MULTIPOINT MAPPING OF LINKAGE GROUP I

by

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a Thesis

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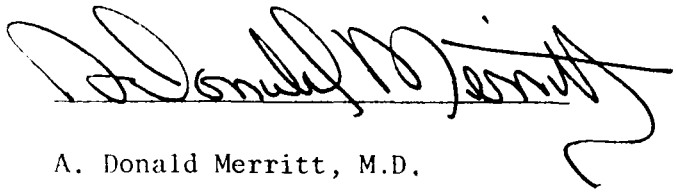

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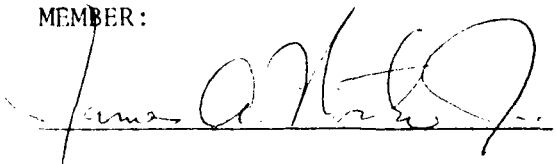

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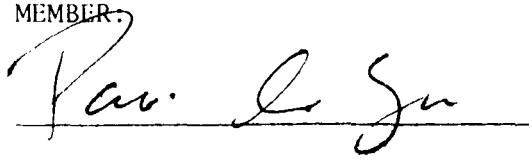

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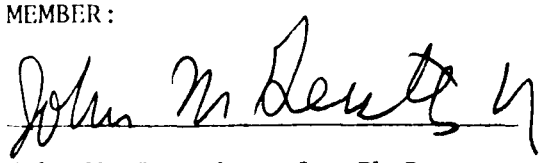

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ABSTRACT

The directional and linear order, with corresponding map distances, have been defined for loci on chromosome 1 (linkage group I) in man. A general method of linkage analysis was developed which permits the evaluation of data from three or four loci without assuming a mapping function or a prior probability of linkage.

The method of maximum likelihood was used to analyze data from the families of individuals who are doubly, triply or quadruply heterozygous for the loci investigated. Likelihood equations were derived for each class of multiple heterozygotes and the resulting functions combined so that maximum likelihood estimates of the parameters could be calculated from the joint likelihoods. Estimates of the recombination fractions between the loci and the level of interference with crossing over in the region of the loci were obtained for the various orders of the three or four loci analyzed simultaneously. The maximum lod score (logarithm of the likelihood ratio) was derived for each order and these lod scores were then compared to one another to give the relative odds of each order.

Extended data were obtained from families, ascertained by the Department of Medical Genetics, Indiana University School of Medicine, who were informative for genetic linkage analysis of the following markers: 1qh (heterochromatic region near the centromere on the long arm of chromosome 1), Fy (Duffy blood group), Amy_1 (salivary amylase), Amy_2 (pancreatic amylase), PGM_1 (phosphoglucomutase$_1$), Rh (Rhesus blood group) and PGD (phosphogluconate dehydrogenase).

Analysis of these data began with the calculations of the 2-point lod scores with the maximum likelihood estimate of the recombination fraction for each pair of loci from informative males, females and combined sex data. The 2-point data were then combined with data from triply and quadruply heterozygous parents for multipoint analyses. The lqh, Fy and Amy (Amy_1/Amy_2) loci and the PGM_1, Rh and PGD loci were analyzed by the 3-point method and the groups of loci, lqh, Fy, Amy, PGM_1; Amy, PGM_1, Rh, PGD; lqh, Amy, PGM_1, Rh were analyzed by the 4-point method.

All the 2-point and multipoint analyses were consistent with the order Fy-lqh-Amy-PGM_1-Rh-PGD being most likely. The estimates of the frequency of recombination were larger when the informative parent was female when compared with data derived from informative males in both 2-point and multipoint analyses, with the exception of the lqh:Fy linkage, where the recombination fraction was approximately equal. Closer linkage in males has been repeatedly observed, but only in PGM_1:Rh and now in lqh:Amy and Fy:Amy are the differences in recombination statistically significant ($P < 0.05$). The analyses have resulted in the first linkage map in man, based on family data, in which the most likely order of groups of three or four loci is significantly different (relative odds 20:1) from other orders.

The general method for linkage analysis that has been developed can be applied to the investigation of other linkage groups in man. The refined map of chromosome 1 presented and the methodology derived in this thesis will simplify the task of assigning additional markers and heritable disorders to this autosome.

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