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Brief Communication

Easy Calculations of Lod Scores and Genetic Risks on Small Computers

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SUMMARY

A computer program that calculates lod scores and genetic risks for a wide variety of both qualitative and quantitative genetic traits is discussed. An illustration is given of the joint use of a genetic marker, affection status, and quantitative information in counseling situations regarding Duchenne muscular dystrophy.

INTRODUCTION

Linkage analysis in man has long been restricted to simple Mendelian traits and nuclear families [1–5]. Computations were performed by hand with the help of special tables [5, 6], and the results most often reported as lod scores tables; however, such calculations were both tedious and error-prone. The advent of computers, appropriate algorithms, and computer programs such as LIPED [7] has rendered linkage analysis of more complex phenotype systems or pedigree data manageable [8–10].

If the yield of the family method for linkage analysis has been modest ([11], p. 111), this can be in part ascribed to the restricted number of well-defined polymorphic genetic systems available. The identification of new polymorphisms at the DNA level will be of great value in genetic analysis and will improve the efficiency of the family method [12]. This new wealth of data will coincide with advances in computer technology that will make inexpensive personal computers widely available to researchers. Calculations that once required the help of a

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specialist or the use of large computers now can be done routinely in the laboratory. This calls for easy-to-use interactive programs requiring minimal storage and little computer expertise.

The computer program LINKAGE was developed in response to this need. It can be used for either linkage analysis or calculations of genetic risks from pedigree data. It is an interactive program, allowing an easy dialogue with the investigator. It is written in the PASCAL language, which is most appropriate for recursive calculations as required for pedigrees and is widely available on small computers. The phenotype at a locus may be defined as a dichotomy of affection status, a quantitative trait, or a simple Mendelian system. The modular program structure allows easy extensions. We shall give a brief account of the methods implemented, as well as some possible applications.

METHODS

We shall refer to the two loci that can be jointly considered as the test locus and the main locus, respectively. The test locus is assumed to be a simple Mendelian system that can be treated as a factor-union system [13]. An arbitrary number of factors and alleles is allowed. Phenotypes at the second locus may be given as another factor-union system, as affection status, or as one or more quantitative measurements. For affection status, multiple alleles and incomplete penetrances may be defined. Several quantitative measurements may be considered, allowing for different allelic variants or allelic pleiotropy, with a multivariate normal distribution of errors. Affection status and quantitative measurements may be considered simultaneously. Allowance is made for linkage disequilibrium, sex-linkage, and mutation.

Likelihood calculations are carried out using a recursive algorithm [14, 15]. Loops are treated by duplicating genotypes [16]. Lod scores can be obtained for selected recombination values, or risks may be calculated for certain individuals. LINKAGE may be coupled to the numerical optimization routine GEMPAS, a PASCAL version of GEMINI [17], thereby allowing maximum likelihood estimation and tests of hypotheses regarding the genetic parameters. LINKAGE requires about 20K words of memory for the analysis of a test locus with four alleles and a main locus with two alleles in a pedigree of 100 individuals. However, maximum likelihood estimation using LINKAGE and GEMPAS will require a minimum of an additional 16K words of storage.

A TYPICAL APPLICATION

As an illustration of the efficiency of using jointly affection status and quantitative information in search of linkage to a polymorphic test locus, we present some results obtained for Duchenne muscular dystrophy (DMD) using creatine kinase for carrier detection. Starting from two actual counseling situations, we have simulated segregation of a polymorphic marker similar to that reported by Murray et al. [17].

Parameters at the DMD locus were chosen in agreement with reported figures [11]: a gene frequency of .0003, a mutation rate of .0001, and mean and standard deviations for creatine kinase in normal and obligate carrier women of 1.57 ± 0.242 and 2.10 ± 0.409, as reported by Lubs (see [18]). The phenotypes at the test locus were generated randomly, assuming two codominant alleles with frequencies .85 and .15, in linkage equilibrium with DMD. A recombination rate of .15 was assumed.

