Expectation of Abnormality on Paternal and Maternal Sides: A Computational Model

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Edwards (1960, 1963) has recently pointed out that conditions which have been attributed to the effects of a single major gene of diminished penetrance are also capable of being explained as the result of polygenic factors, if the condition in question is not very infrequent. It is only necessary to suppose that polygenic factors bring about a predisposition which expresses itself in a recognizable apparently qualitative deviation, once it has passed a given threshold. There is, for instance, evidence that the presence or absence of the hare-lip/cleft palate syndrome is due to polygenic factors (Carter, 1965). It is supposed that there is a critical stage in development by which time the embryonic layers involved must have united; a delay in union short of this point is without effect, but beyond it leaves an incomplete state which is never made good.

Edwards has also pointed out that the two alternative hypotheses are very alike in their effects, so that it is difficult to devise tests to distinguish between them. Nevertheless, it is important to make such a distinction if possible, since they are not equivalent. It has been said that the penetrance of every gene is complete, given the right test of its biochemical action. A hypothesis of major gene action, therefore, suggests investigation along biochemical lines. The polygenic hypothesis is of less heuristic value.

It occurred to the writer that it should be possible to distinguish between polygenic inheritance and the effects of a single dominant major gene with diminished penetrance, by noting the distribution of secondary cases among the relatives on the paternal and maternal sides of the ascendance of affected individuals. On the single gene hypothesis one would expect, in the cases where two or more affected relatives were known, that these would be either on the paternal or the maternal side, but not

on both. Relatives coming in question would include uncles and aunts, grandparents, and cousins. If polygenic inheritance was operative, the author imagined that a more even distribution between paternal and maternal sides would be found. It was, however, by no means easy to prove this; and when mathematical geneticists, to whom the problem was offered, showed some disinclination to tackle it along rigorous lines, the attempt was made to find an approximate answer by computation carried out on a simplified model.

It is supposed that the many genes predisposing to a condition *A* are additive in their action; the predisposition to *A*, measured quantitatively, will accordingly be normally distributed. It is also supposed that any individual exceeding $+2\sigma$ above the population mean is liable to pass the threshold and become recognizable as an *A*-deviant. Whether he actually did so or not, might or might not depend on some additional, possibly accidental, factor.

We now classify fathers and mothers in classes, each class covering a span of 0.5σ , and its frequency corresponding to the area of the normal curve between the limiting ordinates. Supposing that mating is at random, we are able to calculate the frequency of any given mating as the product of the frequencies of the maternal and paternal classes severally. As a simplifying hypothesis we may then suppose that the children of this mating are distributed normally about the mid-parental value. We take an example from the Table and consider the cell where mothers between the values of $+1.5$ and $+2.0\sigma$ have mated with fathers between $+2.5$ and $+3.0\sigma$. The log maternal frequency is 2.6440159 , the log paternal frequency is 3.6866184 , and the mating frequency is 4.3306343 . The children of this mating are distributed about a mean of $\frac{1}{2}(1.75+2.75)=2.25\sigma$, and the proportion of them who will deviate from the population mean by 2σ or more will correspond to the area of the normal

TABLE

	-2.5	-2.0	-1.5	-1.0	-0.5	0.0	+0.5	+1.0	+1.5	+2.0	+2.5	+3.0	+3.5	+4.0	+4.5	+5.0
-0.5					1 2 1											
0.0				3 2	7 8 2	9 18 9										
+0.5		1 —	5 —	14 4	30 19 3	49 56 16	58 116 58									
+1.0		4 —	14 1	39 7	81 54 9	125 84 14	140 165 49	112 224 112								
+1.5	1 —	7 —	27 1	74 9	146 33 2	193 85 9	228 167 31	174 216 68	100 200 100							
+2.0	2 —	11 —	37 1	94 7	176 26	245 65 4	250 117 14	182 144 29	100 127 41	39 78 39						
+2.5	3 —	10 —	33 —	80 4	144 14	191 33 1	186 66 4	129 67 9	69 57 12	26 34 11	7 14 7					
+3.0	1 —	6 —	20 —	64 —	80 3	101 12	94 19	63 22 2	32 18 2	12 10 2	3 4 1	— — —				
+3.5		3 —	8 —	19 —	30 1	37 3	33 4	21 5	10 4	4 2						
+4.0			2 —	5 —	8 —	9 —	8 —	5 —	2 —							
+4.5				1 —	1 —	1 —	1 —									
+5.0																

Note: Each cell defines the limits of deviation, in standard deviations, of the two parents from the population mean. The numbers in the cells represent from above downwards the relative probabilities of an individual of such parentage, himself deviating from the population by 2 σ or more, having respectively two sibs of a father, one sib of a father and one sib of a mother, and two sibs of a mother, both deviating from the population mean by 2 σ or more.

curve to the positive side of -0.25σ , the log frequency being $\bar{1}.7772139$. The contribution of this mating to our observed propositi may, therefore, be estimated, in comparison with the contributions of all other cells, as $\bar{4}.1078482$.

