SIGNIFICANT LONE DAUGHTERS AND MUTATIONS IN SEX LINKAGE RISK ESTIMATIONS — A COMPREHENSIVE COMPUTER PROGRAMME

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SYNOPSIS

The insignificant females without sons in sex linkage who are now significant through linkage tests and direct clinical tests, demand a revision in the risk calculations, which must also include the possibility of de novo mutations for the detected heterozygote and for the affected male or son, the omission of which could lead to huge errors of judgement in pedigree analysis. A BASIC microcomputer programme which allows such input in even the most complex pedigree is presented to demonstrate how the problems could be resolved with our approach and to support the arguments embodied in the programme with worked examples.

INTRODUCTION

The traditional teaching that daughters of X-linked carriers without sons have no genetic significance in risk estimations is no longer valid. It was argued that there were not too many inherited diseases amenable to corroborative biochemical tests pertaining to the genetic status of apparently normal individuals of suspect heritage. With the standardization of human chromosome bandings (1-2) which permit gene mapping in specific chromosomes and particular segments of those chromosomes, come maps of highly polymorphic markers (either defined genes or arbitrary DNA sequences known as restricted fragment length polymorphisms, RFLPs) at regular intervals in chromosomes (3) whose peculiar characteristics in a person could be traced in the descendants of a family. This means that we now have an indirect method of finding whether the apparently normal looking daughter could have inherited the defective disease gene from her mother simply by testing for the presence of sufficiently close polymorphic markers in them. When the marker and the disease gene are closely linked then they would be together as one within a family, with the odds against them being transmitted as one given by the crossing-over frequencies. In this way the whole range of single gene inherited diseases where direct clinical investigations have yet to be useful, can be ascertained in suspected carriers or descendants of suspected carriers. The hitherto uninformative lone daughter is no longer uninformative. Family history and pedigree analysis must now include her.

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Furthermore the assumption that an affected son meant a heterozygous carrier mother in x-linkage, requires qualification. This premise is true only if the mutation rate is zero in absolute terms. The son could be affected even if he had inherited a normal x chromosome from his mother because genes could change or mutate in any generation and in any person. The chances of that happening is the rate of change of the gene or the mutation rate. Thus the mother is not an imperative carrier if she has one affected son. The accepted practice is to define the mother cautiously as a "presumptive carrier" if she has at least two affected sons because the multiplication of two or more mutational probabilities would make it much less likely for all the affected to be chance de novo mutations. Even so the probability never reduces to absolute zero, hence the qualification term "presumptive" is applied. The assumption of zero mutation rate and the assumption of an imperative carrier status in "presumptive carriers" are not valid in pedigree studies. The reason is, as we shall see in this paper, that risk values become dramatically inflated by such assumptions when the affected is not an immediate relative. Within a nuclear family without any other significant information, and few members only or just the direct relationship between the mother and her affected son, then such assumptions would make little practical difference, because the risk of the mother as a heterozygote would certainly be high given those considerations. Under those circumstances she has few redeeming factors in favour of not being a heterozygote. The zero mutation rate means zero probability of being affected as a genotypic normal by inheritance or stated simply, means zero probability of being normal in genotype under the circumstances. Now when that declaration is made all further information no matter how valid, which are in favour of the normal status would be made zero in probability by multiplication with zero. Theoretically, the artificial assignment of over-riding and unassailable weightage to a prior event is ironically anti-Bayesiasn within purportedly Bayesian risk calculations (4) in fact a reversion to classical probability concepts. If mutation rate is not zero as is the case in reality or else the defective gene would not be in existence in the first place, and if the lone daughter is not uninformative, then the new information should be incorported into the risk calculations.

Presented here is a Pet BASIC computer programme that will calculate the risks of a female being a carrier for a sex linked trait from even multiple generations of descendant information and in addition it will allow (a) input of probability vectors from, hitherto ignored, lone daughter through linkage information, (b) input of variable mutation rates at any point in the pedigree and (c) input of information from clinical data or tests on female members as heterozygotes, before judgement is finally made. It does so without bias weightage down to 1e-39 at which the limits of BASIC arithmetic forces an absolute zero return. At this point Bayesian probability ceases by technical default rather than by calculation. The upper limit of accuracy is 99.9999999 percent (again a technical limitation due to the 9 digit BASIC in the computer) because further decimal places are zeroed by rounding off. The return of 100 percent probability as a carrier due to rounding off limitation beyond 9 nines would force a printout of zero probability as a normal (since probability cannot exceed 100 percent), but the memory array is not absolute zero. That still holds 1e-7 or less, and until the content in the array diminishes to 1e-39, the probability as a normal could still be upgradable by significant information and therefore not equivalent to a declaration of zero mutation rate. A pedigree with 8 generations of significant information would require about 20 kilobytes of memory to analyse, so that microcomputers with at least 32 kilobytes of directly accessible memory could cope with most pedigrees in practice. Hardcopy prints of all vectors and calculated probabilities are provided for each significant female member up to the consultand thus providing a useful base for further consultation with any particular member of the pedigree. The consultand is considered here for illustration convenience, as the daughter of a carrier. Thus by anterior information she has an equal chance as a carrier or as a genotypic normal. Then based on all available posterior information, the programme would give the calculated risks of the consultand without requiring any calculation or knowledge of genetics on the part of the user of the programme, thus serving to remove those exercises and burdens from the genetic counsellor who may be a family physician or even a public health nurse (5). Such is the philosophy behind present thinking on computer 'intelligence'.

