Essay on the Linkage Between Colourblindness and Haemophilia

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The linkage between the genes for colourblindness and haemophilia in man.

By Julia Bell and J. B. S. Haldane

It is well established that colour-blindness and haemophilia are due to sex-linked genes. These genes are generally recessive in the females. ~~However it h~~ If this were always the case it would follow that colour-blind or haemophilic women invariably had haemophilic fathers. But colourblind women whose putative fathers are not colour-blind occur too frequently to be explained by illegitimacy (Bell 19). And in at least ~~two~~ three pedigrees haemophilic women whose fathers ~~are~~ were not haemophilic while some brothers were so have been reported. It seems likely that these diseases are not ~~fully~~ always recessive. However they are completely so in the ~~po~~ new pedigrees here presented.

There are two distinct forms of colour-blindness, protanopia and deuteranopia. According to Waaler ( ) ~~they~~ genes determining them form a series of five allelomorphs with the normal gene and those for protanomalia and deuteranomalia. Haldane (1935) suggested that there are at least two allelomorphic genes for haemophilia.

Morgan (1910) showed that in *Drosophila melanogaster* genes which are sex-linked and therefore completely linked in spermatogenesis, are partly linked in oögenesis. This principle has since been extended to other species of *Drosophila*, to poultry ~~(Haldane 19)~~ to pigeons (Cole and Kelley 1919) poultry, and other organisms, and on the basis of the data so obtained the chromosomes have been mapped.

It is important to demonstrate that the principles of linkage worked out in other animals hold for man. Since over 2% of males are ~~haem~~ colour-blind and ~~considerably~~ a somewhat larger fraction are anomalous trichromats, it was decided to seek for haemophilics, and to test their colour vision and that of their non-haemophilic brothers, following up the family

$-0.000106z^5$.

Using the values given by this formula we find $X = .015$. We do not of course know whether the discrepancy between the frequency of crossing over and that of genes is as large in woman as in *Drosophila*. But it is certain that any irregularity will reduce the value below 3.1%, and reasonably sure that the human X chromosome shows some irregularity. We may conclude that the frequency of crossing over between the loci of haemophilia and colour blindness is probably less than 3%.

Discussion.

It is evident that the linkage between the genes for haemophilia and colourblindness is so close that it has been possible to demonstrate it on a quite small amount of material. If such close linkage is typical of the human species, ~~so~~ ~~whether~~ the search for further linkage will be greatly facilitated, and its results will be of considerable eugenic value. The case here reported has no prognostic value, since haemophilia can be detected earlier than colour-blindness. If however, to take a possible example, an equally close linkage were found between the genes for blood group membership and that for Huntingdon's chorea, we should be able, in many cases, to predict which children of an affected person would develop the disease, and to advise on the desirability or otherwise of marriage.

Meanwhile, as a means to the mapping of the X-chromosome, it is most desirable that all persons suffering from any disease due to a sex-linked gene, and their unaffected ~~b~~ brothers, should be examined for colour-blindness, and if possible, anomalous trichromatism. Since about 8%. of Western European males show one or other of these defects, the yield of cases should be considerable. This research would lead to a determination of the approximate distances of the loci of these genes from that for colour-blindness

$$P(x,0) = (y^2+x)\,y\left(\tfrac{1}{2}y + \tfrac{1}{2}x + \tfrac{1}{4}x + \tfrac{1}{2}y^2\right) + (xy+y)\,x\left(\tfrac{1}{2}x + \tfrac{1}{2}y + \tfrac{1}{4}y + \tfrac{1}{2}xy\right)$$

$$= \tfrac{1}{4}y\left(4y^3 + 8xy^2 + 17x^2y + 7x^3\right)$$

$$= \cancel{y^2 + \tfrac{13}{4}x^2y + \tfrac{7}{4}x^3}y.$$

$$y^2 + \tfrac{7}{4}x^2y + \tfrac{3}{2}x^2y^2.$$

Hence the leading term is y^2, and $n=2$.

To calculate $P(\tfrac{1}{2},p)$ we note that the only possible second source of deuteranopia is the husband of $\frac{\text{III}\,2}{\text{IV}\,2}$. The probability that he was normal is $1-p$. If so the value of P is $\frac{9}{16}$, as found above. The probability that he was a deuteranope is p. If so his daughters are equally likely to ~~have~~ be $\frac{+}{c}$ or $\frac{c}{c}$. Hence the probability that V 5 is a deuteranope is $\frac{3}{4}$, and similarly for V 8. The probability that neither is a deuteranope is $\frac{1}{16}$. Hence

$$P(\tfrac{1}{2},p) = \tfrac{9}{16}(1-p) + \tfrac{1}{16}p$$

$$= \frac{9-8p}{16}.$$

It is worth noting that had IV 7 and IV 8 been examined and found to have normal colour vision the probability that $\frac{\text{III}\,2}{\text{IV}\,2}$'s husband was a deuteranope would have been reduced to $\frac{1}{4}p$, and $P(\tfrac{1}{2},p)$ would have been raised to $\frac{36-5p}{64}$.

To calculate $P(x,p)$ we note that if the husband of $\frac{\text{III}\,2}{\text{IV}\,2}$ was normal the analysis of Table 2 holds good. If he was deuteranopic the corresponding probabilities are given in Table 3. Hence in this case the contribution to $P(x,p)$ is:

$$p\left[x^2y\left(\tfrac{1}{4}y + \tfrac{1}{2}x^2\right) + x^2y\left(\tfrac{1}{4}x + \tfrac{1}{2}xy\right)\right]$$

$$= \tfrac{1}{4}px^2y(\cancel{3y}\,\cancel{x}\,3x+y).$$

$$\text{So } P(x,p) = \tfrac{1}{4}(1-p)\,y\left(4y^3+8xy^2+17x^2y+7x^3\right) + \tfrac{1}{4}px^2y(y+3x)$$

$$= \tfrac{1}{4}y\left(4y^3+8xy^2+17x^2y+7x^3\right) - py\left(y^3+2xy^2+4x^2y+x^3\right)$$

$$(1-p)y^4 + \cancel{(2-2p)}\cdot\left(\frac{7}{4}-p\right)x^2y + \left(\frac{3}{2}-2p\right)x^2y^2$$

$$=(1-p)\left[y^4 + \frac{\frac{7}{4}-p}{1-p}x^2y + \frac{\frac{3}{2}-2p}{1-p}x^2y^2\right)$$

$$=(1-p)\left[y^4 + \frac{7-4p}{4-4p}x^2y + \frac{3-4p}{2-2p}x^2y^2\right)$$

$p = .014$

$$\frac{7-4p}{4-4p}\times\frac{4}{7} = \frac{7-4p}{7-7p} = 1+\frac{3p}{7(1-p)}$$

$$= \cancel{1+}\ \underline{\cancel{1.042}}$$

$$1+ \quad \frac{.014\times3}{7\times.986} = 1+\frac{.006x.}{.986}$$

$$\frac{2}{3}\times\frac{3-4p}{2-2p} = \frac{3-4p}{3-3p} = 1-\frac{p}{3(1-p}$$

.014
.005

Pedigree 2

To avoid circumlocution it is desirable to re-write the relevant part of pedigree 2 as Fig 3. Given the pedigree of haemophilia and the fact that M is a deuteranope, we have to find the probability P that I, L, and N are deuteranopes, while E, F, G, H, and K are not. It is clear that α, β, γ, ζ, and η were $\frac{+}{h}$, whilst ϵ may be so. It may be remarked that the values of P are unaltered if we start our calculation with any of the four known haemophilic deuteranopes.