We now have to make some rough-and-ready assumptions about the paternal and maternal relatives. Uncles and aunts will tend to be distributed about means of $+0.875$ on the maternal and $+1.375$ on the paternal side; mothers and fathers, of course, deviate by twice those margins, but more distant relatives by a lesser amount. At this point we may treat all relatives as if they were sibs of the parents. Maternal relatives will accordingly need to exceed their expected mean by 1.125σ , and paternal relatives by 0.625σ , to attain the critical value of $+2.0\sigma$. We may call the probabilities of these deviations respectively m and p , with log values in this case of $\bar{1}.1149360$ and $\bar{1}.4248623$, respectively.

We now consider the relative probabilities of

finding two affected relatives on the paternal side, of finding one paternal and one maternal affected relative, and of finding two affected maternal relatives. Supposing that n relatives are examined on each side, these probabilities reduce to being proportionally $(n-1)p^2(1-m)^2$, $2npm(1-p)(1-m)$, and $(n-1)m^2(1-p)^2$. Omitting coefficients in terms of n , they are in the cell we have instanced in log form $\bar{2}.7284660$, $\bar{2}.6459025$, and $\bar{3}.9612790$, respectively. Adding to these the log of the cell probability, $\bar{4}.1078482$, we get figures whose antilogs are respectively 6.9 , 5.7 , and 1.2×10^{-6} . The Table has been so prepared as to include all matings which gave a value for the log cell probability added to the log of $p^2(1-m)^2$ in excess of $\bar{7}.0$, stretching over three orders of magnitude. The probabilities of one paternal and one maternal relative affected, and of two maternal relatives affected, are entered also, where they exceed this figure.

We may now use this table to compute the relative expectations of finding two paternal relatives

affected, two maternal relatives, or one of each. The section of the bivariate expanse shown in the Table should have been extended symmetrically on the other side of the diagonal marked in heavy outlines, so that paternal figures become maternal ones and vice versa. Adding up the figures for the entire area so described we obtain the numbers 4675:4193:4675, or approximately 11 : 10 : 11.

A similar computation was made on the basis that all relatives were equivalent to mothers or fathers. This produced the proportions 31233 : 12454 : 31233, or approximately 5 : 2 : 5. It was not thought necessary to make yet another computation, to take care of the cases in which information was obtained about more remote relatives. In their case, the proportion of cases in which both a paternal and a maternal relative were ascertained should exceed the proportion of cases in which two paternal, alternatively maternal, relatives were ascertained.

We now have to take account of the value we set on n . In the limiting case, in which n is large, n and $(n - 1)$ approach equality, and the proportions above noted remain undisturbed. At the other limit, where $n = 2$, the expected proportion of cases in which one paternal and one maternal relative are ascertained has to be doubled relatively to unilateral distributions. In practical application, one could make an estimate of the mean number of paternal and maternal relatives per family, on which information was available, in the course of collecting the information designed to test the alternative hypotheses of polygenic or monogenic inheritance. This empirically found value of n could then be used to adjust the expectations against which comparison was to be made.

Summary

It is difficult to distinguish the effects of inheritance by a dominant major gene with diminished penetrance from polygenic inheritance. Nevertheless, it seems to be worth while making the distinction in the case of genetically determined abnormalities, if this is practicable. The possibility has been considered that, if families are sought for in which relatives on the paternal or maternal side include two or more secondary cases of the condition under investigation, single gene inheritance might be exhibited in a preponderance of cases on either the paternal or maternal side, while polygenic inheritance might tend to go with a more even distribution of secondary cases between the two sides of the ascendance. A computational model, making use of some simplifying hypotheses, has been set up to test this possibility. It is found that, in the cases of near relatives such as parents or sibs of parents, even with polygenic inheritance, one expects a unilateral preponderance of secondary cases, rather than a more even distribution. This does not exclude the possibility of distinguishing between the consequences of the two alternative hypotheses, if reliable accounts of more distant relatives are available, or if use can be made of families with three or more secondary cases.

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