RESULTS AND DISCUSSION

The pedigree in Fig. 1 is analyzed by the programme

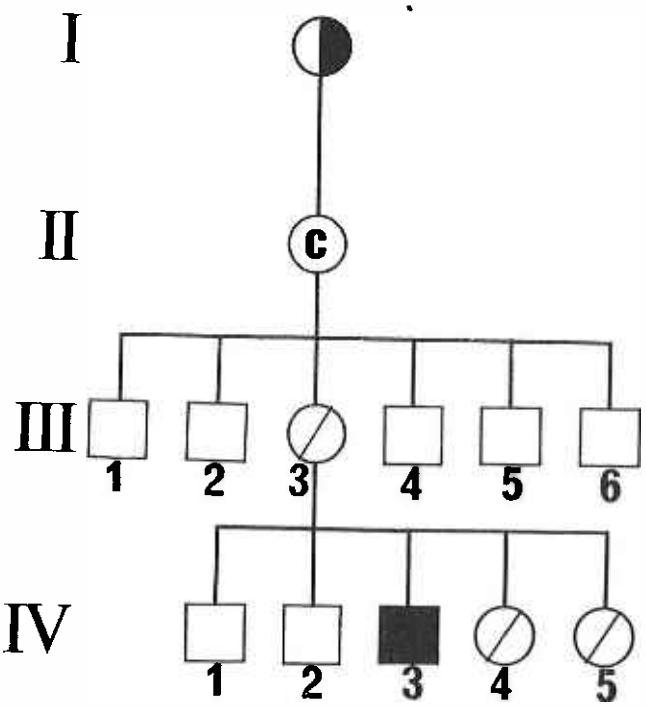

FIGURE 1:
The consultand is at generation 2 and labelled with a "c" and is the daughter of a heterozygote in generation 1. The consultand has 5 normal sons and one daughter 3(3), who is defined by linkage studies as having a 10 percent probability as a carrier and a 90 percent probability as a normal. 3(3) is also defined by 2 normal sons and one affected son, and two 'lone daughters' who are themselves defined by linkage studies. 4(4) lone daughters has a 20 percent probability as a carrier and an 80 percent probability as a normal. 4(5) lone daughter has a 30 percent probability as a carrier and a 70 percent probability as a normal. The mutation rate is 1 per 1000 for the analyses in Tables 2 and 3 but zero for the analysis in Table 4.

with questions and explanatory texts as given in Table 1, which are screen dumps during actual execution. The user has to key in the numbers and either "y" for yes or "n" for no against the question marks. Generation numbers in pedigree diagrams are written in Roman numerals, whereas members of each generation are enumerated from left to right in arabic numerals. The calculated results are given in Table 2. Some programmed 'intelligence' or 'artificial intelligence' is built in to allow for human error. For example, if you had started by keying in the generation number of the youngest mother of a significant daughter as 2 instead of 3 for the pedigree illustrated in Fig. 1, thereby missing one entire generation of significant information, the programme will still provide the correct calculated risk values for the consultand, as given in Table 3. It is able to cope with so much apparent information loss because the algorithm provides for every generation to have significant descendants who are significant because of their own significant information and or their descendants' significant information. This is known as 'common sense intelligence' as opposed to 'specific intelligence' in which once started the calculations that lead from generation to generation up the family tree produce cues of the relevant members of a lineage within the limits of the information that you have entered. It makes correct calculated guesses or 'intelligent guesses' for you, so that for simple lineages, it is a case of pressing the return key repeatedly (to signify agreement with the given cues) until the consultand is reached. The hand calculated arithmetic in matrix form is given in Appendix 1, for the pedigree in Fig. 1.

Table 4 presents the results of the pedigree in Fig. 1 when the mutation rate is entered as absolute zero for the affected son 3(2). The final status of the consultand is then totally different from that presented in Tables 2 and 3. The denial of any chance of mutation has given the consultand an obligatory 100 percent heterozygous status, instead of 10.1 percent if the mutation rate is not zero.