To calculate $P(x, 0)$ we note that if there was only one source of deuteranopia, D must have been a deuteranope. Hence ~~β was~~ η was $\frac{+\,+}{c\,h}$, which has a probability y, and the further probability that N is a deuteranope is also y, giving a cumulative probability y^2. Since D was a deuteranope the probability that β was $\frac{+\,+}{c\,h}$ is y, that she was $\frac{+\,h}{c\,+}$ x. The cumulative probabilities of these two contingencies are thus y^3 and xy^2.

If β was $\frac{+\,+}{c\,h}$, the probability that ~~D, F, and E~~ E, F, and G are non-deuteranopes is y^3, the same probability for K being $\frac{1}{4}(3x^2+5xy+4y^2)$ as found in the similar case in pedigree 1. Further β must have received both c and h from α, ~~who was therefore $\frac{+\,+}{c\,h}$~~. The probability that α was $\frac{+\,+}{c\,h}$ is y, that that she was $\frac{+\,h}{c\,+}$ is x. So the probability that γ was $\frac{+\,+}{c\,h}$ is x^2+y^2; since ζ is known to have been $\frac{+}{h}$. Given this, the further probability that H and I are as found is y^2. The probability that L is a deuteranope is also y^2. Thus the cumulative probability from β onwards is $\frac{1}{4}y^7(3x^2+5xy+4y^2)$.

If however β was $\frac{+\,h}{c\,+}$, the probability that E, F, G, and K were as found is $\frac{1}{4}x^3(2x^3+7xy+3y^2)$. Further A must have been c+, so ϵ was $\frac{+\,h}{c\,+}$. The probability that I and J were as found is x^2; that of K being as found is xy. Hence the cumulative probability from β onwards is $\frac{1}{4}x^6y(2x^2+7xy+3y^2)$

It follows that

$$= y^2 + \frac{7}{4}x^2y + \frac{3}{2}x^2y^2 - p(y^2 + x^2y + 2x^2y^2).$$

It is obvious that we could calculate $P(x, p)$ directly, and deduce the other values, however their calculation furnishes a useful check. It is also clear that the correction for a second source of deuteranopia is of the order of p, and therefore negligible. The calculation is however given for the sake of rigour, and also for the following reason. Had V 5 been a deuteranope the leading terms in $P(x, p)$ would have been $xy - py^2$. Since, as we shall see, x is a quantity of the same order as p, the correction would have been very important. If enough pedigrees are investigated such a case will probably arise, and a method has therefore been devised which is capable of dealing with it.

$$y^4 + 2xy^3 + \frac{17}{4}x^2y^2 + \frac{7}{4}x^3y$$

$$= y^2\left(y^2 + 2xy + \frac{17}{4}x^2 + \frac{7}{4}\frac{x^3}{y}\right)$$

$$= y^2\left(1 + \frac{13}{4}x^2 + \frac{7}{4}\frac{x^3}{y}\right)$$

$= y^2$ ~~$\left[1+\frac{13}{4}\frac{x^2}{y^2}(1+\right.$~~ $= y^2\left[1 + \frac{13x^2}{4(y+x)^2} + \frac{7}{4}\frac{x^3}{y(y+x)^2}\right]$

$$= y^2\left[\left(1 + \frac{13x^2}{4y^2}\left(1+\frac{x}{y}\right)^{-2} + \frac{7}{4}\left\{\frac{x^3}{y^3}\left(1+\frac{x}{y}\right)^{-2}\right]$$

$$= y^3\left[1 + \left(\frac{13}{4}t^2 + \frac{7}{4}t^3\right)(1+t)^{-2}\right]$$

$$= y^3\left[1 + \frac{t^2}{4}(13\cancel{t} + 7t)(1+t)^{-2}\right].$$

$$= y^3\left[1 + \frac{13}{4}t^2 - \frac{19}{4}t^3 + \frac{25}{4}t^4 \ldots\right.$$

$1 + nt + \frac{n(n-1)}{2}t^2$

$1 - 2t + \frac{6}{3}t^2 \pm \frac{2.3.4}{2.3}t^3$

$1 - 2t + 3t^2 - 4t^4$

$$\begin{array}{l} \quad 1 - 2 + 3 - 4 + 5 \\ \quad 13 + 7 \\ \hline 13 - 26 + 39 - 52 + 65 \\ \quad\; + 7 + -14 + 21 - 28 \\ \hline 13 - 19 + 25 - 31 + 37 \end{array}$$

The detection and estimation of linkage

We have now to obtain from the data as much information as possible about the frequency x of crossing-over between the loci of the genes c and h. ~~Our~~ We have on the one hand to ~~obtain as much~~ find whether it departs significantly from $\frac{1}{2}$, its value in the absence of linkage, and on the other to obtain an estimate of its actual value. Our task is made more difficult by four considerations.

1. The gene h may arise by mutation. While this is a rare event in the population as a whole, it is frequent among the immediate ancestors of haemophilics, since it has been shown by Haldane (1935) that the frequency of mutation is about one quarter of the frequency of the disease.

2. The gene c is not very rare in the population. It is excessively unlikely that haemophilia should arise from two different sources in one pedigree. Protanopia or deuteranopia might do so with a probability which is by no means negligible.

3. Our estimate of x by any of the classical inverse probability methods involves the presupposition that all values of x in the neighbourhood of that found are equally probable _a priori_. We shall see that this is not the case.

4. As no cross-overs have so far been observed, the estimated value of x is at present zero. But this is ~~certainly~~ almost certainly incorrect. The probable distribution of the true value must be ascertained.

The method which we have adopted is as follows. We estimate the frequency p of deuteranopia in the general population. We make out a pedigree showing the descent of the gene h in each pedigree. Taking this as given ~~twe~~ we determine for each pedigree:-

1. $P(x, p)$ The probability, as a function of x and p, that given that the first observed deuteranope was actually a deuteranope, all other ~~males in~~ relevant males in the pedigree possessed the type of vision which they actually did.

$\frac{t}{c} \times c$

Drs $\frac{c}{c}$ or $\frac{c}{t}$
Sons of $\frac{c}{t}$ drs. c or t

2. $P(\frac{1}{2}, p)$. The same probability for $x = \frac{1}{2}$, that is to say the probability of obtaining the observed result in the absence of linkage. In our case this is sufficient. Had a cross-over been observed we should have had to calculate the probability of obtaining the observed result or one still more favourable to the hypothesis of linkage.

3. $P(x, 0)$. The same probability for $p = 0$, that is to say neglecting the possibility that deuteranopia could have a double origin

4. $P(\frac{1}{2}, 0)$. The same probability for $x = \frac{1}{2}$, and $p = 0$

The last is the easiest to calculate, and the first the hardest. We shall see that all these values approximate closely to $(1-x)^n$; where n is a number, not in general integral, which may be roughly described as the number of ova tested for crossing-over with a negative result.

