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Familial Mediterranean Fever (FMF) in Moroccan Jews: Demonstration of a Founder Effect by Extended Haplotype Analysis

Ivona Aksentijevich,* Elon Pras,* Luis Gruberg,† Yang Shen,§ Katherine Holman,§ Sharon Helling,* Leandrea Prosen,* Grant R. Sutherland,§ Robert I. Richards,§ Michael Dean,‖ Mordechai Pras,‡ and Daniel L. Kastner*

*Arthritis and Rheumatism Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda; †Department of Medicine F and ‡Heller Institute for Medical Research, Sheba Medical Center, Tel-Hashomer, Israel; §Department of Cytogenetics and Molecular Genetics, Adelaide Children's Hospital, North Adelaide, South Australia; ‖Laboratory of Viral Carcinogenesis, National Cancer Institute, Frederick Cancer Research and Development Center, Frederick, MD

Summary

Familial Mediterranean fever (FMF) is an autosomal recessive disease causing attacks of fever and serositis. The FMF gene (designated "*MEF*") is on 16p, with the gene order *16cen-D16S80-MEF-D16S94-D16S283-D16S291-16pter.* Here we report the association of FMF susceptibility with alleles at *D16S94, D16S283,* and *D16S291* among 31 non-Ashkenazi Jewish families (14 Moroccan, 17 non-Moroccan). We observed highly significant associations at *D16S283* and *D16S291* among the Moroccan families. For the non-Moroccans, only the allelic association at *D16S94* approached statistical significance. Haplotype analysis showed that 18/25 Moroccan FMF chromosomes, versus 0/21 noncarrier chromosomes, bore a specific haplotype for *D16S94-D16S283-D16S291.* Among non-Moroccans this haplotype was present in 6/26 FMF chromosomes versus 1/28 controls. Both groups of families are largely descended from Jews who fled the Spanish Inquisition. The strong haplotype association seen among the Moroccans is most likely a founder effect, given the recent origin and genetic isolation of the Moroccan Jewish community. The lower haplotype frequency among non-Moroccan carriers may reflect differences both in history and in population genetics.

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease of unknown etiology, characterized by recurrent, self-limited attacks of fever with sterile peritonitis, pleurisy, and/or synovitis (Sohar et al. 1967). Patients may also develop systemic amyloidosis. Although the biochemical basis of this disease is unknown, the clinical manifestations of FMF suggest a lesion in a molecule important to the understanding of inflammation in general. We recently mapped the FMF susceptibility gene, designated by the gene symbol "*MEF*" (McAlpine et al. 1991), to chromosome 16p (Pras et al. 1992). Subsequent genetic linkage analysis of 31 non-Ashkenazi Jewish families from Israel placed *MEF* between *D16S80* and *D16S94,* a genetic interval of about 9 cM (Aksentijevich et al., in press). The mapping of *MEF* to chromosome 16p has been confirmed in Armenian families from California (Shohat et al. 1992).

Data associating particular alleles of marker loci with disease-causing mutations are sometimes helpful in the refined localization of a disease gene. Theoretically, there should be an inverse relationship between the degree of allelic association and physical or genetic distance (Hill and Robertson 1968). Allelic associations have focused interest on the appropriate physical map interval for the positional cloning of the genes causing cystic fibrosis (Kerem et al. 1989) and Huntington disease (Huntington's Disease Collaborative Research

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Address for correspondence and reprints: Daniel L. Kastner, M.D., Ph.D., National Institutes of Health, Building 6, Room 112, Bethesda, MD 20892.

Group 1993). Linkage disequilibrium studies have also supported the mapping of the genes causing Friedreich ataxia (Fujita et al. 1990) and myotonic dystrophy (Harley et al. 1991).

In addition, when allelic or haplotype associations are uniquely found in specific subpopulations, this may provide evidence for a founder effect. Examples of this include choroideremia among Finns (Sankila et al. 1987), Friedreich ataxia among Louisiana Acadians (Sirugo et al. 1992) and southern Italians (Pandolfo et al. 1990), myotonic dystrophy among French Canadians (Harley et al. 1991), idiopathic torsion dystonia among Ashkenazi Jews (Ozelius et al. 1992), and cystic fibrosis among Hutterites (Fujiwara et al. 1989).

In the present study we examined allelic associations between FMF and chromosome 16p markers in a panel of 31 non-Ashkenazi Jewish families, in the hope that linkage disequilibrium would help further localize the disease gene within the *D16S80-D16S94* interval. Since a sizable subset of these families (14) had emigrated to Israel from Morocco, we looked for evidence of a founder effect in this separate group.