TABLE 1: SCREEN DUMP OF QUESTIONS AND TEXT IN THE ANALYSIS OF FIG. 1

```
MAX NO. OF GENERATIONS IN FAMILY ? 4
MAX NO. OF MEMBERS PER GENERATION? 6
MEMMORY= 16801
A SIGNIFICANT DAUGHTER = ONE WITH
SIGNIFICANT INFORMATION....
 *OWN INFORMATION AND 1ST, 2ND, 3RD ETC.
 DEGREE INFORMATION INCLUSIVE*
 NAMELY HERSELF DEFINED BY TEST VECTORS
 ONLY & WITHOUT ANY CHILDREN, OR HERSELF
 BEING FOUND AFFECTED CLINICALLY
 OR SHE HAS SON/S EITHER NORMAL/AFFECTED
 OR HER OWN SIGNIFICANT DAUGHTER/S ETC.

ANY SIGNIFICANT DAUGHTER OF CONSULTAND
  (KEY IN Y FOR YES OR N FOR NO)
? Y
OPTIMUM DECIMAL PLACES OF OUTPUT DATA
? 7
MUTATION RATE (RETURN 0 IF NO OVERTLY
AFFECTED MEMBERS)
? .001

E X P L A N A T I O N S.....
DIRECT SIGNIFICANT DAUGHTER=ONE WITH OWN
 SONS/S (NORMAL/AFFECTED), &/OR 'NORMAL'
 DAUGHTERS DEFINED BY TESTS VECTORS ONLY
 &/OR DAUGHTERS WHO ARE PHENOTYPICALLY
 AFFECTED CLINICALLY
 OR VECTORS & FIRST DEGREE VECTORS ONLY

MOSD = ACRONYM FOR MOTHER OF SIGNIFICANT
 DAUGHTER
MOSD# = ACRONYM FOR MOTHER OF *DIRECT*
 SIGNIFICANT DAUGHTER

GENERATION NO. OF YOUNGEST (= LOWEST)
MOSD#
? 2
MEMBER NO. OF DIRECT SIGNIFICANT DAUGHTE
R OF CONSULTAND
(NOTE:DAUGHTER IS AT GENERATION NO. III )
? 3

DEFINED DSD= 3 ( 3 )
ANY TESTS VECTOR OR AFFECTED CHILDREN
OF DSD 3 ( 3 )
? Y
NO. OF AFFECTED OFFSPRING/S
? 1
MUTATIONAL RATE
? 1E-03
OVERT TRAIT OR TESTS VECTOR OF 3 ( 3 )
? Y
IS 3 ( 3 ) HERSELF PHENOTYPICALLY AFFEC
TED
? N
ANY TEST VECTOR
? Y
CARRIER LIKELIHOOD (CLINICAL TEST)? 1

NORMAL LIKELIHOOD (CLINICAL TEST)? 9

MORE TESTS VECTOR
? N
NO. OF NORMAL SON/S FROM DSD 3 ( 3 )
? 2
NORMAL DAUGHTER WITH TESTS VECTOR FROM
 3 ( 3 )
? Y
MEMBER NO. OF 'VECTOR' DEFINED DAUGHTER
? 4
'VECTOR' DAUGHTER IS 4 ( 4 )
CARRIER LIKELIHOOD OF DAUGHTER
(BY CLINICAL TEST)? 2

NORMAL LIKELIHOOD OF DAUGHTER
(BY CLINICAL TEST)? 8

MORE DAUGHTERS WITH TESTS VECTORS FOR 3
 ( 3 )
? Y
MEMBER NO. OF 'VECTOR' DEFINED DAUGHTER
? 5
'VECTOR' DAUGHTER IS 4 ( 5 )
CARRIER LIKELIHOOD OF DAUGHTER
(BY CLINICAL TEST)? 3

NORMAL LIKELIHOOD OF DAUGHTER
(BY CLINICAL TEST)? 7

MORE DAUGHTERS WITH TESTS VECTORS FOR 3
 ( 3 )
? N

*
*
ANY OTHER DIRECT SIGNIFICANT DAUGHTER
 OF CONSULTAND
? N
ANY OWN NORMAL SONS OF CONSULTAND?
? Y
NUMBER OF NORMAL SON/S OF CONSULTAND
? 5
*
*
ANY TESTS VECTOR OR AFFECTED CHILDREN OF
 CONSULTAND
? N
CONSULTAND'S FINAL STATUS

 2       =   10.1206875  PERCENT FINAL LI
KELIHOOD AS CARRIER
 2       =   89.8793124  PERCENT FINAL LI
KELIHOOD AS NORMAL

DECIMAL PLACES LIMITED TO  7

READY.
```

TABLE 2: X-LINKED RISKS FROM ANALYSIS OF FIG. 1 PEDIGREE

```
(FEMALE)      CUMULATIVE/PERSON
 PERSON       CONDITIONAL STATUS    CAUSATION

                                    VECTOR 1  =( 2 , 8 ) @ 4 ( 4)
 3 ( 3 )=     38.4615384  % CARRIER  ←PERSON 4( 4 ) 1VECTOR/S
 3 ( 3 )=     61.5384615  % NORMAL   ←PERSON 4( 4 ) 1VECTOR/S

                                    VECTOR 1  =( 3 , 7 ) @ 4 ( 5)
 3 ( 3 )=     30.8641975  % CARRIER  ←PERSON 4( 5 ) 1VECTOR/S
 3 ( 3 )=     69.1358025  % NORMAL   ←PERSON 4( 5 ) 1VECTOR/S

 3 ( 3 )=     10.0401606  % CARRIER  ← 2 SON/S
 3 ( 3 )=     89.9598394  % NORMAL   ← 2 SON/S

                                    MUTATION RATE= 1E-03
                                    VECTOR 1  =( 1 , 9 ) @ 3 ( 3)
 3 ( 3 )=     86.1238256  % CARRIER  ← 1[redacted]+ 1VECTOR/S
 3 ( 3 )=     13.8761744  % NORMAL   ← 1[redacted]+ 1VECTOR/S

(FEMALE)      DISCRETE
CONSULTAND    CONDITIONAL STATUS    CAUSATION

 2            =    78.2764473  % CARRIER  ←PERSON 3( 3 )
 2            =    21.7235527  % NORMAL   ←PERSON 3( 3 )

 2            =     3.0303030  % CARRIER  ← 5 SON/S
 2            =    96.9696970  % NORMAL   ← 5 SON/S

CONSULTAND  FINAL STATUS FROM ALL SIGNIFICANT INFORMATION

 2            =    10.1206875  PERCENT FINAL LIKELIHOOD AS CARRIER
 2            =    89.8793124  PERCENT FINAL LIKELIHOOD AS NORMAL

DECIMAL PLACES LIMITED TO  7
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TABLE 3: X-LINKED RISKS FROM ANALYSIS OF FIG. 1 PEDIGREE (cf. TABLE 2)

