

## Cystic fibrosis: progress in mapping the disease locus using polymorphic DNA markers. I.

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The conventional approach to the identification of the affected genes in inherited diseases is through the demonstration of specific biochemical abnormalities in patients, their tissues, or cells. This approach has, unfortunately, been unsuccessful in the case of cystic fibrosis (CF), the most common severe autosomal recessive disorder in Caucasians (reviewed in Talamo et al, 1983). An alternative approach is to locate the CF gene by linkage studies with chromosomal markers. We report here our results of testing 39 DNA restriction fragment length polymorphic (RFLP) markers using a panel of 45 two-generation Canadian families each with two or more affected children. The probability of linkage between each marker and CF was analyzed by the lod score method (Morton, 1955) using the LIPED program (Ott, 1973) on a VAX minicomputer. The results of these analyses show that none of the markers tested is closely linked to the disease locus. Furthermore, using a lod score of  $-2$  as criterion for no linkage, these and other published data (Steinberg and Morton, 1956; Steinberg et al, 1956; Goodchild et al, 1976; Scambler et al, 1985; Tsui et al, 1985) have allowed us to eliminate approximately 25% of the human genome as being the site of the CF gene.

We wish to thank those individuals (see table I) who provided the DNA probes for this study. Part of this work has been presented in recent meetings (Tsui et al, 1984a, b).

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Table I. Linkage information for DNA markers tested

Probe (gene/locus)	Chromosome location	Number of families <sup>a</sup>			Lod scores (at $\theta$ value of ) <sup>b</sup>			
		total	info	n-inf	0.01	0.05	0.10	0.15
N8C6 ( <i><math>\beta</math>NGF</i> )	1pter-p21	44	27	17	-18.838	-6.813	-2.661	-0.871
pAT1.2 ( <i>AT3</i> )	1q23	40	24	16	-15.941	-6.253	-2.771	-1.189
renin ( <i>REN</i> )	1p21-qter	22	12	10	-7.385	-3.982	-1.898	-0.938
p5G1 ( <i><math>\gamma</math>-crystallin</i> )	2q33-q35	16	13	3	-12.777	-5.125	-2.439	-1.244
HS3 ( <i>D3S1</i> )	3q12	14	5	9	-5.273	-2.590	-1.530	-0.973
22/13	3q12	42	26	16	-17.029	-9.453	-5.238	-3.139
pDL27A	(?)	8	5	3	-7.012	-3.606	-2.219	-1.462
G8 ( <i>D4S10</i> )	4p16	21	14	7	-9.367	-4.124	-2.159	-1.203
G9 ( <i>D4S2</i> )	4p	15	12	3	-9.377	-4.174	-2.261	-1.348
pHM6 ( <i>MTII<math>\psi</math></i> )	4p11-q21	39	29	10	-17.488	-6.720	-2.986	-1.346
HD1 ( <i>D5S1</i> )	5	11	8	3	-7.686	-3.686	-2.129	-1.325
pHPT30 ( <i>HPRT<math>\psi</math></i> )	5	23	9	14	-3.931	-0.907	0.021	0.344
pAS1 ( <i>AASP3</i> )	9q11-q12	14	8	6	-9.450	-4.246	-2.325	-1.399
p5-1 ( <i>D10S1</i> )	10	26	14	12	-7.078	-2.493	-0.888	-0.210
pKAT1 ( <i>CAT</i> )	11p13	43	30	13	-12.109	-4.091	-1.489	-0.461
CosHColl ( <i>COLL</i> )	12	23	11	12	-6.596	-2.758	-1.395	-0.774
pDL32B	12q14.3-qter	17	14	3	-13.510	-5.697	-2.817	-1.447
p12-16 ( <i>D12S2</i> )	12q14-q22	12	6	6	-9.720	-4.963	-3.044	-2.011
7F12 ( <i>D13S1</i> )	13q12	12	12	0	-12.240	-5.614	-3.073	-1.796
pHU26 ( <i>D13S7</i> )	13q22	22	7	15	-5.775	-2.531	-1.337	-0.761
9D11 ( <i>D13S2</i> )	13q22	38	24	14	-13.085	-4.373	-1.475	-0.295
1E8 ( <i>D13S4</i> )	13q22	21	13	8	-8.696	-3.583	-1.768	-0.940
pHUB8 ( <i>D13S5</i> )	13q22	17	8	9	-3.330	-1.391	-0.687	-0.358
9A7 ( <i>D13S3</i> )	13q33-q34	18	10	8	-7.959	-3.381	-1.683	-0.874
pAT4.6 ( <i>PI</i> )	14q24.3-q32.31	17	12	5	-13.005	-5.824	-3.151	-1.848
pAW101 ( <i>D14S1</i> )	14q31.1-q32.2	31	30	1	-30.433	-11.283	-4.557	-1.602
$\gamma$ -constant ( <i>IGHC</i> )	14q32.3-qter	19	18	1	-8.791	-3.063	-1.070	-0.210
$\mu$ -switch ( <i>IGHC</i> )	14q32.3-qter	15	13	2	-10.606	-4.172	-1.867	-0.820
DOSLC-3 ( <i>D15S1</i> )	15	19	10	9	-8.574	-3.956	-2.208	-1.339
DOSLC-4 ( <i>D17S1</i> )	17pter-p13	24	13	11	-7.610	-3.126	-1.526	-0.791
pDL27B	17cen	22	13	9	-11.545	-4.976	-2.517	-1.323
DOSLC-6 ( <i>D18S1</i> )	18	40	30	10	-17.892	-6.583	-2.747	-1.131
pRI2.21	20p12	18	12	6	-17.193	-8.328	-4.820	-3.000
DOSLC-2 ( <i>D20S4</i> )	20	27	20	7	-12.843	-5.654	-2.980	-1.688
D2054	20	23	13	10	-4.287	-1.169	-0.133	0.273
22/25	21	33	25	8	-12.752	-5.001	-2.203	-0.918
DOSLC-8 ( <i>D22S1</i> )	22pter-q13	33	24	9	-12.631	-4.983	-2.293	-1.087
22/34	22q11	33	25	8	-19.743	-8.763	-4.753	-2.830
sis ( <i>SIS</i> )	22	13	6	7	-5.962	-2.741	-1.564	-0.989