The possibility of a founder effect among Moroccan Jews appeared reasonable, given the history and genetics of this population. Most of the Moroccan Jewish community is relatively new, having been established by Jews who left Spain and Portugal around the time of the Spanish Inquisition (1492). There have been subsequent population "bottlenecks" due to religious persecution (Roth 1972). Genetically, Moroccan Jews have been relatively isolated. They have a much higher rate of Tay-Sachs disease than do other non-Ashkenazi populations, and mutations seen in Moroccan patients are different from those seen in Ashkenazi Jewish Tay-Sachs patients (Navon and Proia 1991). The Moroccan Jewish community also has a high rate of consanguinity (Sohar et al. 1961), which tends to obscure recombination and thereby extends the detection of founder chromosomes over more generations. The relatively recent origin, genetic isolation, and inbreeding in the Moroccan Jewish population all favor the identification of founder effects.

Subjects and Methods

Families and DNA Samples

Families were recruited from a clinic at the Sheba Medical Center, Tel-Hashomer, Israel. This project was approved by the Human Experimentation Committee at that institution. The study included 31 families with a total of 200 individuals (94 affected). Peripheral blood lymphocytes were immortalized with Epstein-Barr virus, and DNA was extracted by standard techniques. Among the 31 non-Ashkenazi families, 14 were of Moroccan origin (41 affected individuals); 9 were of Libyan, Tunisian, or Egyptian origin (33 affected individuals); 7 were of Iraqi or Kurdish origin (18 affected individuals); and 1 was of Greek origin (2 affected individuals). Our panel included 12 consanguineous families, with seven first-cousin, one half-first-cousin, and two uncle-niece marriages, as well as two marriages where the exact relationship of the partners was unknown.

DNA Markers

The following probes were used for DNA markers flanking the *MEF* candidate region: *D16S84* (CMM65/*Taq*I), *D16S80* (24-1/*Taq*I), and *D16S82* (41-1/*Sac*I) as RFLP markers; and *D16S291* (16AC2.5), *D16S283* (SM7), and *D16S94* (VK5) as PCR markers. The latter three were typed as 8-allele, 11-allele, and 6-allele polymorphisms, respectively. In our study population we observed 44 haplotypes derived from these three loci.

DNA analysis by Southern blotting was performed by conventional procedures (Pras et al. 1992). PCR typing was done by using the published primers (Harris et al. 1991; Callen et al. 1992; Thompson et al. 1992), and reaction conditions were as described elsewhere (Aksentijevich et al., in press).

Statistical Analysis

For each pedigree, we identified the parental alleles associated with disease susceptibility. For the 12 consanguineous marriages in the panel (see above), *MEF* and the associated chromosomal region usually appeared to be derived from a single ancestral chromosome. In these cases the disease-associated allele was counted only once. Control allele distributions were drawn from the noncarrier chromosomes in the same families. Haplotypes were derived so as to minimize recombinants.

To evaluate linkage disequilibrium, the Yule association coefficient was calculated according to the formula

$$|A| = |(ad-bc)/(ad+bc)| ,$$

where a is the number of noncarrier chromosomes with allele A, b is the number of FMF chromosomes with allele A, c is the number of noncarrier chromosomes with allele B, and d is the number of FMF chromo-

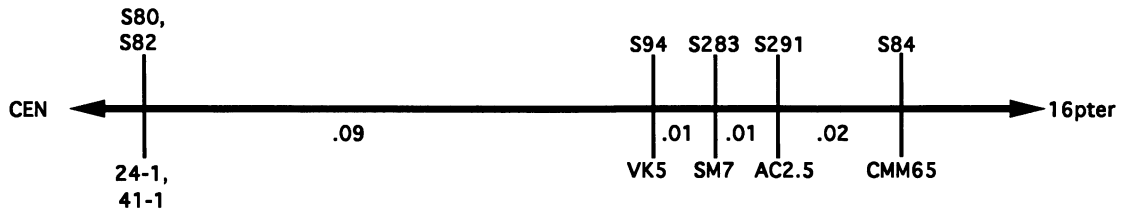

Figure 1 Genetic map of the relevant region of chromosome 16p, showing the markers used in this study. Sex-averaged recombination frequencies are taken from published sources (Breuning et al. 1990; Reeders et al. 1991) and from our own data.

somes with allele B. The SD of the Yule coefficient was estimated according to Bishop et al. (1975). For multiallelic loci, the Yule coefficient was calculated for the allele that was overrepresented on FMF chromosomes, compared with all other alleles combined.