On multiplying our values of P for the four pedigrees we obtain a cumulative value. The cumulative value of $P(\frac{1}{2}, p)$ gives us the probability that the data which appear to prove linkage could really be due to sampling error. The cumulative value of $P(x, p)$ will enable us to estimate x. Thus by maximizing it we obtain the maximum likelihood estimate of x.

This estimate turns out to be zero. Our next task is to find a median value X such that x is as likely to be greater than X as less than it. We may, if we wish, call this the probable error of our value zero, provided it is understood that only positive deviations are admissible. Some such calculation would be necessary even had there been one or ~~more~~ two cross-overs, since the distribution of the probability of x round its mode would still be far from normal or even symmetrical.

~~Here~~ Now x must lie between 0 and 1 inclusive, and by analogy with other animals between 0 and $\frac{1}{2}$. If all ~~values of~~ positive values of x in the neighbourhood of zero are equally probable *a priori* then the calculation of the median is simple. If ~~it~~ the *a priori* probability is unevenly distributed we shall have to take this fact into account.

57
36
4)83
4)20·75
5·1875
3

4)93
4)23·25
5·8125
3
17·4375
3
52·3125

h	n
4	1
3	4
·7	2

f.8v

$\frac{35^4}{31}$ selfs.

$13^{35}/33$ Brown selfed. (ex yrCc x part) gave

YRC	10
YRc	5
Yr	7
yRC	7
yRc	0
yr	2
prim Rc	2
" rc	2

13^{32} self. 12 primrose r

$\frac{13^4}{33}$ " 30 part, 4 yRCP, 11 primrose

~~Between~~ as 13^4 x yrcP gave 52 RC, 30 YRc 34 yRc.

13^{23} x yrc . 12 Yr, 13 yr ∴ 13^{23} was Yy?

" x yRc . 45 RC ∴ 13^{23} was CCrr

$\frac{28^{45}}{33}$ (half-sister of 13/33) ~~gave Yr~~ YRc

gave

YRc	Yr	yR	yr	prim R	prim r
22	12	13	3	13	1

∴ primrose is recessive, say l. Yll is primrose. What is yll?

28/33 was yrc $\frac{2^{17}}{30}$ x ~~y~~ YyRrCbCc $\frac{35^4}{31}$. also Ll

so $28^{45}/33$ was $\frac{YRlc}{yrLc}$

Hence $P(x, p) = P(x, 0) = y^3(y + x^2 y) + x^3(x + xy^2)$

$= y^6 + 2xy^5 + 2x^2y^4 + 2x^4y^2 + 2x^5 y + x^6$

$= y^4 + x^2y^4 + x^4(1+y^2)$

and $n = 4$.

$P(\frac{1}{2}, p) = P(\frac{1}{2}, 0) = 5 . 2^{-5}$

Combination of the data.

The product of the four values of $P(\frac{1}{2}, 0)$ is $3^4.5.2^{-24}$, or 2.42×10^{-5}. The product of the four values of $P(\frac{1}{2}, p)$ is the same number multiplied by a factor less than $1+5p$ or 1.07. So the probability that the facts which we interpret as due to linkage could be due to sampling is about 2.6×10^{-5}, or 1 in 40,000. ~~As~~ We may therefore take the existence of linkage as certain. It remains to estimate its intensity.

The product of the leading terms of the expressions for $P(x,0)$ or $P(x,p)$ is $y^{\Sigma x}$ or $y^{20\frac{3}{4}}$. On the assumption that all ~~values of x~~ positive values of x in the neighbourhood of zero are equally probable a priori we have then to find X such that $\int_0^X P\,dx = \frac{1}{2}\int_0^1 P\,dx$.

If $P=(1-x)^n$, $X =$ ~~$1-2^{-n-1}$~~ $1-2^{\frac{-1}{n+1}}$

Since $n = 20\frac{3}{4}$, $X =$ ~~.0324~~, .0313

That is to say the value of x is as likely to exceed 3.24 per cent as to fall below it.

We next consider the correction to be made for the squares and higher powers of x. The product of the values of $P(x,0)$ is

$$y^{\frac{83}{4}} + x^2 y^{18}\left(\frac{7}{4} y^{\frac{7}{4}} + \frac{165}{128} + y^{\frac{11}{4}}\right) + \cdots$$

$$= y^{\frac{83}{4}} + \frac{517}{128} x^2 y^{18}$$

Substituting this value of P in the equation $\int_0^X P\,dx = \frac{1}{2}\int_0^1 P\,dx$ we have:-

$$\frac{4}{87}(1-X)^{\frac{87}{4}} + \frac{517}{128}\left[\frac{(1-X)^{19}}{19} - \frac{2(1-X)^{20}}{20} + \frac{(1-X)^{21}}{21}\right] = \frac{2}{87} + \frac{517}{256}\left(\frac{1}{19} - \frac{2}{20} + \frac{1}{21}\right)$$

so

$$(1-X)^{\frac{87}{4}} = \frac{1}{2} + \frac{517}{128.19.20.21}\left[1-(1-X)^{19}{}_2(1+19X+190X^2)\right]$$

Putting $X = \overset{.0313}{\cancel{.0324}}$, the right-hand side becomes $\frac{1}{2} - 4.784 \times 10^{-4}$

Hence $X = .0314$, and the correction is entirely negligible.

The correction to the leading term due to not neglecting α second sources of deuteranopia is equivalent to multiplying it by

$\frac{1}{4}$ for $\frac{3}{4}, \times\frac{1}{2}$ for $\frac{1}{4}, \frac{3}{4}$

$\frac{1}{2}$ or $\frac{5}{2}$

$9.2^{-13}\cdot(1-\frac{13}{4}p)+$

$\frac{1}{2}p.\,9.2^{-11}+\frac{1}{2}p\,.3\,2^{-12}+\frac{1}{4}p\,9.2^{-12}+p.9.2^{-13}+p.27.2^{-13}$

$=9.2^{-13}+p\left[-13.9.2^{-15}+9.2^{-12}+3.2^{-13}+9.2^{-14}+9.2^{-13}+27.2^{-13}\right]$

$=9.2^{-13}+p.2^{-15}\left[-117+72+12+18+36+108\right]$

$=9.2^{-13}+129.2^{-15}p$

$=9.2^{-13}\left(1+\frac{129p}{9.4}\right)$

$=9.2^{-13}\left(1+\frac{43p}{18}\right)$

72
30
36
108
246
117
129

$P=y^{+\frac{51}{4}}$.