```
(FEMALE)      DISCRETE
CONSULTAND    CONDITIONAL STATUS    CAUSATION

                                    MUTATION RATE= 1E-03
                                    VECTOR 1  =( 1 , 9 ) @ 3 ( 3)
                                    VECTOR 2  =( 2 , 8 )'VECTOR'DAUGHTER 4 ( 4 )
                                    VECTOR 3  =( 3 , 7 )'VECTOR'DAUGHTER 4 ( 5 )
 2            =    78.2764473  % CARRIER  ←PERSON 3( 3 ) 1[redacted]+ 3VECTOR/S + 2
SON/S
 2            =    21.7235527  % NORMAL   ←PERSON 3( 3 ) 1[redacted]+ 3VECTOR/S + 2
SON/S

 2            =     3.0303030  % CARRIER  ← 5 SON/S
 2            =    96.9696970  % NORMAL   ← 5 SON/S

CONSULTAND  FINAL STATUS FROM ALL SIGNIFICANT INFORMATION

 2            =    10.1206875  PERCENT FINAL LIKELIHOOD AS CARRIER
 2            =    89.8793124  PERCENT FINAL LIKELIHOOD AS NORMAL

DECIMAL PLACES LIMITED TO  7
```

Classically, in sex linkage, the affected are sons, but not daughters even if heterozygous. However some traits with quantifiable phenotypes such as G6PD deficiency or HGPRT deficiency, some extent of the phenotypic expression could be objectively defined in heterozygotes (6-7). This is because the random inactivation of one of the two x chromosomes in the female to form the Barr body or x chromatin body, is initiated only at the 16 cell stage in humans and completed by 42nd day of development, which is well into gastrulation when the embryo has over a thousand cells (8). As an illustration, even if we assume the founder colony of cells to be 300 only, the probability of having exclusively all the normal x chromosomes inactivated or all the defective (carrying the disease gene) x chromosomes inactivated in the 300 cells is, according to the binomial expansion, in the order of less than 1e-90. Thus the female heterozygote would be neither completely 'normal' nor completely 'abnormal'. Now with large numbers, the binomial distribution approximates the normal distribution, telling us that carrier females with an intermediate level of phenotypic expression would be highest in frequency while carriers with greater than intermediate level or lesser than intermediate level of phenotypic expression would recede in frequency towards zero. This means that only some carriers (heterozygous females) would be detected clinically as 'affected' if detection is possible, for the same trait. The extent of that detection being governed by the clinical expertise and by the sensitivity of the tests when applicable. It is allow for such variability in the detection of heterozygotes that (a) negative results from tests and clinical findings do not exclude a heterozygous status and (b) positive results do not imply similar success with all heterozygotes. A positive clinical identification of heterozygosity in the mother of an affected son does imply that the son is affected through presumptive transmission of the defective x chromosome from the mother, but does not suggest that the trait must necessarily be one descended from any other higher ancestors because the 'affected' (detected) female heterozygote just like the affected male (hemizygote) could be a fresh mutation at that point. Given this possibility, and the Bayesiasn context of risk calculations, the detected heterozygote must be entered as a prior probability vector for that person, but not be taken as a declaration of heterozygosity in all females in the lineage and cessation of further calculations and considerations. In our programme, the clinically defined heterozygote is entered into the risk calculations with the above

TABLE 4: X-LINKED RISKS FROM ANALYSIS OF FIG. 1 PEDIGREE (ZERO MUTATION RATE)

```
(FEMALE)      CUMULATIVE/PERSON
 PERSON       CONDITIONAL STATUS    CAUSATION

                                    VECTOR 1  =( 2 , 8 ) @ 4 ( 4)
 3 ( 3 )=    38.4615384  % CARRIER  ←PERSON 4( 4 ) 1VECTOR/S
 3 ( 3 )=    61.5384615  % NORMAL   ←PERSON 4( 4 ) 1VECTOR/S

                                    VECTOR 1  =( 3 , 7 ) @ 4 ( 5)
 3 ( 3 )=    30.8641975  % CARRIER  ←PERSON 4( 5 ) 1VECTOR/S
 3 ( 3 )=    69.1358025  % NORMAL   ←PERSON 4( 5 ) 1VECTOR/S

