

## No evidence for heterogeneity in oculopharyngeal muscular dystrophy

Oculopharyngeal muscular dystrophy (OPMD) is a rare, late onset, autosomal dominant myopathy with dysphagia, bilateral ptosis, and a slowly progressive weakness of facial and limb girdle muscles. Characteristic intranuclear filaments of 10 nm in diameter can be found in muscle biopsies by electron microscopy. We describe multipoint linkage analysis in two large German families with OPMD confirming the gene locus on chromosome 14q11.2-q13. Neither family has

any French ancestors and they are not related, as shown by the different risk haplotypes.

Oculopharyngeal muscular dystrophy (OPMD) is clinically characterised by the following features: bilateral ptosis of the eyelids, dysphagia, and weakness and wasting of other extraocular, facial, and limb girdle muscles with slow progression. The age of onset is usually after 45 years.<sup>1</sup> Inheritance is clearly autosomal dominant with complete penetrance late in life. Intranuclear filaments are seen in a small percentage of skeletal muscle nuclei by electron microscopy. These filaments are considered specific for OPMD.<sup>2</sup> Their relationship to the pathogenetic mechanism and their mode of formation are unknown.

In the absence of a family history, two differential diagnoses should be considered: myasthenia gravis and a mitochondrial myopathy (for example, Kearns-Sayre syndrome). Although abnormal mitochondria have been described in muscle biopsies of OPMD patients,<sup>3</sup> neither a biochemical defect of the respiratory chain nor mutations in the mtDNA have been found.<sup>4</sup>

The majority of cases and families have been reported in French Canadians, where they could be traced back to common French ancestors.<sup>5</sup> Independent cases have been described in more than 20 countries,<sup>6</sup> including Germany.<sup>7,8</sup> Recently the gene locus for OPMD has been localised to chromosome 14q11.2-q13 in the region of the cardiac alpha and beta myosin heavy chain genes

