Linkage analysis in dominant acrocephalosyndactyly¹

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SUMMARY Linkage analysis was performed on a previously reported family in which multiple dominantly inherited acrocephalosyndactyly syndromes were present. An underlying axiom of linkage analysis is that the trait analysed be monogenic. This prerequisite was presumptively established in the single kindred analysed because acrocephalosyndactyly was observed in multiple cases in multiple generations.

The acrocephalosyndactylies (ACS) are a clinically similar group of disorders manifesting premature craniosynostosis and varying degrees of brachydactyly and syndactyly (McKusick, 1975; Gorlin *et al.*, 1976). McKusick (1975) most recently listed 4 types of ACS, Pfeiffer, Apert, Chotzen, and Vogt, all of which are dominantly inherited. The distinctness of these categories has, however, been questioned by 2 lines of evidence. Firstly, it has been suggested (Degenhardt, 1950) that Pfeiffer and Apert syndromes involve the same gene defect based upon close clinical similarity. That this is a viable possibility is shown by Escobar and Bixler (1977a,b), who documented Apert, Pfeiffer, and transitional phenotypes in multiple generations of a single family. Additionally, 2 other families have been reported in which multiple ACS types have been found in the same family (Robinow and Sorauf 1975; Jackson *et al.*, 1976). Secondly, Escobar and Bixler (1977a) have recently reported a unique metacarpophalangeal pattern profile which discriminates 2 ACS types (Pfeiffer and Chotzen) from normal individuals, but not from each other.

Although most investigators consider the dominantly inherited ACS syndromes to be the result of different (though possibly allelic) genes, the above evidence raises a second possibility; this being that the multiple ACS phenotypes are the result of a single gene with a highly variable expression. This hypothesis is testable by performing linkage analysis on informative families, that is, those previously mentioned which show multiple ACS types segregating within a single kindred. This paper gives the results of such an

analysis performed on the family previously characterised both phenotypically and radiographically by Escobar and Bixler (1977a,b).

Methods and materials

The family involved in this analysis (Fig. 1) was ascertained in the Department of Medical Genetics through a proband diagnosed as having Pfeiffer syndrome. Detailed phenotypic findings for each family member have been previously published (Escobar and Bixler, 1977b).

The marker loci employed in this analysis included 7 blood groups: ABO, Rhesus, MNSs, Kidd, Kell, Duffy, and P traits. Three other traits were haptoglobin, determined from serum, and the red blood cell enzymes phosphoglucomutase and acid phosphatase.

Computation of the likelihood and lod scores for various recombination fractions was done for each of programme (Ott, 1974). This programme computes the likelihood of linkage recursively, as proposed by Elston and Stewart (1971), starting with the more recent generation and working back into the pedigree.

Results

The lod scores for various recombination fractions are given in the Table for each locus analysed.

Discussion

The results shown in the Table indicate that the hypothesised single gene resulting in the dominantly

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