 3 ( 3 )=    10.0401606  % CARRIER  ← 2 SON/S
 3 ( 3 )=    89.9598394  % NORMAL   ← 2 SON/S

                                    MUTATION RATE= 0
                                    VECTOR 1  =( 1 , 9 ) @ 3 ( 3)
 3 ( 3 )=   100.0000000  % CARRIER  ← 1[AFFECTED CHILD]+ 1VECTOR/S
 3 ( 3 )=     0.0000000  % NORMAL   ← 1[AFFECTED CHILD]+ 1VECTOR/S

(FEMALE)      DISCRETE
CONSULTAND    CONDITIONAL STATUS    CAUSATION

 2          =   100.0000000  % CARRIER  ←PERSON 3( 3 )
 2          =     0.0000000  % NORMAL   ←PERSON 3( 3 )

 2          =     3.0303030  % CARRIER  ← 5 SON/S
 2          =    96.9696970  % NORMAL   ← 5 SON/S

CONSULTAND   FINAL STATUS FROM ALL SIGNIFICANT INFORMATION

 2          =   100.0000000  PERCENT FINAL LIKELIHOOD AS CARRIER
 2          =     0.0000000  PERCENT FINAL LIKELIHOOD AS NORMAL

DECIMAL PLACES LIMITED TO  7
```

APPENDIX 1 (refers to pedigree in Fig. 1)

The likelihood vectors at generation 4 are:

$L4(1) = [0 \quad 1]$

$L4(2) = [0 \quad 1]$

$L4(3) = [1 \quad \mu]$ where $\mu = 0.001$ (the mutation rate)

$L4(4) = [2 \quad 8]$

$L4(5) = [3 \quad 7]$

where l1=likelihood with the defective x, and l2=likelihood with a normal genotype.

Since the mother#child matrix=

	affected child	normal child
carrier mother	1	1
normal mother	0	2

and linkage defined $3(3) = [1 \quad 9]$,

$$L3(3) = \begin{bmatrix}1\\9\end{bmatrix} \lambda \begin{bmatrix}1\\4\end{bmatrix} \lambda \begin{bmatrix}1.001\\0.002\end{bmatrix} \lambda \begin{bmatrix}10\\16\end{bmatrix} \lambda \begin{bmatrix}10\\14\end{bmatrix} = \begin{bmatrix}100.100\\16.128\end{bmatrix}$$

thus,

$$L2(c) = \begin{bmatrix}116.228\\32.256\end{bmatrix} \lambda \begin{bmatrix}1\\32\end{bmatrix} = \begin{bmatrix}116.228\\1032.192\end{bmatrix}$$

On normalisation and conversion to percentage,

the consultand has a 10.12068755 percent chance as a carrier

and a 89.87931245 percent chance as a normal

(using a 10 digit calculator)

However, when mutation rate, μ,= zero

$L4(3) = [1 \quad 0]$ consequently,

$$L3(3) = \begin{bmatrix}1\\9\end{bmatrix} \lambda \begin{bmatrix}1\\4\end{bmatrix} \lambda \begin{bmatrix}1\\0\end{bmatrix} \lambda \begin{bmatrix}10\\16\end{bmatrix} \lambda \begin{bmatrix}10\\14\end{bmatrix} = \begin{bmatrix}100\\0\end{bmatrix} = \begin{bmatrix}1\\0\end{bmatrix}$$

in which case,

$$L2(c) = \begin{bmatrix}1\\0\end{bmatrix} \lambda \begin{bmatrix}1\\32\end{bmatrix} = \begin{bmatrix}1\\0\end{bmatrix}$$

On conversion to percentage,

the consultand has a 100 percent chance as a carrier

and a zero percent chance as a normal.

A detailed exposition of the Bayesian matrices is given in (6)

considerations, as illustrated in Table 5 and Fig. 2, where the consultand has a calculated risk of 0.0000091 percent probability as a carrier. Exactly the same calculations with a rerun of the programme but using a zero mutation rate, produce an imperative heterozygous consultand, see Table 6, with a risk of 100 percent probability as a carrier. The zero mutation rate has created an almost complete reversals of the calculated risks, even when entered for heterozygous females.

