A search for linkage in cystic fibrosis

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Summary. Linkage between the locus for cystic fibrosis and other genetic markers was explored in 40 families from Birmingham and 20 from Manchester. No strong evidence was found for linkage with any of the markers examined. There was evidence against close linkage with ABO, HLA, and Rh.

Cystic fibrosis, known originally as cystic fibrosis of the pancreas, is the commonest recessive lethal disease in most Caucasian populations. Death usually results from chronic lung disease, and few cases survive beyond young adulthood. In addition, fertility is greatly impaired in the male and probably impaired in the female. The basic defect is unknown and the evidence for its recessive nature is based entirely on its incidence in sibs (Carter, 1952), in other relatives also (Danks, Allan, and Anderson, 1965), and on its varied incidence in different racial groups, even when living in the same community (Wright and Morton, 1968).

Linkage between two loci means that they are sited on the same chromosome. Establishment of a linkage between the locus, or one of the loci, for cystic fibrosis, and a locus determining some other phenotype, would provide information for chromosome mapping. Such data could indicate also whether cystic fibrosis is determined at one locus or at several loci; in addition, definition of the position of a locus close to a cystic fibrosis locus could permit prenatal diagnosis in some families.

A previous linkage study in cystic fibrosis (Steinberg et al, 1956; Steinberg and Morton, 1956), did not reveal strong evidence for linkage between cystic fibrosis and any of the eight blood group loci; however, Steinberg et al (1956) stated that 'the data for the P locus indicate that it may be profitably tested further'.

The present work concerns an attempt to define a locus for cystic fibrosis by means of a linkage study which included other markers, including the normal chromosomal variants often evident with modern staining techniques.

Patients and methods

This study was based on the families of 40 cystic fibrosis children attending clinics at the Birmingham Children's Hospital and of 20 more cystic fibrosis children attending clinics at the Royal Manchester Children's Hospital, West Park Hospital Macclesfield, and the Blackburn Royal Infirmary. Each family included at least two children, of which at least one was affected, and two parents. Whenever possible grandparents were included.

A linkage study involving a recessive condition, such as cystic fibrosis, gives limited information if the heterozygous grandparent and sib cannot be identified. Unfortunately, so far, there is no reliable method for the detection of the carrier in cystic fibrosis.

Blood samples were taken, with parental permission, into lithium heparin tubes. In Birmingham, lymphocyte separations for HLA typing were made using a Ficoll–Triosil density gradient technique, cell samples were washed to remove platelets, and typing was carried out in Falcon plastic trays using a modification of the technique of Terasaki and McClelland (1964). In Manchester, samples were taken into Boots' preservative-free heparin and typed on Searle glass plates. At both centres, tests included six specificities at the first locus and eight at the second. This was sufficient for haplotyping all these families.

Lods, an acronym for 'logarithms of the odds ratios', provide a simple additive measure of the evidence for linkage at any defined recombination fraction (θ). Values within the range $-1.0$ to $+2.0$ give very limited evidence either against or for linkage at any defined value of θ. Lods were computed by a generalization of Morton's method (Morton, 1955; Edwards, 1972; Chautard-Freire-Maia, 1974). Data published previously from

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Boston by Steinberg et al (1956) were analysed using our computer programme, as were data from eight families from Leeds, kindly supplied by Dr M. d'A. Crawford. Data from the latter families were examined for linkage with P, but on analysis the lods from these families almost cancelled out, providing virtually no information (lods $-0.01$ at both $\theta=0.1$ and $\theta=0.3$).

**Results**

Total lods for the informative families from Birmingham and Manchester are shown together in Table I, and lods derived from the published data of Steinberg et al (1956) in Table II. Total lods from all sources are given in Table III. There is no strong evidence for close linkage between the loci for CF and any of the markers examined.

Chromosomal banding (illustrated in detail for chromosome six in Family W., Fig. 1) was uninformative due to a failure to detect any clearly segregating marker chromosomes in any of the 14 families studied. Particular attention was paid to chromosome 6, since the first analyses of our data were suggestive of linkage of cystic fibrosis to both HLA and P, and there is evidence that the HLA and P loci are linked (Fellous et al., 1971).

**Discussion**

The position of the locus, or if several, the major locus, carrying the allele or alleles determining cystic fibrosis remains unknown. Information provided in this study gives no strong evidence for
linkage with any of the markers investigated. Nevertheless, the fairly high negative lods for ABO and cystic fibrosis (−4.22, \(\theta = 0.1\), Table III), for HLA and cystic fibrosis (−2.73, \(\theta = 0.1\), Table III) and for Rh cystic fibrosis (−4.14, \(\theta = 0.1\), Table III) exclude close linkages. The lods for linkage between P and cystic fibrosis were positive in the data of Steinberg et al (1956) and in our data at \(\theta = 0.3\). However the total lod for linkage with P of 0.22 at \(\theta = 0.3\) (Table III) is very weak evidence for loose linkage between P and cystic fibrosis. The P locus is probably on chromosome 6 (Fellous et al, 1971), though not near to the HLA locus (Edwards et al, 1972; Lamm et al, 1975).

The absence of any strong evidence of linkage in a study of 60 families with a recessive disorder is hardly surprising, since the chance of the locus being sufficiently close to any of the markers tested is small, and probably less than 1 in a 100. Though many recessive disorders may be the result of the locus being lost by a chromosomal deficiency, the likelihood of such a deficiency being within the range of optical microscopy is low. The chromosomal studies on parents probably exclude any deficiency of more than half a band or interband width. Very close linkage between a major cystic fibrosis locus and HLA had been excluded already by absence of association (Polymenidis, Ludwig, and Götz, 1973; Goodchild, Nelson, and Anderson, 1973).

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REFERENCES


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