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A linkage study of malignant hyperthermia (MH)

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Five German families segregating for malignant hyperthermia (MH) were tested for linkage relationships using 35 serological and biochemical markers. Slightly positive lod scores were obtained with MNS, EsD, C3 and P. The relation with the C3 locus on chromosome 19p13.3–13.2 ($\hat{z}=0.72$, $\hat{\theta}=0.11$) is of some interest, since genetic linkage of MH with several polymorphic DNA markers from the 19q12–13.2 region has been reported (McCarthy et al. 1989).

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Malignant hyperthermia (MH) is a rare genetic myopathy, inherited as an autosomal dominant trait (Kalow 1970). An MH crisis is characterized by hypermetabolism of skeletal muscle due to an increase in intracellular calcium that can result in hyperthermia, muscle contractures and sometimes rhabdomyolysis. The episodes are usually triggered by potent inhalation anaesthetics or depolarizing muscle relaxants (Ashley & Abdul-Rasool 1988). A clinically similar disease with many biochemical identities to the human condition occurs in the Landrace pig (Britt & Kalow 1970), but here inheritance is autosomal recessive. At the locus in the pig named HAL (halothane sensitivity), are found the alleles N and n; pigs of genotype HAL^{nn} are halothane reactors. Recently Davis et al. (1988), using a cloned porcine glucosephosphate isomerase (GPI) cDNA, detected close HAL: GPI linkage ($\hat{z}=7.22$, $\hat{\theta}=0.0$) on chromosome 6 of the pig. The human GPI gene, however, is located on chromosome 19 at q12–q13.2 (McMorris et al. 1973). Considering the evolutionary conservation of very close linkages (Nadeau & Taylor 1981), it might be predicted that the human HAL homologue is also located on chromosome 19 with possible linkage relationships to the LE – C3 – (SE – PEPD) – LU synteny group (Eiberg et al. 1983). Indeed, McCarthy et al. (1989) demonstrated genetic linkage with three polymorphic DNA markers located at 19q12–13.2 in two large Irish MH families.

We report here the results of a linkage study in five German pedigrees segregating for the MH disease with respect to chromosome 19 markers. A spectrum of other serological and biochemical genetic markers with well-defined chromosomal locations was also tested to enable the construction

Table 1

Linkage relations of MH for 23 marker loci

Locus (chromosomal assignment)	Sex	Lod scores at recombination fraction, θ				
		0.05	0.1	0.2	0.3	0.4
RH	M	−1.44	−0.97	−0.49	−0.22	−0.07
(1p36.2–p34)	F	−0.68	−0.30	−0.05	+0.11	+0.05
	J	−1.88	−1.11	−0.37	−0.09	−0.02
PGM1	M	−0.59	−0.45	−0.27	−0.16	−0.07
(1p22.1)	F	−1.56	−1.49	−0.73	−0.45	−0.20
	J	−1.94	−1.19	−0.68	−0.49	−0.25
FY	M	−2.16	−1.33	−0.58	−0.23	−0.06
(1p21–q23)	F	−0.72	−0.44	−0.19	−0.08	−0.02
	J	−2.88	−1.77	−0.77	−0.35	−0.08
F13B	M	−2.50	−1.72	−0.93	−0.49	−0.20
(1q32)	F	+0.23	+0.32	+0.36	+0.30	+0.18
	J	−2.24	−1.39	−0.57	−0.19	−0.02
ACPI	M	+0.03	+0.02	+0.01	0.00	0.00
(2p25 or p23)	F	−0.46	−0.04	−0.02	−0.01	0.00
	J	−0.46	−0.24	−0.07	−0.01	0.00
TF	M	−0.03	−0.01	+0.01	+0.01	0.00
(3q21–q26.1)	F	−0.02	−0.02	−0.01	0.00	0.00
	J	−0.51	−0.25	−0.06	−0.01	0.00
GC	M	+0.23	+0.20	+0.15	+0.10	+0.05
(4q12–q13)	F	−0.92	−0.60	−0.29	−0.14	−0.04
	J	−1.62	−0.86	−0.27	−0.07	0.00
MNS	M	+0.12	+0.33	+0.42	+0.36	+0.21
(4q28–q31)	F	−0.60	−0.26	−0.01	+0.04	+0.02
	J	−0.52	+0.04	+0.39	+0.39	+0.23
BF	M	−0.13	+0.08	+0.22	+0.21	+0.14
(6p21.3)	F	−2.36	−1.53	−0.64	−0.21	−0.02
	J	−2.93	−1.59	−0.44	0.00	+0.11
GLO	M	+0.25	+0.21	+0.12	+0.05	+0.01
(6p21.3–p21.1)	F	−0.72	−0.41	−0.12	−0.01	+0.04
	J	−0.33	−0.11	+0.03	+0.06	+0.05
PGM3	M	−0.71	−0.44	−0.19	−0.07	−0.02
(6q12)	F	−0.60	−0.43	−0.20	−0.08	−0.02
	J	−1.92	−1.21	−0.50	−0.18	−0.04
PLG	M	−0.19	−0.16	−0.11	−0.07	−0.03
(6q26–q27)	F	+0.08	+0.07	+0.04	+0.02	0.00
	J	+0.04	+0.01	−0.03	−0.04	−0.03
GPT	M	+0.37	+0.31	+0.19	+0.09	+0.02
(8q23–qter)	F	−1.05	−0.53	−0.12	+0.03	+0.05
	J	−0.69	−0.23	+0.07	+0.12	+0.07
ABO	M	+0.02	+0.01	+0.01	0.00	0.00
(9q34.1–q34.2)	F	−0.25	−0.20	−0.13	−0.07	−0.03
	J	−0.35	−0.24	−0.13	−0.07	−0.03
ESD	M	+0.29	+0.23	+0.13	+0.06	+0.06
(13q14)	J	+0.29	+0.23	+0.13	+0.06	+0.06
PI	M	+0.25	+0.32	+0.35	+0.28	+0.17
(14q32.1)	F	−2.62	−1.65	−0.74	−0.30	−0.09
	J	−1.69	−0.86	−0.23	+0.02	+0.08