The complexity of the pedigree in Fig. 2 serves to illustrate the ability of the programme to handle such information, with calcualted probabilities for all significant members. The probabilities are increased sequentially for members who are not consultand, in accordance with the indicated significant information. Thus for a particular member, the last entry of significant information would produce the calculated probability of that member with not only that entry but all previous entries for the member taken into consideration. For the consultand the cumulation is presented as her final status. The information accumulated up to the generation below the consultand and her own vectors are presented as discrete contributions to the consultand's conditional status. This presentation allows one to read the pedigree manually in stepwise fashion. The programme has a unique number formatter written specially for this programme to align probability values in scientific notations with normal displays. THe correct number pf decimal palces in scientific notation between the values 0 and 0.01 would be generated to match the other probability value and yet align neatly with that value (see Table 5). Without this formatter, the printout with scientific notation mixed with normal numerals in a probability (a) may not always add up to 100 percent with an overflow of decimal places in scientific notation and (b) wil be untidy and difficult to read due to the non alignment between scientific notations and normal display which will also throw the rest of the text off their columns in the table. A printout of the programme listing is given in Appendix 2.

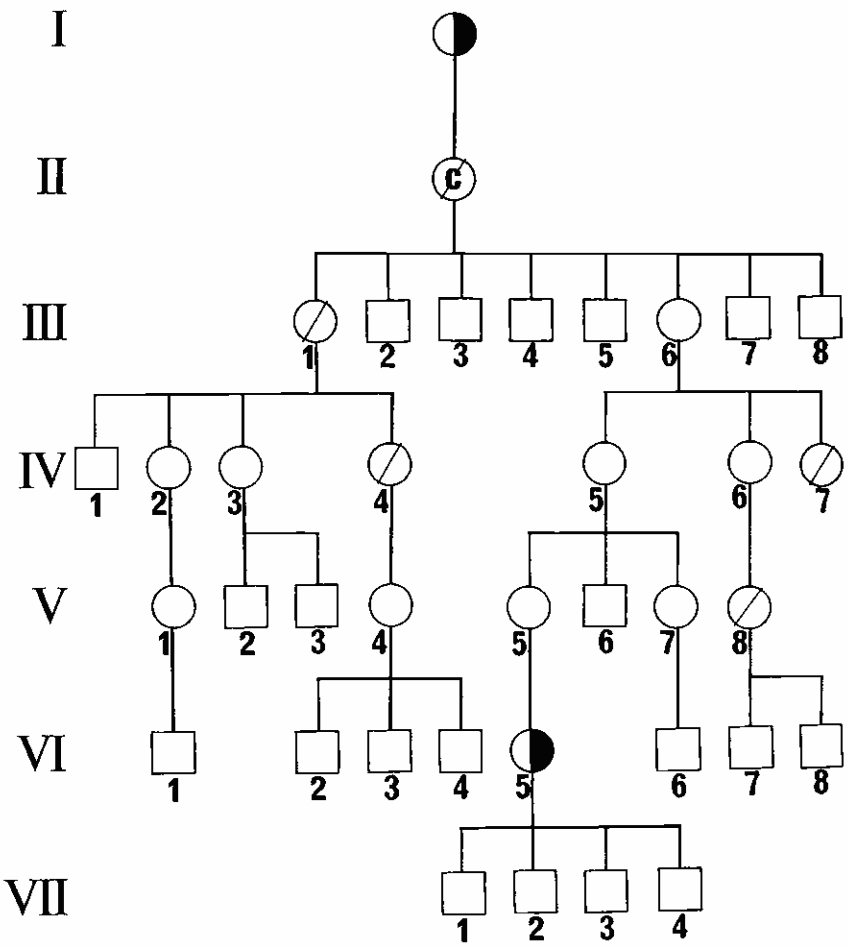

FIGURE 2:
The consultand 'c' at generation 2 has very complex posterior information and a linkage defined vector of 0.0015 percent probability as a carrier and a 99.9995 percent probability as a normal. 3(1) has a linkage defined vector of 0.001 percent probability as a carrier and a 99.999 percent probability as a normal. 4(4) has a linkage defined vector of 0.1 percent probability as a carrier and a 99.9 percent probability as a normal. 4(7) is a 'lone daughter' who is significant by virtue of the linkage defined vector of 0.002 percent probability as a carrier and 99.998 percent probability as a normal. 5(8) has a linkage defined vector of 0.2 percent probability as a carrier and 99.8 percent probability as a normal. 6(5) is a heterozygote defined by direct clinical data. 6(5) is also defined by her 4 normal sons, which constitute her posterior information. The heterozygote status of 6(5) is a prior probability of 6(5), which according to Baye's theorem must be multiplied with the posterior probability, in order to obtain her conditional status at that point of time. The mutation rate is 1 per 1000 for the analysis in Table 5, but zero for the analysis in Table 6.

TABLE 5: X-LINKED RISKS FROM ANALYSIS OF FIG. 2 PEDIGREE

```
(FEMALE)     CUMULATIVE/PERSON
PERSON       CONDITIONAL STATUS    CAUSATION

                                   VECTOR 1  =( 1 , 1E-03 )AFFECTED PERSON 6
5 ( 5 )=    96.9465649  % CARRIER  ←PERSON 6( 5 ) 1VECTOR/S + 4 SON/S
5 ( 5 )=     3.0534351  % NORMAL   ←PERSON 6( 5 ) 1VECTOR/S + 4 SON/S

4 ( 5 )=    94.2446043  % CARRIER  ←PERSON 5( 5 )
4 ( 5 )=     5.7553956  % NORMAL   ←PERSON 5( 5 )