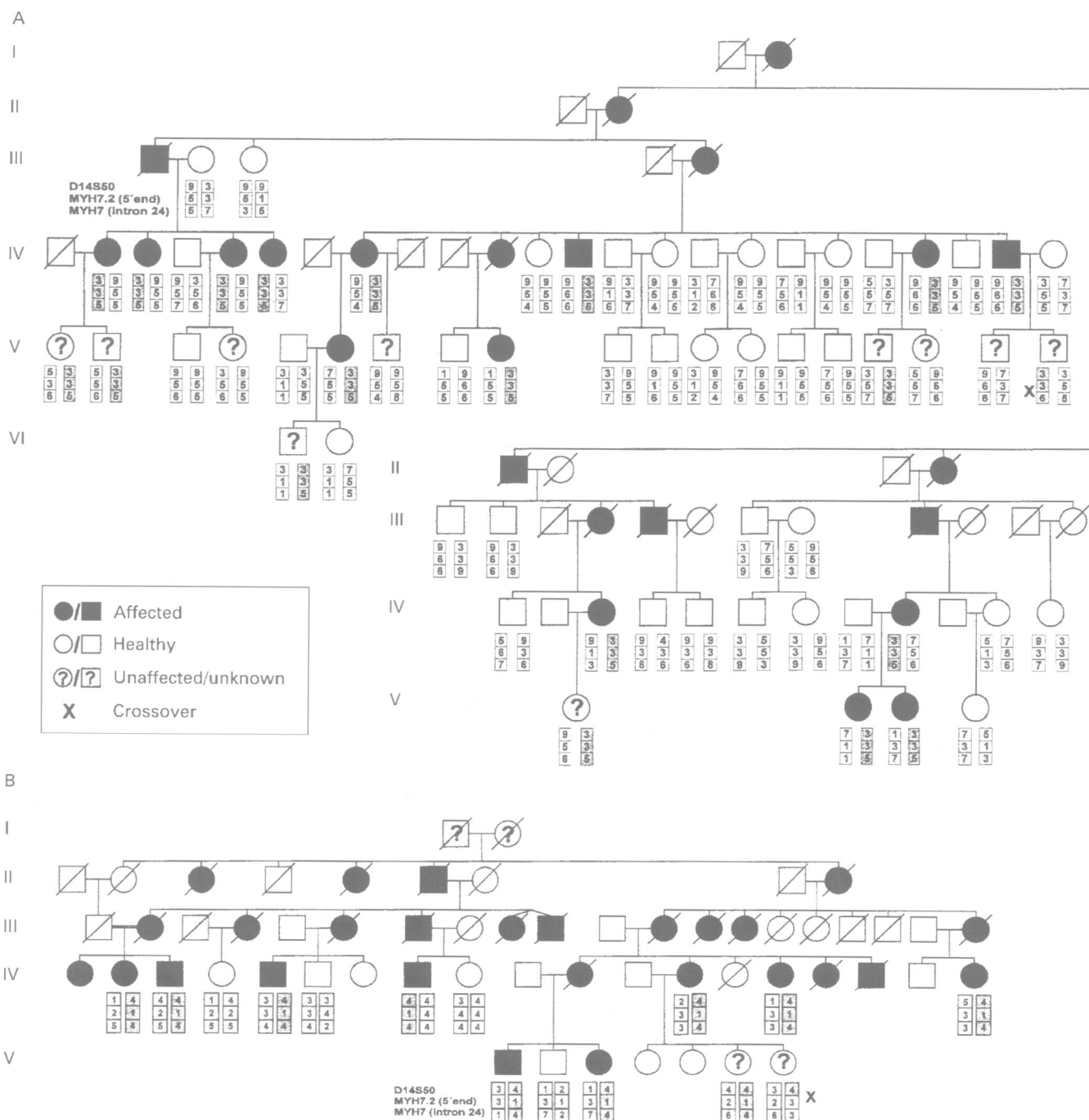


Figure 1 (A) Pedigree of the Friesian family and (B) pedigree of the Bavarian family. Haplotypes given for the three closest STS markers; the risk haplotype is marked in grey.

Table 1 Lod score table of OPMD v TCRD, D14S50, MYH7.2, MYH7, and D14S54

	Lod score at $\theta$ of						
	0	0.01	0.05	0.10	0.20	0.30	0.40
TCRD							
Family 1	−∞	−8.56	−4.33	−2.59	−1.08	−0.42	−0.13
Family 2	−8.94	−3.16	−1.48	−0.79	−0.25	−0.09	−0.05
Total	−∞	−11.73	−5.81	−3.37	−1.33	−0.52	−0.18
D14S50							
Family 1	6.44	6.31	5.80	5.14	3.78	2.37	0.98
Family 2	2.36	2.31	2.10	1.84	1.30	0.77	0.31
Total	8.80	8.62	7.90	6.98	5.08	3.15	1.29
MYH7.2 (5' end)							
Family 1	5.69	5.58	5.12	4.54	3.36	2.16	0.99
Family 2	2.23	2.20	2.05	1.82	1.30	0.77	0.31
Total	7.92	7.78	7.17	6.36	4.66	2.93	1.29
MYH7 (intron 24)							
Family 1	4.67	4.58	4.20	3.71	2.67	1.58	0.58
Family 2	3.69	3.61	3.28	2.87	2.04	1.22	0.50
Total	8.36	8.19	7.48	6.58	4.71	2.80	1.09
D14S54							
Family 1	−50.85	−1.95	−0.12	0.44	0.66	0.54	0.30
Family 2	1.45	1.41	1.25	1.06	0.70	0.39	0.14
Total	−49.40	−0.54	1.13	1.50	1.36	0.93	0.45

(MYH7) by linkage analysis of flanking and intragenic markers.<sup>5</sup>

We studied two large German pedigrees, one from northern Germany (Friesland)<sup>4</sup> and the other from Bavaria.<sup>9</sup> Both pedigrees can be traced back to before the Huguenot immigration from France to Germany in the 17th/18th century, and there are no French ancestors. The risk haplotype (fig 1) is not shared by the members of our two families. Haplotype analysis was performed with the STR markers TCRD, D14S50, MYH7 (intron 24), MYH7.2 (5' end), and D14S54 in order to confirm linkage and to exclude heterogeneity in OPMD.