$\frac{43\times.014}{18}=\frac{43\times.007}{9}$

9)301
.033

$\left(1-\frac{13}{4}p\right)P(x,0)+\frac{1}{2}py^{-2}P(x,0)+\frac{1}{4}py^{-12}+0+py^{\frac{43}{4}}+py^{\frac{51}{4}}$

$=\frac{1}{2}py^{\frac{43}{4}}$

$=\left(1-\frac{9p}{4}\right)y^{\frac{51}{4}}+\frac{3}{2}py^{\frac{43}{4}}+\frac{1}{4}py^{12}$

$=y^{\frac{51}{4}}-py^{\frac{51}{4}}\left[-\frac{9}{4}+\frac{3}{2}y^{-2}+\frac{1}{4}y^{-\frac{3}{4}}\right)$ $(1-x)^{-2}=1+2x+\cdot$

$=y^{\frac{51}{4}}-\frac{1}{4}py^{\frac{51}{4}}\left[-9+6y^{-2}+y^{-\frac{3}{4}}\right)$

$\text{"}\ -\frac{1}{4}py^{\frac{51}{4}}\left[-9+6+12x+1+\frac{3}{4}x\right)$

$=\text{"}\ -\frac{1}{4}py^{\frac{51}{4}}\left[-2+12\tfrac{3}{4}x\right]$

$=\left(1-\frac{1}{2}p\right)y^{\frac{51}{4}}+\frac{51}{16}pxy^{\frac{51}{4}}$

$y^{\frac{51}{4}}\left(1+\frac{51px}{16}\right)$

$=y^{\frac{51}{4}}(1-x)^{-\frac{51p}{16}}$

$\frac{51\times.014}{16}=\frac{102\times.007}{16}$

$=\frac{.714}{16}$

4).714
4).1785
.044625

$$P(x,0) = \tfrac{1}{4}y^{10}(y^2+x^2)(4y^2+5xy+3x^2) + \tfrac{1}{4}y^3x^7 \Big| (3y^2+7xy+2x^2)$$

$$= \tfrac{1}{4}y^3(4y^{11}+5\cancel{y}xy^{10}+7x^2y^9+5x^3y^8+3x^4y^7+13x^8y^3+19x^9y^2+11x^{10}y+2x^{11})$$

$$= 1 - \frac{51}{4}x + \frac{153}{2}x^2 - \frac{1161}{4}x^3 + \cdots$$

$$= y^{\frac{51}{4}} + \frac{165}{128}x^2y^{11} + \frac{39}{128}x^2y^{12} + \cdots$$

$$= y^{\frac{51}{4}}\left(1 + \frac{23x^2}{16y^2} - \frac{45x^2}{64y^2} + \cdots\right)$$

$$P(\tfrac{1}{2},0) = 3^2 \cdot 2^{-13}.$$

It is to be noted that $y^{12\frac{3}{4}}$ is a far better approximation than $1-12\frac{3}{4}x$. Since $n = 12\frac{3}{4}$ we may say that the genes c and ~~b~~ h have had $12\frac{3}{4}$ opportunities of separating, and have taken none. The steps in the pedigree contributing unity to n are:- Mη, $\overset{D\beta}{\eta N}$, βE, βF, βG, βα, αγ, γH, γI, γζ, and ζL. The step βK contributes $\frac{3}{4}$. We can at once apply this simple method to any given case with fair accuracy. The residual terms represent relationships involving two or more cross-overs. They are negligible if x is small, but important in the calculation of $P(\frac{1}{2},0)$. For this reason in a large pedigree it is simplest to calculate $P(\frac{1}{2},0)$ ~~separately~~ and n separately.

The calculation of $P(\frac{1}{2},p)$ and $P(x,p)$ is somewhat more complicated. There are five possible hypotheses which would give two sources of deuteranopia.

(1) δ contributed a c+ gamete to η. Since J ~~was~~ is not a deuteranope, δ cannot have been $\frac{c+}{c+}$, and had she been $\frac{++}{c+}$, the probability of J being a deuteranope would have been $\frac{1}{2}$. Hence the probability that δ contributed a c+ gamete is reduced from its a priori value of p to $\frac{1}{2}p$.

(2). B was c+. This again has an a priori probability p. But, if so, the probability that his $\frac{+}{c}$ wife should have born a ~~[illegible]~~ non-deuteranopic daughter who bore a non-deuteranopic son is $\frac{1}{4}$. Hence the probability that B was c+ is $\frac{1}{4}p$. This treatment is sufficient for the calculation

~~(3). A was c+, and ~~β~~ α was $\frac{+}{c}$. As α bore two daughters each of whom had a non-deuteranopic son the probability is $\frac{1}{4}p$.~~

f.12 23a

~~The~~ On this hypothesis as to a *priori* probability value the ~~set~~ mean estimate of x, namely $\dfrac{\int_0^1 x P(x) dx}{\int_0^1 P(x) dx} = \dfrac{1}{n+2}$ for $P(x) = (1-x)^n$. For $n = 20 \cdot 75$, this estimate is $\cdot 044$, and it is clear that it will be somewhat larger, approximating to $\dfrac{X}{\log_e 2}$, for any value of n. The mean is, of course, the probability that the next male observed in a pedigree of the type considered will be a cross-over.

$$\sigma^2 = \frac{k(n-k)}{n^3} \sim \frac{k}{n^2}$$

$\hat{x}$ Mode $= \frac{k}{n}$

$\bar{x}$ Mean. $$\frac{\int_0^1 x^{k+1} y^{n-k}\,dx}{\int_0^1 x^k y^{n-k}\,dx} = \frac{(k+1)!\,(n-k)!}{(n+2)!} \div \frac{k!\,(n-k)!}{(n+1)!}$$

$$\therefore \quad \sim \frac{k+1}{n+2}$$

$$\text{Diff} = \frac{k+1}{n+2} - \frac{k}{n} = \frac{kn+n-kn-2k}{n(n+2)} = \frac{n-2k}{n(n+2)}$$

$$\bar{x} - \hat{x} = \frac{n-2k}{n(n+2)}$$

$$\frac{\bar{x}-\hat{x}}{\hat{x}} = \frac{n-2k}{n(n+2)} \div \frac{k}{n} = \frac{n-2k}{k(n+2)} \sim \frac{1}{k}$$

within a few years. Mapping would not be possible until another common sex-linked, or incompletely sex-linked gene substitution has been discovered. The search for new sero-logical properties may be expected to reveal such a gene within a few years. Should Haldane's (1936) claim to have discovered a group of incompletely sex-linked genes be confirmed, it is also desirable that male cases of xeroderma pigmentosum and recessive epidermolysis bullosa dystrophica, ~~should be made~~ and brothers of patients, should be investigated in the same manner.

The theoretical method used in this paper has been unduly cumbrous. But it has been adopted for ~~two~~ three reasons. In the first place it was necessary to prove that certain corrections can be neglected. ~~While~~ ~~And secondly~~ Secondly the correction ~~will be needed~~ for a second source of colourblindness will be necessary the moment a colourblind man of an unexpected class, who might be a cross-over, is discovered. Thirdly the later terms in the expansion of $P(x, 0)$ will be important if in ~~another~~ the case of another sex-linked gene, x turns out to be larger. Thus if there were 20% of crossing over between the genes for colour-blindness and anidrosis, the ~~two~~ coefficient of x^2 could not be neglected.

The following simplified method may however be used for the further investigation of the linkage between colourblind-ness and haemophilia.