4 ( 5 )=    92.4705882  % CARRIER  ←PERSON 5( 7 ) + 1 SON/S
4 ( 5 )=     7.5294117  % NORMAL   ←PERSON 5( 7 ) + 1 SON/S

4 ( 5 )=    85.9956236  % CARRIER  ← 1 SON/S
4 ( 5 )=    14.0043763  % NORMAL   ← 1 SON/S

4 ( 2 )=    42.8571428  % CARRIER  ←PERSON 5( 1 ) + 1 SON/S
4 ( 2 )=    57.1428571  % NORMAL   ←PERSON 5( 1 ) + 1 SON/S

4 ( 2 )=    27.2727272  % CARRIER  ← 1 SON/S
4 ( 2 )=    72.7272727  % NORMAL   ← 1 SON/S

4 ( 4 )=    36.0000000  % CARRIER  ←PERSON 5( 4 ) + 3 SON/S
4 ( 4 )=    64.0000000  % NORMAL   ←PERSON 5( 4 ) + 3 SON/S

4 ( 4 )=    21.9512195  % CARRIER  ← 1 SON/S
4 ( 4 )=    78.0487805  % NORMAL   ← 1 SON/S

                                   VECTOR 1  =( .1 , 99.9 ) @ 4 ( 4)
4 ( 4 )=      .0281452  % CARRIER  ← 1VECTOR/S
4 ( 4 )=    99.9718547  % NORMAL   ← 1VECTOR/S

                                   VECTOR 1  =( .2 , 99.8 ) @ 5 ( 8)
4 ( 6 )=    33.3444648  % CARRIER  ←PERSON 5( 6 ) 1VECTOR/S + 2 SON/S
4 ( 6 )=    66.6555351  % NORMAL   ←PERSON 5( 8 ) 1VECTOR/S + 2 SON/S

4 ( 6 )=    20.0080152  % CARRIER  ← 1 SON/S
4 ( 6 )=    79.9919847  % NORMAL   ← 1 SON/S

3 ( 1 )=    40.7407407  % CARRIER  ←PERSON 4( 2 )
3 ( 1 )=    59.2592592  % NORMAL   ←PERSON 4( 2 )

3 ( 1 )=    25.5867545  % CARRIER  ←PERSON 4( 4 )
3 ( 1 )=    74.4132454  % NORMAL   ←PERSON 4( 4 )

3 ( 1 )=    17.6889856  % CARRIER  ←PERSON 4( 3 ) + 2 SON/S
3 ( 1 )=    82.3110144  % NORMAL   ←PERSON 4( 3 ) + 2 SON/S

3 ( 1 )=     9.7026423  % CARRIER  ← 1 SON/S
3 ( 1 )=    90.2973577  % NORMAL   ← 1 SON/S

                                   VECTOR 1  =( 1E-03 , 99.999 ) @ 3 ( 1)
3 ( 1 )=     1.074E-04  % CARRIER  ← 1VECTOR/S
3 ( 1 )=    99.9998926  % NORMAL   ← 1VECTOR/S

3 ( 6 )=    78.1196581  % CARRIER  ←PERSON 4( 5 )
3 ( 6 )=    21.8803418  % NORMAL   ←PERSON 4( 5 )

3 ( 6 )=    69.0562359  % CARRIER  ←PERSON 4( 6 )
3 ( 6 )=    30.9437640  % NORMAL   ←PERSON 4( 6 )

                                   VECTOR 1  =( 2E-03 , 99.998 )'VECTOR DAUGHTER 4
( 7 )
3 ( 6 )=    35.8121971  % CARRIER  ← 1 SON/S
3 ( 6 )=    64.1878028  % NORMAL   ← 1 SON/S

(FEMALE)     DISCRETE
CONSULTAND   CONDITIONAL STATUS    CAUSATION

2            =    33.3333572  % CARRIER  ←PERSON 3( 1 ) 1VECTOR/S
2            =    66.6666428  % NORMAL   ←PERSON 3( 1 ) 1VECTOR/S

2            =    43.7875138  % CARRIER  ←PERSON 3( 6 )
2            =    56.2124861  % NORMAL   ←PERSON 3( 6 )

2            =     1.5384615  % CARRIER  ← 6 SON/S
2            =    98.4615385  % NORMAL   ← 6 SON/S

                                   VECTOR 1  =( 1.5E-03 , 99.9995 ) @ 2 (CONSULTAN
D)
2            =     1.4999E-03 % CARRIER  ← 1VECTOR/S
2            =    99.9985000  % NORMAL   ← 1VECTOR/S


CONSULTAND  FINAL STATUS FROM ALL SIGNIFICANT INFORMATION

2            =     9.1E-0600  PERCENT FINAL LIKELIHOOD AS CARRIER
2            =    99.9999909  PERCENT FINAL LIKELIHOOD AS NORMAL

DECIMAL PLACES LIMITED TO  7
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TABLE 6: X-LINKED RISKS FROM ANALYSIS OF FIG. 2 PEDIGREE (ZERO MUTATION RATE)

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(FEMALE)     CUMULATIVE/PERSON
 PERSON      CONDITIONAL STATUS    CAUSATION

                                   VECTOR 1   =( 1 , 0 )AFFECTED PERSON 6 ( 5)
 5 ( 5 )=   100.0000000  % CARRIER  ←PERSON 6( 5 ) 1VECTOR/S + 4 SON/S
 5 ( 5 )=     0.0000000  % NORMAL   ←PERSON 6( 5 ) 1VECTOR/S + 4 SON/S

