0.2997	0.2791	0.2837	0.3134	0.3539	0.4000	0.4494	0.5008	0.5537	0.6076	0.6622	0.200
0.300	0.4225	0.4215	0.4174	0.4127	0.3852	0.3694	0.3710	0.3956	0.4320	0.4750	0.5223	0.5726	0.6248	0.6785	0.7334	0.300
0.400	0.4900	0.4894	0.4869	0.4841	0.4667	0.4558	0.4578	0.4786	0.5099	0.5500	0.5941	0.6417	0.6919	0.7440	0.7957	0.400
0.500	0.5625	0.5622	0.5607	0.5590	0.5483	0.5416	0.5446	0.5625	0.5903	0.6250	0.6647	0.7083	0.7548	0.8036	0.8542	0.500
0.600	0.6400	0.6398	0.6389	0.6380	0.6319	0.6285	0.6324	0.6474	0.6706	0.7000	0.7342	0.7723	0.8134	0.8570	0.9029	0.600
0.700	0.7225	0.7225	0.7220	0.7215	0.7186	0.7172	0.7216	0.7336	0.7517	0.7750	0.8025	0.8335	0.8676	0.9042	0.9429	0.700
0.800	0.8100	0.8100	0.8098	0.8079	0.8085	0.8085	0.8124	0.8210	0.8336	0.8500	0.8695	0.8919	0.9169	0.9440	0.9733	0.800
0.900	0.9025	0.9025	0.9025	0.9016	0.9023	0.9027	0.9052	0.9098	0.9164	0.9250	0.9354	0.9475	0.9610	0.9763	0.9930	0.900
1.000	I.	I.	I.	I.	I.	I.	I.	I.	I.	I.	I.	I.	I.	I.	I.	1.000

studied, will draw their conclusions, as far as hereditary factors are involved, from the result of this comparison. In fact, this means that one considers the importance of environmental factors to be the same in each type of twins; on the average, these factors are considered to be equally important for the establishment of concordance.

In conclusion, it appears to be justified to consider φ to have the same value in both mono- and dizygous twins.

We feel, that only in case of some specific characters, specific as far as their sensitivity to environmental influences is concerned, this attitude may lead to erroneous conclusions. It is to be remarked, however, that in particular twins of both types are used to test the sensitivity of certain characters to exogeneous factors. In some cases a vicious circle may result.

The expressions for C_1 and C_2 respectively may now be used to solve the two unknowns p and φ .

Solving these two equations algebraically is quite a laborious task. A graphic method will lead much quicker to the answers and will be sufficiently accurate in all practical cases.

With the aid of the figures given in table 1 and 2, the reader may draw a number of curves like those in our figures 2 and 3. A horizontal, determined by the observed values C_1 and C_2 respectively, will intersect a number of the curves in each of the figures analogous to our figs. 2 and 3. The coordinates of these points of intersection belonging to an observed value of C_1 (e.g. $C_1 = 0.77$), may be used to draw a part of the curve showing the relation between p and φ for a constant (observed) C_1 -value (curve I; fig. 4).

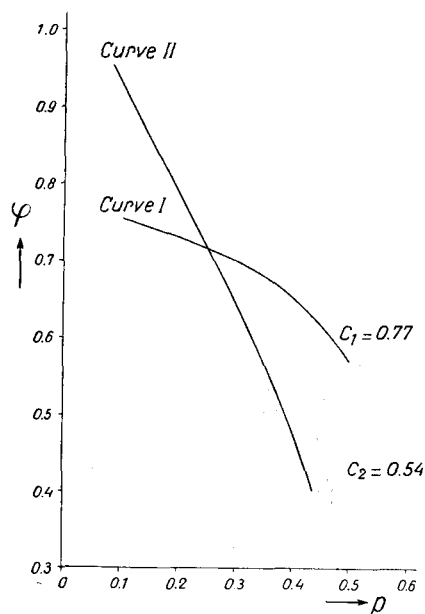


Fig. 4. Determination of gene frequency (p) and mode of inheritance (φ) from percentages of concordance

A curve of the same kind is to be drawn for this relation for the observed C_2 -value (e.g. $C_2 = 0.54$; curve II, fig. 4).