1. The pedigrees of haemophilia and colour-blindness are determined. In each case crossing over is assumed not to have occurred unless there is evidence that it has occurred. A single source only of each abnormality is assumed.

2. A number n, of gametes tested, is determined by the following conventions. For each relationship between a doubly heterozygous mother and a child ~~of~~ whose genotype ~~which~~ is known or deduced, n is increased by unity. ~~In "coupling"~~ pedigrees A daughter of a double heterozygote who has born s non-haemophilic sons of normal vision and no abnormals increases n by $2^{-s-1}(2^s+1)$. Similar formulae can be given for

of $P(\frac{1}{2}, p)$. However if we are ~~considering~~ calculating $P(x, p)$ matters are more complicated. It is better for the moment to neglect our knowledge concerning K, and to consider ϵ only and put the probability as $\frac{1}{2}p$.

(3) A was c+ and α was $\frac{+}{c}$. As α bore two daughters each of whom had a non-deuteranopic son the probability is $\frac{1}{4}p$.

(4) A was ++, and α was $\frac{c+}{ct}$. The probability is p.

(5) C was +c. The probability is again p.

Further two or more of these hypotheses may be true at ~~the~~ once. We shall neglect this contingency, which has a probability of about $3p^2$. This is equivalent to neglecting squares and higher powers of p in the expansion of P.

To calculate $P(\frac{1}{2}, p)$ we multiply $P(\frac{1}{2}, 0)$ by $1-3p$, and add terms corresponding to each of the five hypotheses. ~~The terms are:~~

~~(1) implies that γ was $\frac{c+}{ct}$, so that M and N were necessarily deuteranopes, whereas in the calculation of $P(\frac{1}{2}, 0)$~~

We shall not carry out the rather tedious calculation, which ?de increases $P(\frac{1}{2}, 0)$ by an amount of the order of $3p$, or 5%. The calculation ~~for~~ of $P(x, p)$ is somewhat easier, since we can neglect everything but the leading ~~term, i.e. two~~ terms, i.e. neglect px as we have neglected p^2. In other words we shall neglect the possibility that crossing over and a second source of deuteranopia have both occurred in our pedigree. On this simplifying assumption:—

(1) implies that α was $\frac{c+}{ct}$, whence A and B were necessarily deuteranopes. The contribution is $\frac{1}{2}p\,y^{-2}P(x, 0)$ or $\frac{1}{2}p$, so $P(x, p)$ is unaffected.

(2) implies that ϵ was $\frac{++}{c+}$. The contribution to $P(x, p)$ is thus $\frac{1}{4}p$.

(3) implies that no less than γ cross-overs ~~had occ~~ have occurred. The contribution to $P(x, p)$ is negligible.

(4) implies that B and γ were both $\frac{++}{ct}$, so $P(x, p)$ is unaffected.

(5). increases the probability that K was a deuteranope to x^2+y^2; so again $P(x, p)$ is unaffected.

In fact only (2) is relevant, and this makes

$$P(x, p) = (1-\tfrac{1}{2}p)\,P(x, 0) + \tfrac{1}{4}p \text{, approximately.}$$

Estimation of the frequency of crossing over

We shall first consider the estimation of x on the hypothesis that all small positive values have an equal *a priori* probability.

The product of the leading terms in the product of the six values of $P(x, p)$ is

$$x(1-x)^{27.45}$$

If this is plotted we get a very skew frequency curve giving the probability that x lies between any given limits. The modal or maximum likelihood value is $x = \frac{1}{28.45} = 0.035$. This result is however rather misleading. The mean value is

$$\frac{\int_0^1 Px\,dx}{\int_0^1 P\,dx} = \cancel{.065}\ \cancel{.067}\ .065$$

This is the estimate of the probability that the next individual observed will be the result of crossing over (if only a single cross over is possible). The median X is given by

$$\int_0^X P\,dx = \tfrac{1}{2}\int_0^1 P\,dx$$

and is equal to $\cdot 057$. That is to say the ~~cross over~~ frequency of recombination based on a large sample is as likely to exceed 5.7 % as to fall below it. The quartile values are $\cdot 032$ and $\cdot 088$, so this estimate is very uncertain.

We have next to determine the corrections due to omission of the terms involving x^3 on the one hand and p on the other. T~~he val~~ ~~R~~ The product of the $P(x, 0)$ values is

$$xy^{27.45} + \frac{83}{16}x^3y^{25.45} + \cdots$$

The second term ~~produces~~ increases the mean by ~~1.038%~~ 3.8%, and has similar effects on the other estimates. These are clearly quite negligible. But they would not be so if a very large body of data were available. The effect of the terms involving x^4 and higher powers is still smaller.

The effect of not equating p to zero is still more negligible

For the product of the various expressions for $P(x,p)$ will be of the form
$$xy^{24.75}f_1(p) + \frac{83}{16}x^3y^{25.75}f_2(p) + \dots$$

where $f_1(p), f_2(p)$ etc differ from unity by small multiples of p. But since the estimates of x are unaltered when $P(x,0)$ is multiplied by a constant, the whole effect of the correction for secondary sources will be to alter the correction for the second term, which is itself negligible. It follows that in future work this correction may be neglected, except when a supposed case of crossing over can be accounted for by a double source of colourblindness.

complicated. There are five possible hypotheses which would give two sources of deuteranopia

1. δ contributed a c+ gamete to η
2. B was c+
3. A was c+ and α was $\frac{+}{c}$.
4. A was ++ and α was ~~++~~ $\frac{c+}{c+}$.
5. C was +c.

Each of these contingencies has an a priori probability p. Further two or more of these contingencies may be simultaneously true except (3) and (4). This however will give rise to terms involving p^2 and higher powers, which will be neglected.

To calculate $P(\frac{1}{2}, p)$ we multiply $P(\frac{1}{2}, 0)$ by $(1-5p)$ and add terms corresponding to the various contingencies.

1. δ ~~was~~ is not colourblind, which multiplies the contribution by $\frac{1}{2}$. On the other hand η ~~was~~ is $\frac{c}{c}$, so M and N must have been colourblind. Hence the contribution is $\frac{1}{2} . 4 . P(\frac{1}{2}, 0)p$ or $9.2^{-12}p$

2. The probability that a colour blind man B married to a heterozygous wife β should have a normal daughter whose only son is normal is $\frac{1}{4}$, as opposed to $\frac{3}{4}$ if B was normal. The contribution is therefore $3.2^{-13}p$.

3. As β and γ both bore non-deuteranopic sons neither was $\frac{c}{c}$. Hence the contribution is $\frac{1}{4}P(\frac{1}{2}, 0)p$ or $9.2^{-15}p$.