 4 ( 5 )=   100.0000000  % CARRIER  ←PERSON 5( 5 )
 4 ( 5 )=     0.0000000  % NORMAL   ←PERSON 5( 5 )

 4 ( 5 )=   100.0000000  % CARRIER  ←PERSON 5( 7 ) + 1 SON/S
 4 ( 5 )=     0.0000000  % NORMAL   ←PERSON 5( 7 ) + 1 SON/S

 4 ( 5 )=   100.0000000  % CARRIER  ← 1 SON/S
 4 ( 5 )=     0.0000000  % NORMAL   ← 1 SON/S

 4 ( 2 )=    42.8571428  % CARRIER  ←PERSON 5( 1 ) + 1 SON/S
 4 ( 2 )=    57.1428571  % NORMAL   ←PERSON 5( 1 ) + 1 SON/S

 4 ( 2 )=    27.2727272  % CARRIER  ← 1 SON/S
 4 ( 2 )=    72.7272727  % NORMAL   ← 1 SON/S

 4 ( 4 )=    36.0000000  % CARRIER  ←PERSON 5( 4 ) + 3 SON/S
 4 ( 4 )=    64.0000000  % NORMAL   ←PERSON 5( 4 ) + 3 SON/S

 4 ( 4 )=    21.9512195  % CARRIER  ← 1 SON/S
 4 ( 4 )=    78.0487805  % NORMAL   ← 1 SON/S

                                   VECTOR 1   =( .1 , 99.9 ) @ 4 ( 4)
 4 ( 4 )=      .0281452  % CARRIER  ← 1VECTOR/S
 4 ( 4 )=    99.9718547  % NORMAL   ← 1VECTOR/S

                                   VECTOR 1   =( .2 , 99.8 ) @ 5 ( 8)
 4 ( 6 )=    33.3444648  % CARRIER  ←PERSON 5( 8 ) 1VECTOR/S + 2 SON/S
 4 ( 6 )=    66.6555351  % NORMAL   ←PERSON 5( 8 ) 1VECTOR/S + 2 SON/S

 4 ( 6 )=    20.0080152  % CARRIER  ← 1 SON/S
 4 ( 6 )=    79.9919847  % NORMAL   ← 1 SON/S

 3 ( 1 )=    40.7407407  % CARRIER  ←PERSON 4( 2 )
 3 ( 1 )=    59.2592592  % NORMAL   ←PERSON 4( 2 )

 3 ( 1 )=    25.5867545  % CARRIER  ←PERSON 4( 4 )
 3 ( 1 )=    74.4132454  % NORMAL   ←PERSON 4( 4 )

 3 ( 1 )=    17.6889856  % CARRIER  ←PERSON 4( 3 ) + 2 SON/S
 3 ( 1 )=    82.3110144  % NORMAL   ←PERSON 4( 3 ) + 2 SON/S

 3 ( 1 )=     9.7026423  % CARRIER  ← 1 SON/S
 3 ( 1 )=    90.2973577  % NORMAL   ← 1 SON/S

                                   VECTOR 1   =( 1E-03 , 99.999 ) @ 3 ( 1)
 3 ( 1 )=     1.074E-04  % CARRIER  ← 1VECTOR/S
 3 ( 1 )=    99.9998926  % NORMAL   ← 1VECTOR/S

 3 ( 6 )=   100.0000000  % CARRIER  ←PERSON 4( 5 )
 3 ( 6 )=     0.0000000  % NORMAL   ←PERSON 4( 5 )

 3 ( 6 )=   100.0000000  % CARRIER  ←PERSON 4( 6 )
 3 ( 6 )=     0.0000000  % NORMAL   ←PERSON 4( 6 )

                                   VECTOR 1   =( 2E-03 , 99.998 )'VECTOR'DAUGHTER 4
 ( 7 )
 3 ( 6 )=   100.0000000  % CARRIER  ← 1 SON/S
 3 ( 6 )=     0.0000000  % NORMAL   ← 1 SON/S

(FEMALE)     DISCRETE
CONSULTAND   CONDITIONAL STATUS    CAUSATION

 2       =    33.3333572  % CARRIER  ←PERSON 3( 1 ) 1VECTOR/S
 2       =    66.6666428  % NORMAL   ←PERSON 3( 1 ) 1VECTOR/S

 2       =   100.0000000  % CARRIER  ←PERSON 3( 6 )
 2       =     0.0000000  % NORMAL   ←PERSON 3( 6 )

 2       =     1.5384615  % CARRIER  ← 6 SON/S
 2       =    98.4615385  % NORMAL   ← 6 SON/S

                                   VECTOR 1   =( 1.5E-03 , 99.9995 ) @ 2 (CONSULTAN
D)
 2       =     1.4999E-03 % CARRIER  ← 1VECTOR/S
 2       =    99.9985000  % NORMAL   ← 1VECTOR/S


CONSULTAND   FINAL STATUS FROM ALL SIGNIFICANT INFORMATION

 2       =   100.0000000  PERCENT FINAL LIKELIHOOD AS CARRIER
 2       =     0.0000000  PERCENT FINAL LIKELIHOOD AS NORMAL

DECIMAL PLACES LIMITED TO  7
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