It might be expected, that the curves I and II will meet. Their point of intersection reveals that (p , φ)-combination that satisfies both the equation for C_1 and for C_2 (here: $p = 0.25$; $\varphi = 0.72$).

In practice it will be found that research of an amount of twins sufficiently large to draw valid conclusions, comprises characters for which the value of the gene frequency p is rather high; otherwise it would have been nearly impossible to collect this amount of twins.

It will be clear, that the mode of inheritance is expressed by the value of φ .

For: $\varphi = 1$ means complete penetrance, i.e. the character studied is based on a gene showing regular or complete dominance;

$\varphi = 0$ means, that none of the heterozygotes will show the character, i.e. the gene a_1 is a recessive;

$0 < \varphi < 1$, is the numerical expression for the 'behaviour' of all those genes showing irregular dominance.

Again, we stress the point, that none of these diagnoses is given by the observed percentages of concordances themselves, nor by a simple comparison of these observables.

It may be concluded, that investigations of twins, guided as described above, may reveal not only the existence of a genetic basis for the character studied, but also the mode of inheritance *in case this character is the effect of only one pair of alleles (monomery)*.

One may remark, that it is easier to arrive at this conclusion with the aid of a more or less extensive pedigree! The line of reasoning described, however, can be applied theoretically to polymeric characters as well; thus, it is to be expected, theoretically, that also more complicated genetic backgrounds are reflected in the percentages of concordance. The important point is, in our opinion, that the considerations given may perhaps contribute to the theory of twin research in human genetics. For, in many textbooks and papers the opinion is expressed, explicitly or implicitly, that twins can only be used to investigate the question whether a genetic basis for a certain character is present or not.

Indeed, the *practical* value of this latter opinion is not to be denied in the majority of cases.

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Summary

Concordance in monomeric characters, studied in a representative series of twins is discussed: one pair of alleles a_1 and a_2 is involved. It is presumed that a homozygous condition, be it a_1a_1 or a_2a_2 , always results in a certain observable. It follows, that homozygosity in monozygous twins implies that the partners are concordant. Discordance in monozygous twins may occur in case the character studied results from the heterozygous condition of an incomplete penetrant gene. In dizygous pairs concordance will also be present when both partners possess the homozygous condition;

however, if one partner is a homozygote, the second *may* be a homozygote. The same applies to the heterozygous condition.

Formulas are derived in which the observed percentages of concordance in mono- and dizygous twins (C_1 and C_2 respectively) are expressed as a function of the gene frequency p and the penetrance φ . A graphic method is described to solve these two equations. The mode of inheritance is expressed by the value of φ .

It is concluded that investigations of twins may reveal not only the existence of a genetic basis for the character studied, but also the mode of inheritance.

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Some penetrance *formulae* in recessive proband material

C.-G. Berglin

Several authors have treated penetrance problems mathematically. Strömngren, (1) in 1938, proposed some formulae applied to population genetics. As a development of v. Verschuer's work (2) in the field of twin probands, Luxenburger (3), in 1940, and Schinz (4), in 1946, laid down formulae, for monozygotic twin probands (cf Gedda 5). Penrose (6), Böök (7), and Essen-Möller (8), have attacked penetrance problems from different points of view. In 1954, Trankell (9), published his first paper on population penetrance, outlining a broader method than before. The method, subsequently developed by Trankell (10, 11, 12), and the author (13), enabled Trankell to demonstrate that the results of three investigations on left-handedness in USA led to nine separate evaluations of a recessive gene, all of them in close accordance with each other, despite the seemingly wide discordance of the original findings. Freire-Maia and Quelce Salgado (14), arrived at similar results on recalculation of findings on arm folding and hand clasping. Penetrance calculus, then, seems to open up definitely new possibilities.