A χ^2 test of the null hypothesis of no linkage disequilibrium was calculated for biallelic loci, with 1 df. The Yates correction was used where appropriate.

For multiallelic loci, two different χ^2 statistics were calculated. In the "combined allele" method, the allele that was overrepresented among FMF chromosomes was defined as one allele, and all of the other alleles were combined to form a second allele. A standard χ^2 statistic was then calculated, with 1 df. In the "multiallele" method, we used a χ^2 statistic previously defined for multiallelic loci by Hill (1975) and Weir and Cockerham (1978). This is given by the formula

$$\chi^2 = N \sum_{i=1}^{m} \sum_{j=1}^{n} D_{ij}^2 / p_i q_j ,$$

where N is the total number of gametes in the sample, m is the number of alleles at the marker locus, n (= 2) is the number of alleles at *MEF*, p_i are the observed allele frequencies at the marker locus, q_j are the observed frequencies of carrier and noncarrier chromosomes, and $D_{ij} = p_{ij} - p_i q_j$. This statistic has $(m-1) \times (n-1)$ df. Since $n = 2$, df $= m - 1$. When there are only 2 alleles, this χ^2 formula yields the same result as a conventional 2×2 χ^2 statistic.

Results

Allelic Associations for All Non-Ashkenazi Families

Our previous study of recombinants among 31 non-Ashkenazi Jewish families placed *MEF* in the interval between *D16S80* and *D16S94* (fig. 1; Aksentijevich et al., in press). We have subsequently analyzed allele frequencies in the same 31 families for the four telomeric and two centromeric loci shown in figure 1. Data for the highly polymorphic microsatellites at the telomeric end of the *MEF* interval are shown in table 1. When it is taken into account that we tested allelic associations at six different loci, the appropriate P value for significance is .0083.

The 86-bp allele for *D16S94* was associated with disease susceptibility in 43 of 56 (77%) carrier chromosomes and was found in 25 of 48 (52%) noncarrier chromosomes. When allowance is made for multiple comparisons, this association approached (but did not reach) significance by both the combined allele and multiallele χ^2 statistics. About 200 kb more telomeric (Harris et al. 1991; Germino et al. 1992), the 93-bp allele for *D16S283* was significantly associated with FMF susceptibility. At *D16S291*, still more telomeric, the 162-bp allele was associated with susceptibility (52% of carrier chromosomes vs. 23% of noncarrier chromosomes). This latter association was significant only by the combined allele method. There was no significant allelic association for *D16S84*, the most telomeric marker examined, nor were there significant associations for either centromeric marker (not shown).

Allelic Associations for Moroccan Families

Families that had emigrated from Morocco to Israel constituted the largest single subpopulation of our sample (14 families). For *D16S94*, the percentages of carrier and noncarrier chromosomes bearing the 86-bp allele were nearly the same in the Moroccans as in the whole panel (table 2), and the Yule coefficients were nearly the same (0.47 vs. 0.51). The disease association for the 86-bp allele at *D16S94* did not approach statistical significance, mainly because of the smaller size of the Moroccan subset. For both *D16S283* and *D16S291*, allelic associations were much higher among the Moroccans than in the whole panel and were highly significant. These latter results are consistent with a founder effect in the Moroccan subpopulation. There were no

Table 1

Allelic Associations for 31 Non-Ashkenazi Jewish Families

Marker and Allele	No. (%) of FMF Chromosomes		χ^2 [a]		
	Carrier	Noncarrier	Combined Allele (*P*)	Multiallele (*P*)	|*A*| [b]
D16S94:					
92 bp....	0 (0)	1 (2)			
90 bp....	1 (2)	3 (6)			
88 bp....	6 (11)	15 (31)	5.63 (.018)	12.07 (.034)	.51 ± .15
86 bp[c]...	43 (77)	25 (52)			
84 bp....	2 (4)	3 (6)			
82 bp....	4 (7)	1 (2)			
D16S283:					
103 bp....	2 (3)	0 (0)			
101 bp....	1 (2)	0 (0)			
99 bp....	2 (3)	2 (3)			
97 bp....	1 (2)	1 (2)			
95 bp....	0 (0)	0 (0)			
93 bp[c]...	31 (53)	9 (16)	17.97 (.000023)	28.82 (.0013)	.72 ± .11
91 bp....	17 (29)	25 (43)			
89 bp....	4 (7)	16 (28)			
87 bp....	0 (0)	2 (3)			
73 bp....	0 (0)	1 (2)			
65 bp....	0 (0)	2 (3)			
D16S291:					
168 bp....	0 (0)	1 (2)			
166 bp....	5 (10)	8 (16)			
164 bp....	13 (26)	14 (29)			
162 bp[c]...	26 (52)	11 (23)	8.81 (.003)	11.44 (.12)	.57 ± .15
160 bp....	1 (2)	3 (6)			
158 bp....	2 (4)	4 (8)			
156 bp....	3 (6)	6 (12)			
152 bp....	0 (0)	1 (2)			

