Letters to the Editor

A COMPUTER PROGRAM TO DETERMINE GENETIC RISKS: A SIMPLIFIED VERSION OF PEDIG (HEUCH AND LI, 1972)

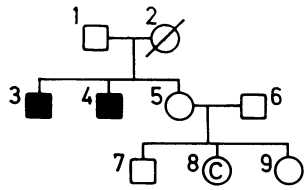
To the Editor: Heuch and Li [1] presented a computer program (PEDIG) for estimating risks in any pedigree with Mendelian inheritance. The program computes the genotype probability distribution for a given consultand in a pedigree without loops conditional on known phenotype information from relatives. A simplified version of the program has been written which allows easy access to clinicians for use in genetic counseling.

Our modifications are as follows: we have put the program on-line to the computer so that an immediate answer may be obtained, used the on-line system to prompt the user as to the information to enter on the keyboard at each stage, simplified the input details, allowed for corrections to the input data, and permitted risks to be calculated for any number of individuals in the same pedigree.

In modifying the program, the original version has been left intact and may be applied as outlined by Heuch and Li [1]. The simplified version allows only one autosomal or X-linked locus with no genetic or environmental modifiers which might vary among families. Mutation rates are fixed at 1×10^{-5} but can be modified if required. Gene frequencies may be specified during execution of the program.

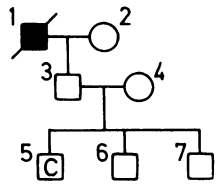
Full details of the original program and logic are given by Heuch and Li [1]. (A detailed monograph is available.) The computational methods used in obtaining the genotype probabilities for the consultand are also given by Murphy and Mutalik [2]. Two examples of the modified program are given in figures 1 and 2. Figure 1 shows a pedigree of Duchenne muscular dystrophy, an X-linked lethal, with serum creatinine kinase (SCK) levels in females at risk. The conditional probabilities of having a normal genotype versus a carrier genotype with the given SCK level are obtained by dividing the proportion of normals with the SCK value by the sum of the proportions of normals and of carriers with similar SCK values. These values are from the laboratory in Edinburgh. Table 1 gives an abbreviated version of the computer input and output for the pedigree in figure 1. The probability that the consultand (individual 8) is a carrier is calculated to be .06, and that of her sister (individual 9) is .33.

Figure 2 is an example of an autosomal dominant with variable age of onset (e.g., Huntington's disease). The probability of normal genotype is the proportion



Ind. No.	SCK (I.U.)	Pr (Normal)
5	51	0·32
8	15	0·88
9	55	0·32

FIG. 1.—Pedigree of Duchenne muscular dystrophy. SCK (I.U.) = serum creatinine kinase activity (international units). Pr (normal) = probability of normal genotype.



Ind. No.	Age	Pr (Normal)
3	55	0·08
5	35	0·66
6	33	0·72
7	30	0·80

FIG. 2.—Autosomal dominant inheritance with variable age of onset. Pr (normal) = probability of normal genotype.

TABLE 1

ABBREVATED VERSION OF COMPUTER INPUT AND OUTPUT FOR PEDIGREE IN FIGURE 1

Input/Format	Value
Family no./xxxx	1328
No. in family/xx	09
No. of consultand/xx	08
Mode of inheritance/xx*	22
Pedigree/xx/xx/xx/x/x/0.xx†	01000011 02000021 03010212 04010212 050102210.32 06000011 07060511 080605210.88 090605210.32

Output	Genotype	Probability
For 08	*AA*	0.94
	Aa	0.06

NOTE.—Program lists input details and allows corrections. Other consultants can be run.
* 11 = AD, 12 = AR, 21 = XLD, 22 = XLR.
† Indiv./fa/mo/sex (1 = M, 2 = F)/state (1 = N, 2 = A)/prob.(N).

of carriers of the deleterious allele who are normal at a given age. The probability that the consultand (individual 5) is a carrier was computed to be .019.

The program is written in a restricted FORTRAN IV and should be compatible with most FORTRAN compilers. The program is quite versatile and can be used in

essentially all cases of Mendelian inheritance with no consanguinity. Elston and Stewart [3] and Gold et al. [4] have also described methods to obtain risks for use in genetic counseling. A program RISKMF for computing risks for quasi-continuous traits based on multifactorial inheritance has been described by Smith [5].

The program and further details on its usage may be obtained from P. M. Conneally.

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NULL PHENOTYPES IN THE PI SYSTEM

To the Editor: While Balakrishnan and Ashton [1] are correct in noting that a "null" phenotype suggesting a null or silent allele has been discovered in the Pi (α_1 antitrypsin) system, and thus in a nonenzyme polymorphism, their implication that ZZ is the null type is incorrect. The null type is distinguishable from ZZ by its absence of anti-enzyme activity (that can be ascribed to α_1 antitrypsin) and a total lack of α_1 antitrypsin protein, whereas ZZ has a small but measurable amount of α_1 antitrypsin protein and low trypsin inhibitory activity. Moreover, the ZZ pattern is detectable by starch gel electrophoresis in combination with antigen-antibody crossed electrophoresis, whereas the null type has no discernible pattern. Talamo et al. [2], Martin et al. [3], and others [4] have reported the null type, and there now appear to be at least 22 discernible "alleles" in the Pi system. The term "alleles" is shown in quotation marks because in the report of the likely Pi-Gm linkage, there was a suggestion of a difference in recombination fractions for "*Z*" and "*S*" when these respectively were segregating with "*M*" in the