Since the great bulk of statistical genetic data, however, is concerned with probands, it appears desirable to try to translate such data into the language of population genetics, in order to make penetrance calculus more easily applicable.

When we state that schizophrenic patients have schizophrenic parents in x per cent and schizophrenic siblings in y per cent, those two concordances are derived in different ways. We cannot compare them directly before we have expressed them in the same mathematical reference system, preferably in the form of population concordances. The child-parent concordance will then remain the same, but the patient-sib concordance may rise to nearly twice its former value, as is well known from Weinberg's sib method (cf. Schulz (15) and a comprehensive survey by Ludwig and Boost (16).

The difference is particularly obvious in completely ascertained samples of pairs, for instance twins, mates, sibships of two.

For the case of recessive diallelomorphs, this is illustrated in diagram 1. From a total population we have drawn a representative sample of unity size, called I. The population contains specimens of a homozygous zygote, called Z. The sum of Z has the proportion z , each Z capable of manifesting the trait A. Actually, though, only some Z show the trait A. Their proportion is a , so that the penetrance of zygotes (zygotrance, 13) in the population is $\frac{a}{z}$. We now pair each member of sample number I with the given co-pairings, who together constitute another representative

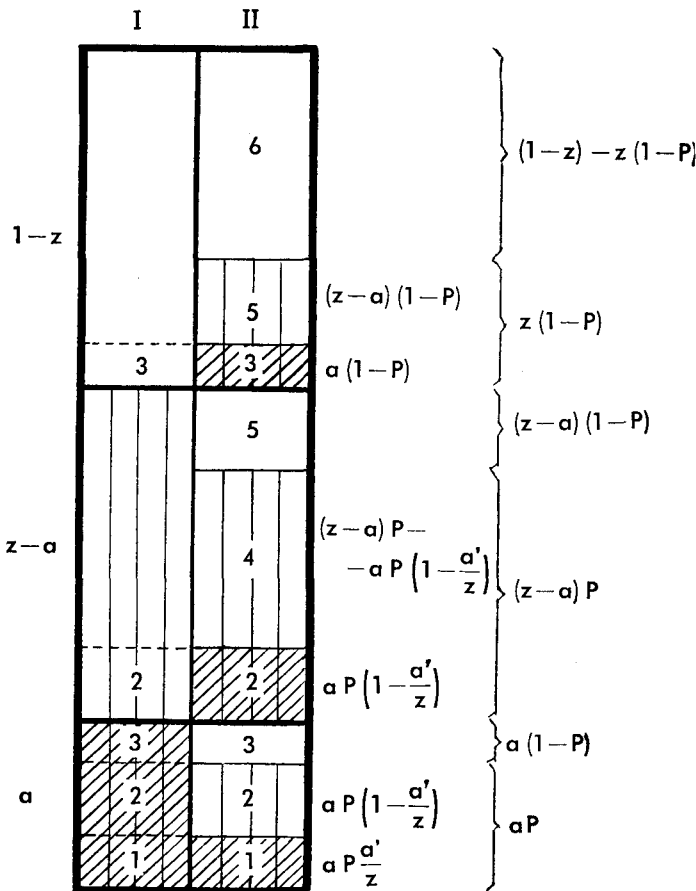


Diagram 1. Paired population samples.

1: unity size of sample; z : zygote proportion ($=.60$); a : trait-carrier proportion ($=.20$); a/z : average penetrance ($=.20/.60 = 1/3$); a'/z : penetrance in zygotes paired to trait-carriers ($=.40$); P : probability of pairing a given zygote Z to another zygote Z ($=.75$). The numbered fields then have the following proportions: 1) .06; 2) .09; 3) .05; 4) .21; 5) .10; 6) .25. Vertical lines: zygotes. Oblique lines: trait-carriers.

If $a' = a$, each zygotrance reduces to the average value.