Table 1 (contd)

Locus (chromosomal assignment)	Sex	Lod scores at recombination fraction, θ				
		0.05	0.1	0.2	0.3	0.4
IGH	M	+0.98	+0.90	+0.72	+0.51	+0.27
(14q32.3)	F	−3.45	−2.31	−1.20	−0.60	−0.23
	J	−2.96	−1.64	−0.54	−0.10	+0.04
HP	M	+0.11	+0.11	+0.11	+0.09	+0.05
(16q22)	F	−1.03	−0.72	−0.37	−0.16	−0.05
	J	−1.42	−0.95	−0.33	−0.09	0.00
JK	M	−0.17	−0.15	−0.10	−0.06	−0.03
(18q11–q12)	F	−0.65	−0.40	−0.11	−0.01	0.00
	J	−0.71	−0.39	−0.13	−0.04	−0.02
LE	M	−0.11	−0.08	−0.05	−0.03	−0.02
(19)	F	+0.25	+0.20	+0.13	+0.07	+0.03
	J	−0.27	−0.08	+0.02	+0.02	+0.01
C3	M	+0.09	+0.07	+0.03	+0.01	0.00
(19p13.3–p13.2)	F	+0.40	+0.50	+0.41	+0.24	+0.07
	J	+0.66	+0.71	+0.53	+0.27	+0.07
P1	F	+0.73	+0.65	+0.46	+0.26	+0.08
(22q11.2–qter)	J	+0.73	+0.65	+0.46	+0.26	+0.08
K	M	−0.70	−0.44	−0.30	−0.08	−0.02
(?)	F	−0.33	−0.24	−0.12	−0.05	−0.01
	J	−0 98	−0.66	−0.32	−0.13	−0.03

* The data are given in three lines: Line M is attributed to recombination in the male only (assuming absence of linkage in the female: z_1 (θ_{male}; $\theta_{female}=0.5$); line F is for the inverse situation: z_2 (θ_{female}; $\theta_{male}=0.5$); line J (joint) gives the lod scores for recombination fractions assumed to be equal in both sexes; z_3 (θ_{male}; $=\theta_{female}$). Usually, but not necessarily, $z_1+z_2=z_3$. Pedigrees with double intercrosses and untested ancestors contribute to the z scores to varying degrees.

of an exclusion map, as an additional contribution towards mapping the MH gene within the human genome.

Subjects and Methods

Families

The genetic data came from five German families with malignant hyperthermia (MH), comprising altogether 78 individuals, 39 of them affected. They are described in detail by Lehmann-Horn et al. (submitted). Diagnosis was made by the Munich MH group according to the protocol of the European Malignant Hyperpyrexia Group (EMHG 1984, Klein et al. 1987). Forty-nine members agreed to participate in the study; 20 of them were classified by the standardized European caffeine/halothane test as MHS (MH susceptible) and 6 as MHE (MH equivocal). From these individuals blood samples were drawn for the analysis of the serological and biochemical markers.

Methods

Thirty-five serological and biochemical markers were tested by standard methods and commercial reagents (Table 1). Lod scores were computed using the LIPED 3 computer program (Ott 1974). Both, MHS and MHE individuals were considered to carry the abnormal allele; a penetrance of 95% was used for the analysis.

Results

The sums of lod scores for the 23 informative maker loci are given in Table 1. The

remaining 12 loci (PGD, AMY2, IGK, AK1, GALT, GOT1, PGP, PEPD, LU, ADA, AHCY and CO) did not segregate in an informative way in any of the families. Slightly positive lod scores were obtained with MNS, EsD, and P and across all three lines for C3 (Table 1), resulting in values for the latter ($\hat{z}=0.72$, $\hat{\theta}=0.11$. Strongly negative lod scores allowed exclusion of the MH gene from the other chromosomal regions examined. In some cases the exclusion encompassed fairly extensive segments, in particular on chromosomes 1 and 6.

Discussion

The HAL gene of the pig is apparently the homologue of the human MH gene (Britt & Kalow 1970), but final confirmation of this assumption requires an understanding of the respective gene structure and protein amino acid sequences. Localization of the genes involved would facilitate their isolation. Knowledge of the HAL gene in the pig has been advanced by the demonstration of its close linkage to the GPI gene on chromosome 6 (Davis et al. 1988). The homologous human GPI gene is located on chromosome 19 at q12–q13.2, a region which is spanned by the LE – C3 – (SE – PEPD) – LU synteny group (Eiberg et al. 1983). In our study, only the LE and the C3 loci were informative for the evaluation of linkage relations. While the LE lod scores contributed little, the possibility of a chromosome 19 locus for the MH gene remains, as inferred from the C3 findings. Three of the five MH families segregated in an informative way and all offered uniformly positive lod scores, but unfortunately the families are not large enough to permit more definitive conclusions. Importantly, our findings are consistent with the data of McCarthy et al. (1989), although these authors recognize the possibility of heterogeneity for MH, as is also indicated by the extensive studies of McPherson & Taylor (1982).

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