<sup>a</sup> total: total number of families screened, info: informative matings, n-inf: non-informative matings

<sup>b</sup> lod:  $\log_{10}$  of odds favoring linkage at given recombination distance ( $\theta$ ) versus no linkage

			Source of probe
0.20	0.25	0.30	
-0.030	0.316	0.384	Ullrioh A
-0.385	0.003	0.147	Orkin S
-0.432	-0.167	-0.041	Chirgwin J
-0.636	-0.319	-0.153	this laboratory
-0.625	-0.391	-0.231	Gusella J
-1.898	-1.119	-0.623	White B
-0.969	-0.625	-0.379	this laboratory
-0.662	-0.346	-0.166	Gusella J
-0.830	-0.511	-0.301	Gusella J
-0.524	-0.114	0.067	this laboratory
-0.833	-0.511	-0.296	Gusella J
0.433	0.408	0.325	Caskey T
-0.866	-0.533	-0.314	Beaudet A
0.090	0.195	0.192	Dryja T
-0.030	0.125	0.014	Gravel R
-0.443	-0.253	-0.140	Driesel A
-0.698	-0.286	-0.077	this laboratory
-1.342	-0.873	-0.535	Balazs I
-1.043	-0.579	-0.297	Cavenee W
-0.433	-0.236	-0.118	Dryja T
0.207	0.372	0.359	Cavenee W
-0.499	-0.256	-0.122	Cavenee W
-0.181	-0.084	-0.034	Dryja T
-0.432	-0.189	-0.065	Cavenee W
-1.095	-0.634	-0.348	Woo SLC
-0.182	0.426	0.569	White R
0.184	0.328	0.325	Ellison J
-0.288	-0.030	0.069	Early P
-0.824	-0.497	-0.284	White R
-0.400	-0.187	-0.076	White R
0.657	-0.278	-0.081	this laboratory
0.377	-0.043	0.075	White R
1.884	-1.153	-0.666	White B
0.958	-0.527	-0.273	White R
0.425	0.442	0.384	White B
0.254	0.072	0.193	White B
-0.470	-0.154	-0.010	White R
-1.725	-1.040	-0.597	White B
0.644	-0.413	-0.251	

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\* Nomenclature as cited in Human Gene Mapping 7 (1984): Seventh International Workshop on Human Gene Mapping. Cytogenet Cell Genet 37:380-392 (1984).