The generality of the construction may be shown in the following way. Suppose z in I consists of any number of sub-groups $z_1 + z_2 + z_3 + \dots = z$, with corresponding penetrant parts $a_1 + a_2 + a_3 + \dots = a$, so that the zygotranes are $\frac{a_1}{z_1}, \frac{a_2}{z_2}, \frac{a_3}{z_3}$ and so on, ranging between 1 and 0. In the first sub-group we have a a_1 penetrant

sample, called II, of the total population. Between the two samples we assume a defined relationship, for instance randomness or some form of consanguinity. The definition implies the probability P , that any Z_I shall find itself paired to a Z_{II} . Opposite to a , we thus find aP zygote-carriers. Opposite to $(z-a)$, we find $(z-a)P$. Opposite to $(1-z)$, we find the rest, that is, $z(1-P)$ zygote-carriers. In the first group, we assume the zygotrance to be equal to or perhaps larger than the population zygotrance, say $\frac{a'}{z}$, so that the trait-carriers are $\frac{a'}{z} \cdot aP$. In the third group, we have no reason to suspect any deviation from the average zygotrance, so that the trait-carriers are $\frac{a}{z} \cdot z(1-P) = a(1-P)$. Since the sum of trait-carriers in II should be a , too, the remaining part, $aP(1 - \frac{a'}{z})$, belongs to the middle group, the zygotrance of which is accordingly $\frac{a}{z} \cdot \frac{z - a'}{z - a}$.

and $(z_1 - a_1)$ non-penetrant individuals, the total sums for all sub-groups being a and $(z - a)$, respectively. In II we find $a_1 P \frac{a_1}{z_1}$ penetrant individuals among the pairings of a_1 , and $(z_1 - a_1) P \frac{a_1}{z_1}$ penetrant individuals among the pairings of $(z_1 - a_1)$, the total sums being $P(a_1 \frac{a_1}{z_1} + a_2 \frac{a_2}{z_2} + \dots)$ in the first case and $P(a_1 - a_1 \frac{a_1}{z_1} + a_2 - a_2 \frac{a_2}{z_2} + \dots)$ in the second case. Since $(a_1 \frac{a_1}{z_1} + a_2 \frac{a_2}{z_2} + \dots)$ is smaller than a , we may substitute it by the pooled expression $a \frac{a'}{z}$. The sums then take the form $aP \frac{a'}{z}$ and $aP(1 - \frac{a'}{z})$ respectively.

The ratio of paired trait-carriers to all trait-carriers (measured from I to II or from II to I) is $aP \frac{a'}{z} : a = \frac{a'}{z} P$. This expression corresponds to the population concordance.

In proband investigations, we start from trait-carriers only. The situation is depicted in diagram 2, combined from those parts of the population that contain trait-

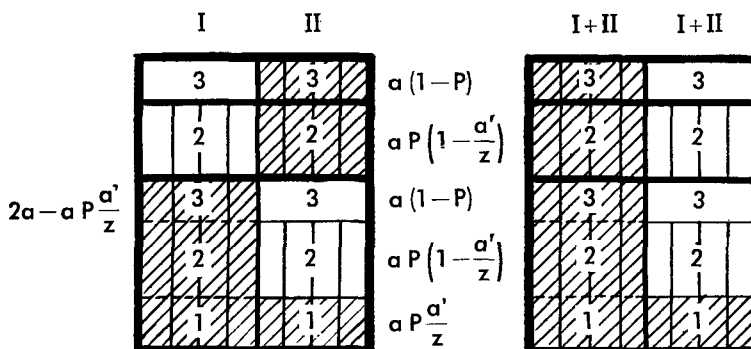


Diagram 2. Paired proband samples.