4. The contribution is $2P(\frac{1}{2}, 0)p$ or $9.2^{-12}p$.

5. The probability, given γ and C, that L ~~was~~ is a deuteranope, is raised from $\frac{1}{4}$ to $\frac{3}{4}$. So the contribution is $3P(\frac{1}{2}, 0)p$ or $27.2^{-13}p$

$$\text{Hence } P(\tfrac{1}{2}, p) = \cancel{2}9.2^{-13}(1-5p) + \overset{243}{\cancel{237}}.2^{-15}p$$
$$= 9.2^{-13} + \overset{93}{\cancel{91}}.2^{-15}p$$

$P(\frac{1}{2}, p)$ is thus increased by a factor $\left(1+\frac{\overset{31}{\cancel{14}}p}{12}\right)$ or ~~1.0255~~ 1.036

In calculating $P(x, p)$ we need only consider the changes in the first three terms, namely $y^{14} + \frac{5}{4}xy^{13} + \frac{7}{4}x^2y^{12}$, in the homogeneous expansion. As before, each contingency contributes a term to be added to $(1-5p)P(x, 0)$.

1. η ~~was~~ is $\frac{c}{c}$, so M and N must be colourblind. The contribution is $y^{-2}P(x, 0)p$

1 − 15 + 85 − 225 + 274 − 120
−6 + 60 − 210 + 300 − 144
+15 − 90 + 165 − 90
−20 + 60 − 40
+15 − 15
−5

0 + 0 10 −15 + 130 − 120
5(−3 + 26 − 24)

165 3 −
85
250

$5(15p^4s(\cancel{4}s_{4-1} - 4s_3 + 6ss_2 - 4s\overset{2}{s}_1 + s^3)$
1 − 10 + 35 − 50 + 24
−4 + 24 − 44 + 24
+6 − 18 + 12
−4 + 4
+1

0 + 0 + 3 − 26 + 24

44
$13\{s_{3-1} - 30s_2 + 21ss_1 - 4s^2$
13 − 78 + 143 − 78
−30 + 90 − 60
+21 − 21
−4

0 − 9 + 83 − 78

$6s_2 - 6s_1 + s^2$

6 − 18 + 12
−6 + 6
+1

1 − 12 + 12

31s − 31
−6s

25s − 31

88 36
26 78
114 114

$-15p^5 + 45p^4 - \overset{45}{\cancel{135}}p^3 + 15p^2 = 15p^2(1 - 3p + 3p^2 - p^3)$
~~25p − 180~~ $5s(5p - 36p^2 + 83p^3 - 78p^4 + 26p^5)$
$5sp(5 - 36p + 83p^2 - 78p^3 + 26p^4)$
1 − 1)(5 − 36 + 83 − 78 + 26(5 − 31 + 52 − 26
1 − 1)5 − 31 + 52 − 26(5 − 26 + 26

5 − 5
−31 + 83
−31 + 31

52 − 78
52 − 52

−26 + 26

5 · 5

+26 + 52
−26 + 26

26 − 26

$= 5spq(5 - 31p + 52p^2 - 26p^3)$
~~(1 = 5 − 5p + 26 = 26~~ $(1-p)^2$

181
360
541

$= 5spq^2[5 - 26p + 26p^2) = 5spq^2(5 - 26pq)$

$1-1)\ 1 - 31p + 180p^2 - 390p^3 + 360p^4 - 120p^5$ (1 − 30 + 150 − 240 − 120

1 − 1

−30 + 180
−30 + 30

150 − 390
150 − 150

−240 + 360
−240 + 240

120 − 1

$= q[1 - 30p(1 - 5p + 8p^2 - 4p^3)$
(1 − 1)(1 − 5 + 8 − 4(1 − 4 + 4

1 − 1

−4 + 8
−4 + 4

4 − 4

$q[1 - 30pq[1 - 4pq)] = q(1 - 30pq + 120p^2q^2)$

1 4 6 4 1
1 5 10 10
1, 6, 15, 20

$E(\alpha^6 - 6ps\alpha^5 + 15p^2s^2\alpha^4 - 20p^3s^3\alpha^3 + 15p^4s^4\alpha^2 - \cancel{p^5s^6}\,6p^5s^5\alpha + p^6s^6)$

$= p^6 s_5 + 15p^5 s_4 + 65p^4 s_3 + 90p^3 s_2 + 31p^2 s_1 + ps$

$-6p^6 s s_4 - 60p^5 s s_3 - 150p^4 s s_2 - 90p^3 s s_1 - 6p^2 s^2$

$+15p^6 s^2 s_3 + 90p^5 s^2 s_2 + 105p^4 s^2 s_1 + 15p^3 s^3$

$-20p^6 s^3 s_2\ \overset{-60}{\cancel{}}p^5 s^3 s_1,\ -20p^4 s^4$

$+15p^6 s^4 s_1 + 15p^5 s^5$

$-5p^6 s^6$

~~$= 5p^6(-3s^2$~~

$= ps\Big[5p^5(-3s^2+26s-24) + 15p^4(3s^2-26s+24) + 5p^3(-9s^2+83s-48)$
$\quad + 15p^2(s^2-12s+12) + p^3(25s-31) + 1\Big]$

$= ps\Big[15s^2p^2(1-p)^3 + 5spq^2(5-26pq) + q(1-30pq+120p^2q^2)\Big]$

$= spq\Big[15s^2p^2q^2 + 5spq(5-26pq) + 1-30pq+120p^2q^2\Big]$

$$E(x^6) = \frac{15s^2p^2q^2 + 25spq - 130sp^2q^2 + 1 - 30pq + 120p^2q^2}{s^2p^2q^2}$$

$$= 15 + 25\frac{k}{s} - \frac{130}{s} + \frac{k^2 - \cancel{1}30k + 120}{s^2}$$

$5\xi k$

$\xi = (x^2-1)$

$E(x^6 - 3x^4 + 3x^2 - 1)$

$= \xi\Big\{\ 15 + \dfrac{25k-130}{s} + \dfrac{k^2-30k+120}{s^2}$

$-9\ \dfrac{\cancel{3}(2k-2)}{s}$

$+3$

-1

H

$8 + \dfrac{22k-124}{s} + \dfrac{k^2-30k+120}{s^2}$

$$E\left(\alpha^4 - 4ps\,\alpha^3 + 6p^2s^2\alpha^2 - 4p^3s^3\alpha + p^4s^4\right)$$

$$= p^4 s(s-1)(s-2)(s-3) + 6p^3 s(s-1)(s-2) + 4p^2 s(s-1) + ps$$

$$-4p^4s^2(s-1)(s-2) \qquad -12p^3s^2(s-1) \qquad -4p^2s^2$$

$$+6p^4s^3(s-1) \qquad +6p^3s^3$$

$$-3p^4s^4$$

$$= ps\left[3p^3(s-2) - 6p^2 3(s-2) + p^2(3s-7) + 1\right]$$

$$= ps\left[3s(p^3 - 2p^2 + p) - 6p^3 + 12p^2 - 7p + 1\right]$$

$$= ps\left[3spq^2 + q(1 - 6pq)\right]$$

$$= pqs\left[3spq - 6pq + 1\right] \qquad = pqs\left[3(s-2)pq + 1\right]$$

$$E(x^4) = \frac{3(s-2)pq+1}{pqs} = \frac{3(s-2)}{s} + \frac{k}{s}$$

$$= 3m^2 + \frac{k-2}{s}$$

25k - 130
-3k + 18
22k - 112

$$\mu_3 = S_3 - 3S_1S_2 + 2S_1^3$$

$$= 15 + 5(5k-6)s^{-1} + (k^2 - 30k + 120)s^{-2}$$

$$-9 - 3(k-6)s_1$$

$$+2$$

$$8$$

496 - 2416
100 - 520
396 - 1896
12)33 - 158)

