Short communication

DNA markers near the cystic fibrosis locus: further analysis of the British population

Ann Harris

Abstract

Genetic analysis of the CF locus in the British Caucasian population has been extended using six DNA probes detecting nine polymorphic loci. Data are presented on (1) diagnostic usefulness of probes, and (2) allele frequencies for each probe in this population. For the probes pXV2C and KM19 (those closest to the CF locus) allele frequencies are further subdivided into male and female derived chromosomes 7. The allele frequencies for both probes on non-CF bearing chromosomes 7, but not on CF carrying chromosomes 7, are substantially different in males and females. Combined haplotypes for pXV2C and KM19 show that, as has been observed in other northern European populations, almost 90% of CF chromosomes in this population carry the pXV2C/KM19, 1/2 (2.1 kb/6.6 kb) haplotype.

Paediatric Research Unit, Division of Medical and Molecular Genetics, United Medical and Dental Schools of Guy's and St Thomas's Hospitals, 8th Floor, Guy's Tower, London SE1 9RT.
A Harris

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DNA typing studies using markers linked to CF have been carried out on 77 families, including three pairs of related families, from the British Caucasian population. The probes used include KM19 (*Pst*I polymorphism¹); pXV2C (*Taq*I polymorphism²); Met D (*Ban*I and *Taq*I polymorphisms³); Met H (*Msp*I and *Taq*I polymorphisms³); pJ3.11 (*Msp*I and *Taq*I polymorphisms⁴); and 7C22 (*Eco*RI polymorphism⁵). These probes carry error risks owing to possible recombination events of less than 1% for KM19 and pXV2C, 1.2% for pJ3.11, 1.6% for the Met probes, and 5.0% for 7C22.

The probe data and allele frequencies on all families, except those referred, in the absence of a living, affected index case, for pXV2C/KM19 haplotyping, are shown in tables 1 and 2. Six families remain only partially informative with one parent being homozygous for all the markers available. Table 1 shows that the KM19 *Pst*I and Met D *Ban*I polymorphisms are the most useful in terms of numbers of families with both parents heterozygous. However, since the pXV2C polymorphism lies substantially closer to the CF locus than does the Met D polymorphism, its use in first round polymorphism screening of new families is indicated.

Of particular interest in table 2 is the section showing KM19 and pXV2C allele frequencies for CF and normal chromosomes in males and females,

Table 1 Usefulness of probes.

Probe and polymorphism	No of families			
	Both parents heterozygous	Only mother heterozygous	Only father heterozygous	Neither parent heterozygous
KM19 <i>Pst</i> I	31	8	15	3
pXV2C <i>Taq</i> I	6	16	23	14
Met D <i>Ban</i> I	12	13	15	16
<i>Taq</i> I	1	12	10	23
Met H <i>Taq</i> I	5	12	13	19
<i>Msp</i> I	6	13	11	17
pJ3.11 <i>Msp</i> I	8	12	10	19
<i>Taq</i> I	0	4	1	28
7C22 <i>Eco</i> RI	1	8	13	19

The first 37 families analysed⁶ were typed with all available probes. The rest of the families were typed with KM19 and pXV2C, the majority with Met D *Ban*I and then only with other probes if they remained partially informative or uninformative.

Table 2 Summary of probes used and allele frequencies observed. (Allele numbers are assigned on the basis of decreasing band size, the largest being 1).

				Allele frequencies					
Probe	Enzyme	Alleles	Size (kb)	Published reports	This study		No of subjects		
					CF chromosome	Normal chromosome			
Met D	<i>BanI</i>	1	7.6	—	0.58	0.47	110		
		2	6.8	—	0.42	0.53			
Met D	<i>TaqI</i>	1	6.0	0.55*	0.77	0.22	82		
		2	4.5	0.45*	0.23	0.77			
Met H	<i>TaqI</i>	1	7.5	0.55*	0.69	0.59	86		
		2	4.0	0.45*	0.31	0.41			
Met H	<i>MspI</i>	1	5.0	0.05*	0	0	86		
		2	2.3	0.50*	0.69	0.56			
		3	1.8	0.45*	0.31	0.44	90		
pJ3.11	<i>MspI</i>	1	4.2	0.32 ¹⁰	0.46	0.31			
		2	1.8	0.68 ¹⁰	0.54	0.69	74		
pJ3.11	<i>TaqI</i>	1	6.0	0.97 ¹⁰	0.97	0.95			
		2	3.2	0.03 ¹⁰	0.03	0.05	74		
7C22	<i>EcoRI</i>	1	7.5	0.76 ⁵	0.73	0.66			
		2	5.1	0.24 ⁵	0.27	0.34	74		
KM19	<i>PstI</i>	1	7.8	CF chromosome	Normal chromosome				
		2	6.6	0.10 ^{1 2}	0.73 ^{1 2}	0.07	0.73	128	
pXV2C	<i>TaqI</i>	1	2.1	0.90 ^{1 2}	0.27 ^{1 2}	0.93	0.27		
		1	2.1	0.88 ^{1 2}	0.48 ^{1 2}	0.90	0.56	120	
		2	1.4	0.12 ^{1 2}	0.52 ^{1 2}	0.10	0.44		
KM19	<i>PstI</i>	1	7.8	—	—	M	F	M	F
		2	6.6	—	—	0.05	0.10	0.78	0.69
pXV2C	<i>TaqI</i>	1	2.1	—	—	0.95	0.90	0.22	0.31
		1	2.1	—	—	0.88	0.92	0.45	0.67
		2	1.4	—	—	0.12	0.08	0.55	0.33
									60 F

*G van de Woude, personal communication.

These data include partial analysis of 37 families with the first seven polymorphisms listed.⁶ The KM19 and pXV2C data are entirely new.

which show differences. Statistical analysis of these data (χ^2 test) showed that only the pXV2C allele frequencies on the female normal chromosomes 7 show significant deviation from the expected population frequencies ($p < 0.01$ for allele 1 and $p < 0.001$ for allele 2). It is unclear why this should be so, though it is unlikely to have bearing on the previously reported unusual segregation of CF alleles.⁷ Combined haplotypes for KM19 and pXV2C are shown in table 3. As has been observed in certain other northern European Caucasian populations,^{2 8 9} the pXV2C allele 1 (2.1 kb) in combination with the KM19 allele 2 (6.6 kb) occurs on nearly 90% of CF bearing chromosomes and approximately six times more often

on a chromosome 7 carrying the CF mutation than on an equivalent non-mutation bearing chromosome 7.

From the accumulated data on pXV2C/KM19 haplotypes in CF Caucasian populations it would appear valid to use these data (1) to modify the risks of carrier status in subjects from families known to be segregating the CF gene but with no living affected index case, and (2) in prenatal diagnosis for pregnancies at a 1 in 4 risk of CF, but no living index case.

The recent cloning of the CF gene¹¹⁻¹³ and data suggesting that the majority of CF patients carry the same mutation fits well with the pXV2C/KM19 haplotype figures. It is probable that subjects with rare pXV2C/KM19 haplotypes or unusual forms of the disease have different mutations in the CF gene.

Table 3 Cystic fibrosis haplotype analysis for carrier testing.

Haplotype	CF	Normal	Total
pXV2C/KM19			
1/1	3	40	43
(2.1/7.8)	(2.8%)	(37.0%)	
1/2	97	16	113
(2.1/6.6)	(89.8%)	(14.8%)	
2/1	4	35	39
(1.4/7.8)	(3.7%)	(32.4%)	
2/2	4	17	21
(1.4/6.6)	(3.7%)	(15.8%)	
Total	108	108	

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