The same symbols as in diagram 1. Total size: $2a - aP \frac{a'}{z}$ ($=.34$). Left model: ordered pairs. Right model: rearranged pairs, the first column selected from trait-carriers only

carriers. Two kinds of situation arise. Sometimes, the probands form the proportion a , as in the example to the left. Often, however, we start from persons forming the combination $a + aP(1 - \frac{a'}{z}) + a(1 - P) = 2a - aP \frac{a'}{z}$, as in the example to the

right. In the first case, we arrive directly at the population concordance $\frac{a'}{z}P$. In the second case, the ratio of trait-carriers among pairlings has the form

$$\text{pairling concordance } k = \frac{a'}{z}aP : \left(2a - \frac{a'}{z}aP\right) \quad (1)$$

The corresponding population concordance may then be written

$$\text{population concordance } \frac{a'}{z}P = \frac{2k}{1+k} \quad (1a)$$

This is a more general form of Luxenburger's and Schinz' formula (without correction for "Auslesegrad") for penetrance in monozygotic twins. In the general population with random pairing, we have $a' = a$ and $P = z$, so that the left member reduces to a , and $k = \frac{a}{2-a}$.

By means of binomial expansion, it is possible to show that (1) is a special form of the general formula (suggested by Weinberg¹⁷)

$$k_s = \frac{1}{s-1} \left(\frac{ps}{1-q^s} - 1 \right) \quad (1b)$$

A trait-carrier, who belongs to a group of s members, for instance a sibship of four sibs, has the risk k_s to find trait-carriers among his co-members (sibs), provided all s -groups that contain trait-carriers have been sampled. The general risk (population concordance) in sibs etc. is p , while $q = 1 - p$. When s grows, k_s will approximate p . The expression $\frac{ps}{1-q^s}$ is wellknown from Bernstein's a priori method and corresponds to the average number of trait-carriers in each group of s members within a complete sample.

Generally speaking, we arrive directly at population concordances, when the members of I and II are not formally interchangeable, e.g. parent-child, uncle-nephew, males-females, ordered random pairs. We arrive at pairling concordances of the k -type as soon as the members of I and II are interchangeable, e.g. twins, sibs, brothers, relatives, mates, random pairs not arranged with respect to order. Such concordances may be considerably involved, for instance when we go from a trait-carrying twin to his trait-carrying sibs. We then have to transform the twin probands into a twin population first, going from the right to the left example in the diagram. If we have started from mixed monozygotic-dizygotic twin probands, the second step is to part them into a monozygotic and a dizygotic population. The third step is to compute the concordances between twins, between concordant twins and their sibs, ultimately between discordant twins (some of which have non- Z co-twins) and their sibs.

Suppose concordant DZ twins have 20 per cent concordant sibs. This is a simple population concordance, since we cannot change the sibs into probands. Suppose further that DZ twins, arranged according to the model on the right in diagram 2, have 14 per cent concordant twins. This is a pairling concordance, corresponding

to a population concordance of about 25 per cent (1a). If we regard DZ twins as sibs born together, they have the same P as ordinary sibs, that is, $\left(\frac{1+r}{2}\right)^2$ when the frequency of the recessive gene is r. The ratio of the two population concordances is then the ratio of the penetrances. In this case, the penetrance in DZ twins is 1.25 times that of sibs.

It is important to remember that the formulae and groupings hitherto considered have their application only upon samples that contain all trait-carrying groups of a certain kind within a given time-space limit. Every trait-carrier in the sample will then have been ascertained as a proband.

When ascertainment is incomplete but all probands registered, the most straightforward procedure is to use Weinberg's proband method, that directly gives the true risk (population concordance) within the investigated relationship. If the probands are not explicitly registered (as often in printed communications), it is often possible to estimate the ratio of the actual sample to the total sample within the given population: Auslesegrad, or u. We may then insert Weinberg's ws-expression: $\frac{ps (1 - (1 - u) (1 - pu)^{s-1})}{1 - (1 - pu)^s}$ (cf Weinberg¹⁷, Schulz¹⁵, p. 71) instead of

$\frac{ps}{1 - q^s}$ in (1 b) and arrive at the population concordance. For incomplete samples of pairs containing at least one trait-carrier, we then have:

$$p = \frac{2k}{2 - u + ku} \tag{1c}$$

When $u = 1$, we arrive at (1 a). When $u = 0$, that is, when only one trait-carrier in each pair is a proband, we have: $p = k$. (An incorrect construction of (1 c) is quoted in textbooks, namely, $M = \frac{K' (r + 1)}{K' r + 1}$ or, in the notation used here:

$p = \frac{k(u + 1)}{ku + 1}$. It leads to a slightly inflated p, with a maximum difference, occurring at $k = .5$ and $u = .5$, of .03.)