[a] χ^2 test of the null hypothesis of no linkage disequilibrium, calculated as described in Subjects and Methods. Significance levels are in parentheses. When allowance is made for the fact that we studied allelic associations for six loci, the appropriate *P* value for significance is .0083.

[b] The Yule association coefficient ± SD.

[c] FMF-associated allele.

significant allelic associations for *D16S84*, nor for either centromeric locus.

Allelic Associations for Non-Moroccan Families

Given the foregoing data, we hypothesized that the strong allelic associations in the Moroccan subpopulation might be the basis for the somewhat weaker associations in the full panel of families. Table 3 shows the data for just the 17 non-Moroccan families. Again using a critical *P* value of .0083, we did not observe significant allelic associations among these non-Moroccan families. Only for the 86-bp allele at *D16S94* did the data approach significance. These findings are consistent with the hypothesis that, for *D16S283* and *D16S291*, allelic associations observed in the whole panel of families result from a founder effect among Moroccans.

Haplotype Associations

Extended haplotypes for *D16S94–D16S283–D16S291* were constructed to identify possible founder haplotypes. Of a possible 528 haplotypes, 44 were observed in our study population. Among Moroccans, the 86-93-162 haplotype accounted for 18/25 (72%) of the carrier chromosomes, whereas this haplotype was not observed among 22 Moroccan noncarrier chromosomes. Among non-Moroccans, 6/26 (23%) carrier chromosomes bore this haplotype, versus 1/28 non-

Table 2

Allelic Associations for 14 Moroccan Jewish Families

Marker and Allele	No. (%) of FMF Chromosomes		χ^2 [a]		
	Carrier	Noncarrier	Combined Allele (*P*)	Multiallele (*P*)	|*A*| [b]
D16S94:					
92 bp....	0 (0)	0 (0)			
90 bp....	0 (0)	2 (7)			
88 bp....	5 (18)	7 (26)	3.00 (.083)	4.33 (.50)	.47 ± .25
86 bp[c]...	21 (78)	15 (56)			
84 bp....	1 (4)	3 (11)			
82 bp....	0 (0)	0 (0)			
D16S283:					
103 bp....	1 (4)	0 (0)			
101 bp....	0 (0)	0 (0)			
99 bp....	0 (0)	0 (0)			
97 bp....	1 (4)	1 (4)			
95 bp....	0 (0)	0 (0)			
93 bp[c]...	22 (79)	4 (15)	19.93 (.000008)	26.01 (.0037)	.91 ± .06
91 bp....	2 (7)	11 (41)			
89 bp....	2 (7)	10 (37)			
87 bp....	0 (0)	1 (4)			
73 bp....	0 (0)	0 (0)			
65 bp....	0 (0)	0 (0)			
D16S291:					
168 bp....	0 (0)	1 (4)			
166 bp....	1 (4)	5 (21)			
164 bp....	1 (4)	7 (29)			
162 bp[c]...	20 (80)	5 (21)	17.15 (.000035)	20.48 (.0046)	.88 ± .08
160 bp....	1 (4)	0 (0)			
158 bp....	1 (4)	2 (8)			
156 bp....	1 (4)	3 (12)			
152 bp....	0 (0)	1 (4)			

[a] χ^2 test of the null hypothesis of no linkage disequilibrium, calculated as described in Subjects and Methods. Significance levels are in parentheses. When allowance is made for the fact that we studied allelic associations for six loci, the appropriate *P* value for significance is .0083.

[b] The Yule association coefficient ± SD.

[c] FMF-associated allele.

carrier chromosomes. The six non-Moroccan haplotype-positive carrier chromosomes included one from a Tunisian family, one from a Libyan family, two from separate Egyptian families, one from a Greek family, and one from an Iraqi family.

Discussion

In 14 Moroccan Jewish families, we have found highly significant allelic and haplotype associations between FMF susceptibility and chromosome 16p markers. These markers—*D16S94, D16S283,* and *D16S291*—are tightly linked with one another at the telomeric end of the *MEF* interval.