For the genetic analysis, the phenotype of the family members was defined according to their clinical and neurophysiological symptoms and status.<sup>4</sup> Intranuclear filaments were found in muscle biopsies of two patients from each family (data not shown). Whereas CK values in the Friesian family were unexpectedly normal in most patients,<sup>4</sup> all affected members in the Bavarian family have raised values (2–6 times normal). Family members less than 45 years of age and three patients with mild muscle weakness because of a rheumatic disease or a carnitine deficiency were considered as unknown with respect to their OPMD status.

Informed consent for blood sampling was given by all family members. DNA was isolated by standard procedures from EDTA blood samples.<sup>10</sup> STS marker typing was done

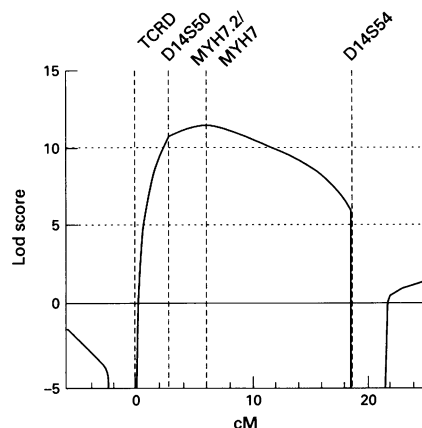


Figure 2 Graph of the multipoint linkage analysis.

as described previously.<sup>5</sup> The pedigrees of the two families are given in fig 1 with the risk haplotypes marked in grey. To allow simultaneous use of all the markers shown in the multipoint analysis, the pedigrees were subdivided into smaller subsets. Multipoint analysis was performed using either GENEHUNTER<sup>11</sup> or VITESSE,<sup>12</sup> depending on the subset studied. Multipoint lod scores were added over all subsets to obtain fig 2. As a genetic model, autosomal dominant inheritance with 100% penetrance above the age of 45 and a gene frequency of 0.00001 were chosen.

The two point lod scores are given in table 1. Unequivocal haplotypes can be derived for the marker alleles in each of the two OPMD families (fig 1). These haplotypes cosegregate with the disease in 14 affected subjects in family 1 and with nine affected subjects in family 2. These data generate a maximum cumulative lod score of  $Z=11.3$  by multipoint linkage analysis. Our results confirm the location of the OPMD gene in close vicinity to the MYH7 locus for both families. They provide no evidence for heterogeneity in populations other than the French Canadians.

A graph of the multipoint lod scores is shown in fig 2. The peak of the curve suggests a position for the OPMD locus which is slightly different from the MYH7 gene. Unfortunately, both probands bearing a recombination between the STS markers are too young for phenotypic classification, so that the region of interest cannot be narrowed further. Interestingly, the gene locus of another autosomal dominant myopathy maps to the same chromosomal region, namely one type of Welander distal myopathy (OMIM 160500). However, the clinical manifestations of this myopathy are quite distinctive from OPMD. Indeed, no mutation of the MYH7 gene has been reported for OPMD patients so far. Given the involvement of MYH7 in familial dilated cardiomyopathy,<sup>13</sup> it is difficult to envisage how other mutations in the myosin heavy chain gene could explain the symptoms of OPMD.

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## Another holoprosencephaly locus at 7q21.2?

In this journal, Benzacken *et al*<sup>1</sup> described four new cases of holoprosencephaly in fetuses with different distal and proximal rearrangements of the long arm of chromosome 7. Three of them showed terminal deletion of 7q, confirming the importance of the 7q36 region in holoprosencephaly. In the fourth fetus (case 2 with semilobar holoprosencephaly and agenesis of corpus callosum and no associated malformations), an apparently balanced *de novo* translocation t(7;13)(q21.2;q33) was found. The authors suggested that this observation could be explained by the existence in 7q21.2 of another structural gene involved in the complex prosencephalon developmental process.

Recently, we had the opportunity to examine a 21 year old, mildly mentally retarded