The correct deduction of (1 c) can be demonstrated graphically from diagram 2.

Remembering that $p = \frac{a'}{z} P$, we see how in a complete sample discordant pairs form the proportion $2a(1 - p)$ and concordant pairs the proportion ap . With incomplete ascertainment, any proband has the chance u to be selected, so that $2a(1 - p)u$ probands are sampled from discordant pairs and $apu + apu$ probands from concordant pairs. Opposite to apu in I we have apu^2 probands and $apu(1 - u)$ concordant secondary cases in II. The rest of the probands in II have the proportion $apu(1 - u)$ with their secondary cases placed in I. Thus, the concordant pairs are: $apu^2 + 2apu(1 - u) = apu(2 - u)$, so that

$$k_2 = \frac{apu(2 - u)}{apu(2 - u) + 2a(1 - p)u} = \frac{2p - pu}{2 - pu}, \text{ and } p = \frac{2k}{2 - u + ku}.$$

The fact that $k_2 = p$ for $u = 0$ is of a general nature. Since Weinberg's w -expression takes the form $1 + p(s - 1)$ for $u = 0$, we find, by inserting it into (1 b), that $k_s = p$ for $u = 0$. This corresponds to the common procedure, where diagram 1 is used irrespective of group sizes, as long as no probands are found among the co-members. The k_s -value is then simply the proportion of trait-carriers among the co-members (sibs etc.) and identical with p , or $\frac{a'}{z}P$, of the investigated relationship.

The probability of Z in pairings of \bar{Z} (non- Z) is another point of interest. The \bar{Z} in I have the proportion $(1 - z)$ and the corresponding Z in II have the proportion $z(1 - P)$, according to diagram 1. The probability is thus

$$P_{Z/\text{non-Z}} = \frac{z(1 - P)}{1 - z} \quad (2)$$

This provides a simple formula for calculating some risks. For $P = \left(\frac{1 + r}{2}\right)^2$ and $z = r^2$, we find immediately by (2) that the risk for dominants to have recessive sibs is $\frac{r^2}{4} \cdot \frac{3 + r}{1 + r}$, a well-known formula from population genetics. A variant of (2) gives the probability that a \bar{Z} shall have an A-pairing, namely

$$P_{A/\text{non-Z}} = \frac{a(1 - P)}{1 - z} \quad (2a)$$

This describes a kind of proband discordance, sometimes used in order to evaluate the incidence of a trait in the normal population. Healthy persons are asked, for instance, how many schizophrenic sibs they have. The found value is always smaller than a , since $P > z$.

The "healthy" incidence has been estimated to values below 1 per cent, the true to 1.24 per cent by Strömberg (1) and to 1.6 per cent by Larsson and Sjögren (18). The discrepancy may of course be due to varying gene frequencies in different populations and to varying methods of ascertainment, but the ($P_{A/\text{non-Z}}$)-effect has probably played an important rôle, too.

We know the theoretical P -values in simple recessive cases (19). It is for parents or children: r , for sibs: $\left(\frac{1 + r}{2}\right)^2$, for half-sibs, grand-parents, grand-children, uncles and nephews: $r\left(\frac{1 + r}{2}\right)$, for first cousins: $r\left(\frac{1 + 3r}{4}\right)$, for step-sibs: r^2 . (In double recessives, we have to apply products of two such formulae, e.g. $\left(\frac{1 + r_1}{2}\right)^2 \left(\frac{1 + r_2}{2}\right)^2$, for sibs.) By inserting into (2a) the risks found in healthy probands, we arrive at a series of estimates of r (as well as of a and P).