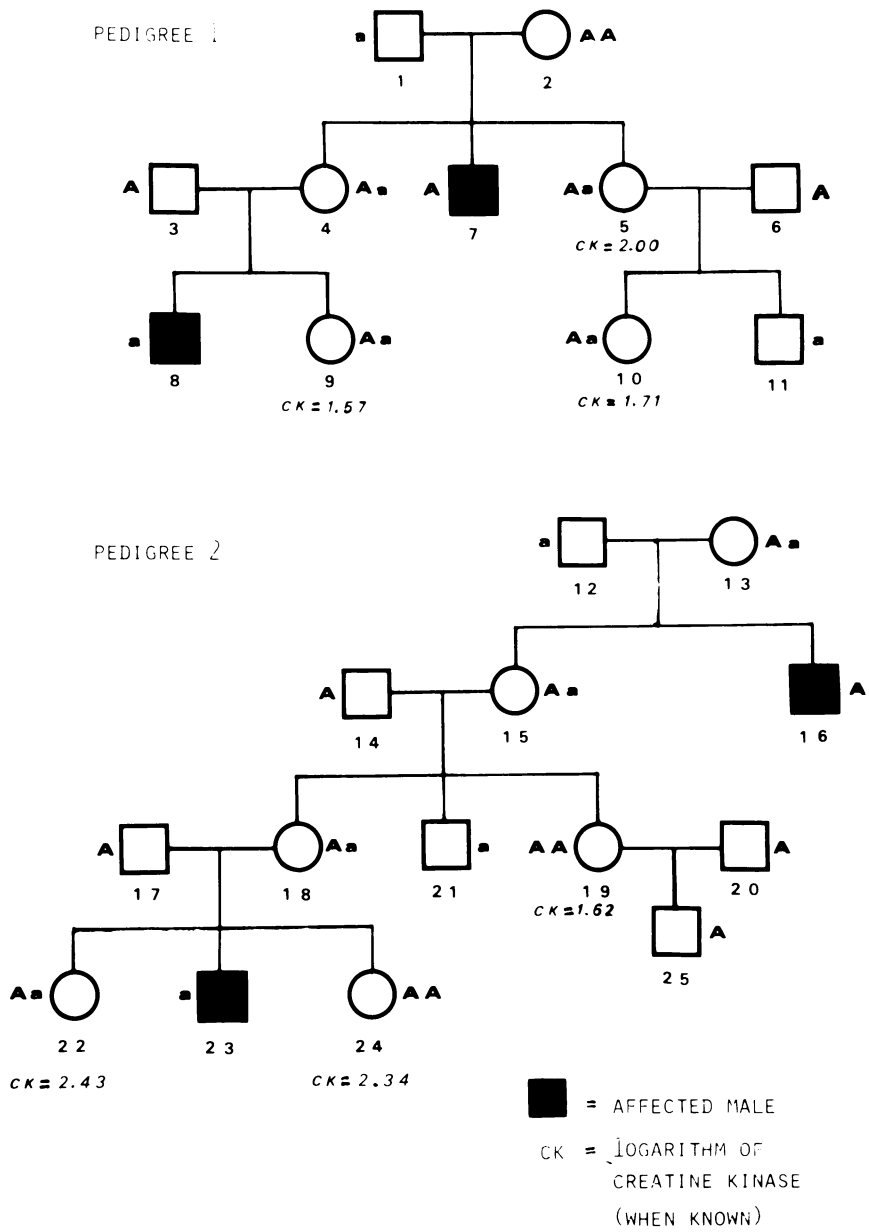

FIG. 1.—Pedigrees from the two counseling applications showing the genotypes in one simulation. Alleles at the test locus are denoted "*A*" (frequency .85) and "*a*" (frequency .15).

TABLE 1

LOD SCORES FROM FIVE REPLICATES OF TWO PEDIGREE TYPES (PEDIGREE TYPES REFER TO THE EXAMPLES SHOWN IN FIGURE 1)

CREATINE KINASE	PEDIGREE	RECOMBINATION VALUE									
		.0	.05	.10	.15	.20	.25	.30	.35	.40	.45
Absent	Type 1	−2.71	−0.18	0.44	0.70	0.79	0.79	0.72	0.60	0.44	0.24
	Type 2	−4.12	−0.34	0.08	0.25	0.32	0.33	0.31	0.26	0.19	0.11
	Total	−6.83	−0.52	0.53	0.95	1.11	1.12	1.03	0.86	0.63	0.35
Present	Type 1	−3.53	0.70	1.04	1.12	1.08	0.98	0.84	0.66	0.46	0.24
	Type 2	−3.10	1.49	2.18	2.37	2.33	2.16	1.88	1.52	1.09	0.58
	Total	−6.62	2.19	3.22	3.49	3.42	3.14	2.72	2.19	1.35	0.83

TABLE 2

RISK CALCULATIONS FOR SOME INDIVIDUALS SHOWN IN FIGURE 1

INDIVIDUAL	PROBABILITY OF BEING A CARRIER USING:			
	Affection status	Affection and CK	Affection and test locus	COMBINED DATA
5	.333	.497	.459	.680
10	.167	.153	.069	.050
22	.500	.995	.150	.975
24	.500	.987	.850	.998

Five replicates were generated for both pedigrees studied, using an assignment of DMD genotypes in agreement with the observed data (examples shown in fig. 1). DMD genotypes were thereafter assumed unknown, and lod scores were computed with and without creatine kinase. Results are presented in figure 1 and table 1. While a maximum lod score of 1.12 is obtained at $\theta = .25$ without creatine kinase, its inclusion leads to a maximum of 3.49 at the true value $\theta = .15$. This illustrates the substantial information that may be provided by a quantitative indicator of liability in certain families.