130
123
65

$$\mu_4 = S_4 - 4S_1S_3 + 6S_1^2S_2 - 3S_1^2$$

$$= 105 + (490k - 2380)s^{-1} + (119k^2 - 2156k + 7308)s^{-2} + (k^3 \ldots)s^{-3}$$

$$-60 - (100k - 520)s^{1} - (4k^2 - 120k + 480)s^{-2}$$

$$+18 + (6k - 36)s^{-1}$$

$$-3$$

$$60 + 12(33k - 158) \qquad + (115k^2 - 2036k + 6828)$$

$P = x(1-x)^{24\cdot75}$ f = Minns' quartic

x	log P	f	Pf	S	
·005	$\bar{3}$·6385615	156·28	0·67989		
·015	$\bar{3}$·9938458	128·74	1·26928	194917	1-2
·025	$\bar{2}$·0928176	108·36	1·34180	329097	2-3
·035	$\bar{2}$·1147006	93·80	1·22153	451250	3-4
·045	$\bar{2}$·0983068	83·89	1·05203	556453	4-5
·055	$\bar{2}$·0585961	77·59	0·88799	645252	5-6
·065	$\bar{2}$·0129353	74·00	0·76237	7·21489	6-7
·075	$\bar{3}$·9304935	72·38	0·61420	782909	7-8
·085	$\bar{3}$·8588452	72·08	0·52426	8·35335	
·095	$\bar{3}$·7747222	72·56	0·43906		
·105	$\bar{3}$·6842755	73·42	0·35489		
·115	$\bar{3}$·5873444	7431	0·28734		
.125	$\bar{3}$·4876348	75·00	0·24138		
·135	$\bar{3}$·3825306	75·32	0·18174		
·145	$\bar{3}$·2734273	76·17	0·14108		
·155	$\bar{3}$·1600051	74·52	9·99684		
·165	$\bar{3}$·0442843	73·38			

$75\int_{\cdot15}^{1} P\,dx$

0·51240
10·51024

10·51240)·51240(·0497
4050
10190 = 5·0%
9461
729

Median 4·7
Quartile 1. 2·5
〃 2. 8·1
Mode about 2·5

$f = xy^n + ax^3y^{n-2}$. $f' = y^n \mp nxy^{n-1} + 3ax^2y^{n-2} \overset{-(n-3)}{\pm_1} ax^3y^{n-3} = 0$

$x = \frac{1}{n+1})$ $\therefore y^3 + xy^2 + 3ax^2y + ax^3 = 0$

if $t = \frac{x}{y}$ $\therefore$ $t^3 + 3t^2 + \frac{t}{a} + \frac{1}{a} = 0$

$\therefore y^3 \mp nxy^2 + 3ax^2y + ~~ax^3~~ = 0$ $\pm(n-3)ax^3$

~~$at^3 + 3at + n$~~

$(n-3)at^3 \mp 3at^2 + nt \mp 1 = 0$

$nt - 1 = a[3t^2 - (n-3)t^3]$

$t = \frac{1}{n}\left[1 + at^2\left[3 - (n-3)t\right]\right]$

$t_1 = \frac{1}{n}$

$t_2 = \frac{1}{n}\left[1 + \frac{a}{n^2}\left[3 - \frac{n-3}{n}\right]\right]$

$= \frac{1}{n} + \frac{a}{n^3}\left(2 + \frac{3}{n}\right)$

$= \frac{1}{n} + \frac{(2n+3)a}{n^4}$

$n = 27.75 = \frac{111}{4}$, $a = \frac{219}{32}$

$t_2 - t_1 = \frac{\left(\frac{111}{2}+3\right)\left(\frac{219}{32}\right)}{\frac{111^4}{256}} = ~~4(~~ \frac{4.117.219}{111^4}$

.6020600
2.0681859
2.3404441
5.0106900
8.1812920
$\bar{4}$.8293980

2.0453230
4
8.181292

$= 6.7515 \times 10^{-4}$
$= .07\%$

$p^2 + q^2 = 1 - 2x$, $p^4 + q^4 = (1-2x)^2 - 2x^2 = 1 - 4x + 2x^2$

$32 - 128x + 64x^2$
$+ 8x - 16x^2$
$+ x^2$
$32 - 120 \quad + 49$

$2 - 8 + 4$
$+ 2 - 8$
$+ 1$
$2 - 6 \quad p + p$

$x = \frac{2}{3}\cdot\frac{1}{3} = \frac{2}{9}$, $P = 2^{-6}\left(32 - 120\cdot\frac{2}{9} + \frac{49\cdot4}{9^2}\right)\left(2 - \frac{6\cdot2}{9} + \frac{4}{9^2}\right]$

$= 2^{-3}\left(8 - \frac{60}{9} + \frac{49}{9^2}\right)\left(1 - \frac{6}{9} + \frac{2}{9^2}\right)$

$= 2^{-3}3^{-4}\left(8\cdot81 - 60\cdot9 + 49\right)\left(81 - 54 + 2\right)$

$$\begin{array}{r} 648 \\ \underline{49} \\ 697 \\ \underline{540} \\ 154 \end{array} \qquad \begin{array}{r} 83 \\ \underline{54} \\ 29 \end{array}$$

$= 2^{-3}\cdot3^{-4}\cdot154\cdot29 = \frac{154\cdot29}{8\cdot81^2}$

$$\begin{array}{r} 154 \\ \underline{29} \\ 314 \\ 1413 \end{array}$$

$648\overline{)4553}\left(\frac{7}{0.}\right.$

$\underline{4536}$

$$\begin{array}{r} 6561 \\ 8 \\ \hline 52488 \end{array}$$

$52488)\ 4553.00(.08678$

$$\begin{array}{r} 4553.00 \\ \underline{4199.04} \\ 355.96 \\ \underline{314.93} \\ 41\ 03 \\ \underline{3674} \\ 429 \end{array}$$

f.20v.

$$P = (1-x)^{23.75} = (1-x)^{\frac{190}{8}}$$

x	log p	Pf	S
·005	$\bar{1}$·9~~37727~~9 48303	138·74	
·015	$\bar{1}$·844110	89·91	228·65
·025	$\bar{1}$·768859	63·64	
·035	$\bar{1}$·632523	40·25	
·045	$\bar{1}$·525081	28·10	
·055	$\bar{1}$·416630	20·25	
∴ S		64·50	