Although recombinant events identify *D16S94* as the closest of the three markers to *MEF* (Aksentijevich et al., in press), there was no significant allelic association for this locus among the Moroccans. This is most likely because the 86-bp *D16S94* allele associated with FMF was also the most common allele in noncarrier chromosomes. In contrast, the 93-bp allele at *D16S283* and the 162-bp allele at *D16S291* were relatively uncommon in noncarriers. Tests of linkage disequilibrium are much more powerful when a disease gene is associated with a marker allele that is rare in the general population (Thompson et al. 1988).

Our data are consistent with the hypothesis that most FMF carrier chromosomes in the Moroccan Jew-

Table 3

Allelic Associations for 17 Non-Moroccan Jewish Families

Marker and Allele	No. (%) of FMF Chromosomes		χ^2 [a]		
	Carrier	Noncarrier	Combined Allele (P)	Multiallele (P)	$\|A\|$ [b]
D16S94:					
92 bp....	0 (0)	1 (5)			
90 bp....	1 (3)	1 (5)			
88 bp....	1 (3)	8 (38)			
86 bp[c]...	22 (76)	10 (48)	4.22 (.04)	12.79 (.025)	.55 ± .21
84 bp....	1 (3)	0 (0)			
82 bp....	4 (14)	1 (5)			
D16S283:					
103 bp....	1 (3)	0 (0)			
101 bp....	1 (3)	0 (0)			
99 bp....	2 (7)	2 (6)			
97 bp....	0 (0)	0 (0)			
95 bp....	0 (0)	0 (0)			
93 bp[c]...	9 (30)	5 (16)	1.66 (.20)	9.16 (.52)	.39 ± .27
91 bp....	15 (50)	14 (45)			
89 bp....	2 (7)	6 (19)			
87 bp....	0 (0)	1 (3)			
73 bp....	0 (0)	1 (3)			
65 bp....	0 (0)	2 (6)			
D16S291:					
168 bp....	0 (0)	0 (0)			
166 bp....	4 (16)	3 (13)			
164 bp....	12 (48)	7 (29)			
162 bp[c]...	6 (24)	6 (25)	.007 (.93)	4.97 (.66)	.03 ± .33
160 bp....	0 (0)	3 (13)			
158 bp....	1 (4)	2 (8)			
156 bp....	2 (8)	3 (13)			
152 bp....	0 (0)	0 (0)			

[a] χ^2 test of the null hypothesis of no linkage disequilibrium, calculated as described in Subjects and Methods. Significance levels are in parentheses. When allowance is made for the fact that we studied allelic associations for six loci, the appropriate P value for significance is .0083.

[b] The Yule association coefficient ± SD.

[c] FMF-associated allele.

ish population are derived from a common ancestor. The 86-93-162 haplotype for *D16S94–D16S283–D16S291* was present in 72% of 25 randomly chosen Moroccan carrier chromosomes. On the basis of allele frequencies in our Moroccan control chromosomes, and by assuming linkage equilibrium among these marker loci, we would have expected a haplotype frequency of .21 × .15 × .56, or 1.8%. On the basis of allele frequencies from other control populations (Harris et al. 1991; Thompson et al. 1992), the figure would be .25 × .04 × .62, or 0.6%. The 86-93-162 haplotype was therefore present in vast excess among Moroccan FMF carrier chromosomes.

To exclude the possibility that the families we studied were not representative of the broader Moroccan FMF population, we determined the city or village of origin for the parental generation of each of these families. We were able to trace the ancestry of these 14 families to 10 different communities, encompassing most of the habitable areas of Morocco. Moreover, none of the families reported any known common ancestry with any other family in the panel.

It is unclear whether the allelic and haplotype associations we observed at the telomeric end of the *MEF* interval actually place the disease gene closer to *D16S94* than to *D16S80*. Both of the centromeric markers we examined, *D16S80* and *D16S82*, are relatively nonpolymorphic, and in both cases the allele as-

sociated with FMF was the common allele in the general population (data not shown). Given the size of our sample, it would be difficult to establish significant allelic associations at these loci, and thus it is probably premature to use linkage disequilibrium data to infer that *MEF* is closer to *D16S94* than to *D16S80*.

The allelic and haplotype associations described here may also provide a basis for carrier screening for FMF. With a frequency of about 70% in Moroccan carriers, the 86-93-162 haplotype is not sensitive enough for diagnostic purposes at present. However, since we did not observe this haplotype at all among 22 Moroccan control chromosomes, the specificity may be very high, and this haplotype might be used to confirm diagnoses. Identification of new markers in the candidate region may broaden the applicability of this approach in selected groups.

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