Formula (2) and (2a) apply also to no-recessive cases, where P will have its average value in (1-2), although it is too low in (z -a) and too high in a .

When we suspect that z is not so small that we may neglect it, healthy persons may to a considerable degree belong to $(z - a)$ in diagram 1. Our denominator then takes the form $(1 - a)$, so that we may check the population incidence (a) and the population concordance $(\frac{a'}{z}P)$ against the probability of trait-carrying relatives in non-carriers ($P_{A/non-A}$) in the following way:

$$P_{A/non-A} = \frac{a(1 - \frac{a'}{z}P)}{1 - a} \quad (3)$$

If we find, for instance, that healthy persons have .85 per cent schizophrenic sibs and that schizophrenic patients have 20 per cent schizophrenic sibs (population concordance), formula (3) takes the form $.0085 = a(1 - .20) : (1 - a)$, so that $a = .0105$.

It should be stressed that (2), (2a) and (3) presuppose that the empirical rates represent population concordances (ordered sibs, etc.). Without such precautions, the rates may give higher, instead of lower, values than the population incidence, because affected persons will accumulate in the second pairing column. The discordance d_2 in pairings of healthy persons will then be:

$$d_2 = \frac{2a(1 - p)}{2(1 - a) - u(1 - 2a + ap)} \quad (3a)$$

The formula, derived in the same manner as (1c), shows that for $u = 0$ the value is the same as in (3); it may grow twice as large, when u rises to unity.

The Bernstein model, from which we may derive

$d_s = \frac{1}{s - 1} \frac{sp(1 - (1 - qu)^{s-1})}{1 - (1 - qu)^s}$, is restricted to cases where $a = p$. It would therefore interpret the present problem incorrectly.

Since the concordance of step-sibs of trait-carriers should be $\frac{a'}{z}$. $z = a'$, we may hope to solve P directly from the population concordance, too. A detailed knowledge of incidences in different kinds of relationship will provide us with several possibilities to test hypotheses of partly penetrant recessive inheritance. The success of the test will of course depend upon the accuracy with which the model depicts the interplay of factors in each case. In comparison with six other models tried out by the author, the one described here has the advantage of being relatively simple and yet supple, making allowance for different penetrance situations in different groups.

Summary

A mathematical model is described, covering the case of paired recessive diallel-morphs with different degree of penetrance in the pairings, according to whether the proband carries 1) the trait, 2) the genotype but not the trait, 3) neither the genotype nor the trait. The incidences of trait-carrying pairings in the three proband groups are expressed in terms of population genetics and formulae given, together with some conclusions.

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RIASSUNTO

Il modello matematico qui sopra descritto si riferisce al caso di individui diallelomorfi recidivi che accostandosi più o meno al proprio fenotipo sono appaiati ad una serie rappresentativa che riportano 1) il fenotipo, 2) il genotipo ma non il fenotipo, 3) nè l'uno, nè l'altro tipo. Le proporzioni tra gli appaiati dei tre gruppi sono espresse in termini della genetica di popolazione, con delle formule e qualche conclusione.

RÉSUMÉ

Le modèle mathématique donné ici se réfère au cas, où des individus récessifs diallélomorphiques, leur phénotype plus ou moins pénétrant, sont appariés à une série représentative de probands, qui portent 1) le phénotype, 2) le génotype mais non pas le phénotype, 3) ni le génotype ni le phénotype. Les proportions pénétrantes parmi les appariés dans les trois groupes sont exprimées in termes de la génétique de population avec des formules et quelques conclusions.

ZUSAMMENFASSUNG

Das beschriebene mathematische Modell entspricht dem Falle, wo recessive diallelomorphe Probanden, die 1) das Merkmal, 2) den Genotypus aber nicht das Merkmal, 3) weder den Genotypus noch das Merkmal tragen, mit anderen Individuen gepaart sind, die auch phänotypisch variieren. Die Formeln sind in einer einheitlichen populationsgenetischen Form ausgedrückt und einige Schlussfolgerungen angegeben.