0-1

1-2

2)445·39

222·69

1	28
322	7960
6769	13132
13068	5040
20,160	20160

176
1624
420
2520

$995^{\frac{190}{8}}$ −·002|6136
200
·522|72
26|136
8)·496|584
·062073

·0065638
200
1·312756
65638
8)1·247122
·155890

·0021767
200
·435340
21767
8)·413573
·051697
·948303

·0109954
200
2·19908
109954
8)2·089126
·231141
·768859

·9845273
·0154727
200
3·09454
154727
8)2·939813
·367477
·632523

·9800034
·0199966
2
3·99932
199966
8)3·799354
·474919
·525081

·9754318
·0245682
2·
4·91364
245682
8)4·667958
·583370
·416630

2·193903
$\bar{1}$·948303
2·142206

2·109714
$\bar{1}$·844110
1·953824

2·034869
$\bar{1}$·768859
1·803728

1·942249
$\bar{1}$·632523
1·604772
24·75

1·923710
$\bar{1}$·525081
1·448792

1·889806
$\bar{1}$·416630
1·306436

$$\int_0^{.94} y^x dy = \frac{y^{x+1}}{x+1} = \frac{.94^{\frac{198}{8}}}{\frac{198}{8}} = \frac{4.x.94^{\frac{99}{4}}}{99} \times 94$$

$\bar{1}$·9731279
−·0268721

2·6872100
·0268721
4)2·6603479
− ·6650870
1·9956352
2·6617272

2 +
·6020600
1·8692317
$\bar{4}$·4712917
2·6617272
~~$\bar{1}$·330189~~
1·8095645
6450

114) 6·0 (·054

1·9

f. 215

A. $\left(1+\frac{13}{4}\frac{x^2}{y^2}\right)$

B. $\left(1+\frac{51}{32}\frac{x^2}{y^2}\right)$

Ri 1

Bi $\left(1+\frac{x^2}{y^2}\right)$

Mu 1

Gr $\left(1+\frac{x^2}{y^2}\right)$

23·75
00·0918

$$\frac{13}{4}+\frac{51}{32}+2 = \frac{104+51+64}{32}$$

$$=\frac{219}{32}=\textcircled{a}$$

$$\begin{array}{r} 104 \\ 51 \\ 64 \\ \hline 219 \end{array}$$

$$\int x^p y^q dx = \frac{p!\,q!}{(p+q+1)!}$$

$$P = xy^n + ax^3y^{n-2} \qquad \boxed{n} = 27.75 = \frac{111}{4}$$

$$\frac{116}{123}$$

$$\bar{x} = \frac{\int_0^1 Px\,dx}{\int_0^1 P\,dx} = \frac{\int_0^1 (x^2y^n + ax^4y^{n-2})\,dx}{\int_0^1 (xy^n + ax^3y^{n-2})\,dx}$$

4.3.2

$$n = 27.75 = \frac{111}{4}$$

$$= \frac{\frac{2!\,n!}{(n+3)!} + \frac{a.4!(n-2)!}{(n+3)!}}{\frac{1!\,n!}{(n+2)!} + a\frac{3!(n-2)!}{(n+2)!}} = \frac{2n! + 24a(n-2)!}{(n+3)[n! + 6a(n-2)!]}$$

$$\begin{array}{l} 123)8.00(.06504 \\ \quad 738 \\ \quad \overline{\ \ 620} \\ \quad \ \ 615 \\ \quad \overline{\ \ \ \ 500} \\ \quad \ \ \ \ 492 \end{array}$$

$$= \frac{2n(n-1)+24a}{(n+3)[n(n-1)+6a]} = \frac{2}{n+3}\cdot\frac{1+\frac{12a}{n(n-1)}}{1+\frac{6a}{n(n-1)}}$$

$$= \frac{2}{n+3}\cdot\left[1+\frac{\frac{6a}{n(n-1)}}{1+\frac{6a}{n(n-1)}}\right]$$

$$\begin{array}{r} 107 \\ 107 \\ 104 \\ \hline 11847 \\ 657 \\ \hline 12534 \end{array}$$

$$\begin{array}{l} 12534)657.00(.0524 \\ \quad\ \ 626.70 \\ \quad\ \ \overline{\ \ 3030} \\ \quad\ \ \ \ 2507 \\ \quad\ \ \overline{\ \ \ \ 523} \end{array}$$

$$= \frac{2}{n+3}\cdot\left[1+\frac{6a}{6a+n(n-1)}\right]$$

$$= \frac{2}{\frac{123}{4}}\left[1+\frac{\frac{3.219}{16}}{\frac{3.219}{16}+\frac{111}{4}\cdot\frac{107}{4}}\right] = \frac{8}{123}\left(1+\frac{657}{657+11847}\right)$$

$$= .6504 \times 1.0524$$

$$\begin{array}{r} .6504 \\ 1.0524 \\ \hline .6504 \\ 325 \\ 13 \\ 5 \\ \hline .6847 \end{array}$$

The effect of not equating p to zero is still more negligible. On the one hand the ratio of the first two terms in the expansion is affected. ~~On the other~~ This is however a correction of the order of p to the addition of 3.8% mentioned in the last paragraph. On the other hand the exponent of y in the 1-x in the leading term is reduced from 24.75 to 24.7054. ~~This reduces the mean x from ·06504 to ·0650 ·065~~ This increases the mean from ·06504 to ·06513, and has smaller effect on the other estimates.

If all the doubtful women were mosaics, and all their non-haemophilic sons derived from their unmutated sectors, we should have n = 23.75, k = 0. The modal value would be zero, the mean 3.88%, the median 2.76%, with quartiles at 1.16% and 5.45%. It must however be remembered that even if these three women were mosaics the chance is remote that all their non-haemophilic sons arose from unmutated tissue.

For each value of p there is a probability P of getting a wholly homozygous sample, and a probability F of getting this sample.

? try $$\frac{\int_0^1 PF\,dp}{\int_0^1 F\,dp} = w$$

$$P = 2^{-6}(32-120x+49x^2)(2-6x+x^2), \text{ where } x = p(1-p)$$

$$F = p^2q^2(p+\tfrac{1}{8}q)^2(\tfrac{1}{2}p+q)^2 = 2^{-8}\{p^2q^2(8p+q)^2(2p+q)^2$$

$$2W = \frac{\int_0^1 P(F+F')\,dp}{\int_0^1 F\delta dp} \quad \text{where } F'_1 = 2^{-8}p^2q^2(p+8q)^2(p+2q)^2$$

$$F+F' = 2^{-8}x^2\left[(7p+1)^2(p+1)^2+(7q+1)^2(q+1)^2\right]$$

$$= 2^{-7}(128x^2-344x^3+49x^4)$$

$$dx = (1-2p)dp$$

$$\therefore W = \frac{\int_0^{\frac{1}{4}} 2^{-6}(32-10x+49x^2)(2-6x+x^2).2^{-7}x^2(128-344x+49x^2)\frac{dx}{\sqrt{1-4x}}}{\int_0^{\frac{1}{4}} 2^{-7}x^2(128-344x+49x^2)\frac{dx}{\sqrt{1-4x}}}$$

$$x = 2y$$

$$W = \frac{\int_0^{\frac{1}{8}} y^2(8-5y+49y^2)(1-6y+2y^2)(32-172y+49y^2)\frac{dy}{\sqrt{1-8y}}}{8\int_0^{\frac{1}{8}} y^2(32-172y+49y^2)\frac{dy}{\sqrt{1-8y}}}$$

Let $4x = \sin^2\theta$

$$\therefore W = \int_0^{\frac{\pi}{2}} \sin^4\theta\left(\frac{8-5\sin^2\theta}{4}+4\right.$$