Exclusion of the familial Mediterranean fever locus as a susceptibility region for autosomal dominant familial Hibernian fever

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Table 1 Pairwise lod scores between chromosome 16p13.3 markers and FHF/autosomal dominant periodic fever. θ =genetic distance in centimorgans

Marker	0.0	0.01	0.05	0.10	0.15	0.20	0.25	0.30	0.40
Family A									
S283	-8.02	-4.71	-3.23	-2.50	-1.91	-1.37	-0.95	-0.63	-0.24
S2617	-2.30	-1.42	-0.76	-0.45	0.39	-0.18	-0.11	-0.06	-0.01
S423	-2.36	-2.28	-1.84	-1.17	-0.69	-0.37	-0.17	-0.05	0.04
S418	-8.56	-6.33	-3.75	-2.31	-1.49	-0.95	-0.58	-0.33	-0.06
Family B									
S283	-5.16	-2.53	-1.17	-0.61	-0.32	-0.16	-0.06	-0.01	0.01
S2617	-2.98	-0.93	-0.30	-0.08	0.01	0.04	0.05	0.05	0.02
S423	-2.43	-2.18	-1.31	-0.78	-0.48	-0.29	-0.16	-0.09	-0.01
S418	-5.46	-2.28	-0.92	-0.38	-0.11	0.03	0.09	0.10	0.05

Abstract

Autosomal dominant periodic fevers constitute a range of syndromes characterised by recurrent attacks of fever and abdominal pain. Familial Hibernian fever (FHF) has been described in only one United Kingdom based family, but two other Irish families have been found with similar clinical features. FHF resembles familial Mediterranean fever (FMF) in several clinical features, but the mode of inheritance of FHF is dominant whereas FMF is recessive. We have investigated whether autosomal dominant periodic fevers, in particular FHF, map to the FMF susceptibility locus (MEFV) on chromosome 16p13.3. We have used informative microsatellite markers flanking this locus to genotype members of the three families mentioned above. Two point and multipoint lod scores definitively excluded linkage to MEFV in the two larger families. A haplotype study confirmed these findings, indicating that FHF is genotypically as well as phenotypically distinct from FMF.

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Autosomal dominant periodic fever syndromes are a poorly categorised collection of conditions found in several ethnic groups including Austrians,¹ Dutch,² Finns,³ Germans, and Swiss.⁴ However, only familial Hibernian fever (FHF) has been specifically described as a separate clinical entity in one United Kingdom based family⁵ and two other Irish families have been reported with similar clinical features.⁶ The clinical presentation of FHF, characterised by recurrent attacks of abdominal pain and

fevers with localised myalgia and painful erythema, resembles familial Mediterranean fever (FMF), but FHF has a dominant mode of inheritance. The prevalence of FHF is lower than FMF, which has prevalence rates as high as 1:250 and 1:1000 in selected populations.⁷ The gene for FMF, designated "MEFV", maps to the short arm of chromosome 16 (16p13.3),⁸ and mutations of the pyrin/marenostrin protein product are likely to be involved in the condition.⁹⁻¹⁰ There is evidence of clinical and genetic heterogeneity within FMF as some Turkish families do not map to MEFV¹¹ and autosomal dominant inheritance of FMF has been described in some Jewish populations.¹² Hyper-IgD syndrome (HIDS) is a further autosomal recessive cause of periodic fever; MEFV has been excluded as the cause of HIDS.¹³

We have examined whether the gene for FHF maps to MEFV in the original FHF family (family A), as well as the two other Irish families (families B and C). Clinical features pertaining to these families have been described⁵⁻⁶ and diagnostic criteria for FHF were applied to each individual family member. Four microsatellite markers providing comprehensive coverage of the MEFV locus over a 15 cM distance were typed: D16S283, 2-5 cM telomeric to MEFV¹⁴; D16S423, 8-15 cM centromeric; D16S418, about 20 cM centromeric of D16S423¹⁵⁻¹⁶; and D16S2617, tightly linked to MEFV.⁹ Fluorescently labelled PCR primers were designed from published sequences and PCR performed using touchdown PCR conditions. Genotypings were performed using the ABI system (373A Automated Sequencer) and fragments analysed using GENESCAN software. Allele classification and frequencies were taken from published sources; additional alleles were seen for D16S283 (at least 12 alleles), D16S423 (16 alleles), and D16S418 (at least 12 alleles) and numbered sequentially from the smallest allele, either published or seen in the study. Two point lod scores between disease and each individual marker were calculated using the MLINK program of the LINKAGE package. Multipoint analysis of the disease against D16S283, D16S2617, and D16S423 was performed using VITESSE.¹⁷ A dominant transmission model was specified, with age specific penetrances of 10%, 70%, and 90% for people of age groups <15 years, 15 to 40, and over 40 years, respectively. These values were based on our observations that there were no unaffected carriers, and that all affected cases had onset by the age of 40 and usually by the age of 25.

Figure 1 Genotypes for the four microsatellite markers arranged according to probable haplotypes in families A and B. To facilitate pedigree drawing all family members have not been included. Top numbers indicate assigned haplotypes. No single haplotype is shared between affected members in either family.

The probability of a normal homozygote being diagnosed as affected was set at 0.001 for each age group, and the frequency of the abnormal allele was set to 0.00001. For the multipoint analysis, the following map was used: D16S283-0.04-D16S2617-0.08-D16S423. The genotypes obtained for the four markers in families A and B are shown in fig 1, arranged according to probable haplotypes. Two point lod scores between the disease and markers, as shown in table 1, are in general strongly negative in both

these families and it is clear that no single haplotype is shared between affected subjects. Multipoint analysis results (fig 2) indicate that the exclusion region (lod less than -2) extends for over 30 cM in family A and about 24 cM in family B, so MEFV has been excluded as a susceptibility locus for periodic fever(s) in these two families. There is insufficient power in family C for a definite result but the multipoint lod score at zero recombination is -1.03. Localisation of the FHF gene(s) by genome screening with

Figure 2 Multipoint lod scores in family A (dashed line) and family B (dotted line). The vertical axis indicates location of the first marker used to study these families (D16S283). The D16S2617 and D16S423 markers are placed respectively at 2-5 cM and 10-20 cM telomeric to D16S283. (D16S418 was not included in the multipoint analysis.)

subsequent identification of the genetic defect will indicate whether genetic heterogeneity of autosomal dominant periodic fever is present in these as well as other ethnically distinct families.

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