Genotype risks for certain individuals in the pedigrees of figure 1 are given in table 2. Individual 5 has probabilities of being a carrier of .33 based on affection status alone, .459 based on affection status and test locus information, and .497 based on affection status and creatine kinase. When all the information is considered simultaneously, her probability of being a carrier is .680. For individuals 10 or 24, the risk estimate is primarily determined either by the test locus or by creatine kinase alone. Individual 22 is of special interest, as she is a recombinant. With information on test locus alone, she has a risk of .150 of being a carrier; creatine kinase alone or in combination with the test locus leads to a risk estimate of .98 or greater.

DISCUSSION

The computer program LINKAGE is suitable for a wide range of applications in linkage studies and genetic counseling. It can be easily implemented on a variety of computing systems including personal computers. It is available with documentation, and will be distributed on magnetic tape in standard ASCII format or on 8-inch DEC-compatible floppy disks.

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NOTE ADDED IN PROOF: The program LINKAGE has been extended for multipoint linkage analysis and risk calculations. This version will be available from the authors at the time this paper appears.

REFERENCES

1. FISHER RA: The use of simultaneous estimation in the evaluation of linkage. *Ann Eugen (Lond)* 6:71–76, 1934

2. FINNEY DJ: The detection of linkage. *Ann Eugen (Lond)* 10:171–214, 1940
3. HALDANE JBS, SMITH CAB: A new estimate of the linkage between the genes for haemophilia and colour-blindness in man. *Ann Eugen (Lond)* 14:10–31, 1947
4. SMITH CAB: The detection of linkage in human genetics. *J R Stat Soc B* 15:153–184, 1953
5. MORTON NE: Sequential tests for the detection of linkage. *Am J Hum Genet* 7:277–318, 1955
6. MAYNARD-SMITH S, PENROSE LS, SMITH CAB: *Mathematical Tables for Research Work in Human Genetics*. London, G. and A. Churchill, 1961
7. OTT J: Estimation of the recombination fraction in human pedigrees: efficient computation of the likelihood for human linkage studies. *Am J Hum Genet* 26:588–597, 1974
8. HASSTEDT S, CARTWRIGHT P: PAP: Pedigree analysis package, Computing Technical Report 13, Dept. of Medical Biophysics and Computing, Univ. of Utah, Salt Lake City, 1979
9. KAPLAN EB, ELSTON RC: GENPED: A general pedigree analysis package. Unpublished program write-up, 1975
10. MORTON NE, LALOUEL JM: Resolution of linkage for irregular phenotype systems. *Hum Hered* 31:3–7, 1981
11. VOGEL F, MOTULSKY A: *Human Genetics: Problems and Approaches*. Berlin, Springer-Verlag, 1981
12. BOTSTEIN D, WHITE RL, SKOLNICK M, DAVIS RW: Construction of a genetic linkage map in man using restriction fragment length polymorphisms. *Am J Hum Genet* 32:314–331, 1980
13. COTTERMAN CW: Regular two allele and three allele phenotype systems. Part 1. *Am J Hum Genet* 5:193–235, 1953
14. ELSTON RC, STEWART J: A general model for the genetic analysis of pedigree data. *Hum Hered* 21:523–542, 1971
15. CANNINGS C, THOMPSON EA, SKOLNICK MH: Probability functions on complex pedigrees. *Adv Appl Prob* 10:26–61, 1978
16. LANGE K, ELSTON RC: Extensions to pedigree analysis. I. Likelihood calculations for simple and complex pedigrees. *Hum Hered* 25:95–105, 1975
17. MURRAY JM, DAVIES KE, HARPER PS, MEREDITH L, MUELLER CR, WILLIAMSON R: Linkage relationship of a cloned DNA sequence on the short arm of the X chromosome to Duchenne muscular dystrophy. *Nature* 300:69–71, 1982
18. MORTON NE, LALOUEL JM: Genetic counselling in sex linkage. *Birth Defects: Orig Art Ser* XV:9–24, 1979