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# 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 Causasions (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; Goodschild 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.

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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[a] | | | Lod scores (at θ value of )[b] | | | |
|---|---|---|---|---|---|---|---|---|
| | | total | info | n-inf | 0.01 | 0.05 | 0.10 | 0.15 |
| N8C6 *(βNGF)* | 1pter-p21 | 44 | 27 | 17 | −18.838 | −6.813 | −2.661 | −0.871 |
| pAT1.2 *(AT3)* | 1q23 | 40 | 24 | 16 | −15.941 | −6.253 | −2.771 | −1.189 |
| renin *(REN)* | 1p21-qter | 22 | 12 | 10 | − 7.385 | −3.982 | −1.898 | −0.938 |
| p5G1 *(γ-crystallin)* | 2q33-q35 | 16 | 13 | 3 | −12.777 | −5.125 | −2.439 | −1.244 |
| HS3 *(D3S1)* | 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 *(D4S10)* | 4p16 | 21 | 14 | 7 | − 9.367 | −4.124 | −2.159 | −1.203 |
| G9 *(D4S2)* | 4p | 15 | 12 | 3 | − 9.377 | −4.174 | −2.261 | −1.348 |
| pHM6 *(MTIIψ)* | 4p11-q21 | 39 | 29 | 10 | −17.488 | −6.720 | −2.986 | −1.346 |
| HD1 *(D5S1)* | 5 | 11 | 8 | 3 | − 7.686 | −3.686 | −2.129 | −1.325 |
| pHPT30 *(HPRTψ)* | 5 | 23 | 9 | 14 | − 3.931 | −0.907 | 0.021 | 0.344 |
| pAS1 *(AASP3)* | 9q11-q12 | 14 | 8 | 6 | − 9.450 | −4.246 | −2.325 | −1.399 |
| p5-1 *(D10S1)* | 10 | 26 | 14 | 12 | − 7.078 | −2.493 | −0.888 | −0.210 |
| pKAT1 *(CAT)* | 11p13 | 43 | 30 | 13 | −12.109 | −4.091 | −1.489 | −0.461 |
| CosHCol1 *(COLL)* | 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 *(D12S2)* | 12q14-q22 | 12 | 6 | 6 | − 9.720 | −4.963 | −3.044 | −2.011 |
| 7F12 *(D13S1)* | 13q12 | 12 | 12 | 0 | −12.240 | −5.614 | −3.073 | −1.796 |
| pHU26 *(D13S7)* | 13q22 | 22 | 7 | 15 | − 5.775 | −2.531 | −1.337 | −0.761 |
| 9D11 *(D13S2)* | 13q22 | 38 | 24 | 14 | −13.085 | −4.373 | −1.475 | −0.295 |
| 1E8 *(D13S4)* | 13q22 | 21 | 13 | 8 | − 8.696 | −3.583 | −1.768 | −0.940 |
| pHUB8 *(D13S5)* | 13q22 | 17 | 8 | 9 | − 3.330 | −1.391 | −0.687 | −0.358 |
| 9A7 *(D13S3)* | 13q33-q34 | 18 | 10 | 8 | − 7.959 | −3.381 | −1.683 | −0.874 |
| pAT4.6 *(P1)* | 14q24.3-q32.31 | 17 | 12 | 5 | −13.005 | −5.824 | −3.151 | −1.848 |
| pAW101 *(D14S1)* | 14q31.1-q32.2 | 31 | 30 | 1 | −30.433 | −11.283 | −4.557 | −1.602 |
| γ-constant *(IGHC)* | 14q32.3-qter | 19 | 18 | 1 | − 8.791 | −3.063 | −1.070 | −0.210 |
| μ-switch *(IGHC)* | 14q32.3-qter | 15 | 13 | 2 | −10.606 | −4.172 | −1.867 | −0.820 |
| DOSLC-3 *(D15S1)* | 15 | 19 | 10 | 9 | − 8.574 | −3.956 | −2.208 | −1.339 |
| DOSLC-4 *(D17S1)* | 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 *(D18S1)* | 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 *(D20S4)* | 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 *(D22S1)* | 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 *(SIS)* | 22 | 13 | 6 | 7 | − 5.962 | −2.741 | −1.564 | −0.989 |

[a] total: total number of families screened, info: informative matings, n-inf: non-informative matings

[b] lod: $\log_{10}$ of odds favoring linkage at given recombination distance (θ) versus no linkage

| 0.20 | 0.25 | 0.30 | Source of probe |
|---|---|---|---|
| -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 | |

# Author Index

# Subject Index



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