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

	Lod score at θ 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.[5]

We studied two large German pedigrees, one from northern Germany (Friesland)[4] and the other from Bavaria.[9] 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 TRCD, 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.[4] 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,[4] 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.[10] STS marker typing was done as described previously.[5] 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[11] or VITESSE,[12] 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.

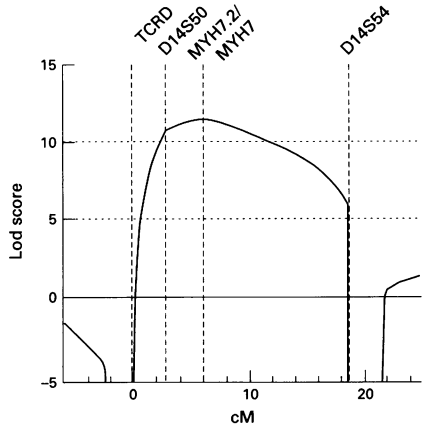

Figure 2 Graph of the multipoint linkage analysis.

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,[13] it is difficult to envisage how other mutations in the myosin heavy chain gene could explain the symptoms of OPMD.

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WOLFRAM KRESS
BIRGIT HALLIGER-KELLER
TIEMO GRIMM

Institute of Human Genetics, Biozentrum, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany

HILDBURG PORSCHKE
Department of Neurology, University Hospital Kiel, Germany

ANDREAS ENGELHARDT
Department of Neurology, University Hospital Erlangen, Germany

HANS-HILMAR GOEBEL
Department of Neuropathology, Johannes Gutenberg-University, Mainz, Germany

BERTRAM MÜLLER-MYSOK
Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany

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Another holoprosencephaly locus at 7q21.2?

In this journal, Benzacken *et al*[1] 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

male with a single central upper incisor as the only minimal "holoprosencephaly sign" and without other dysmorphic symptoms. Prometaphase chromosome studies on a peripheral blood lymphocyte culture showed an apparently balanced 6q;7q translocation, karyotype 46,XY,t(6;7)(q15;q21.2) de novo.

The chromosome 7q21.2 breakpoint in the present patient with a single central upper incisor as the only manifestation of holoprosencephaly is thus identical to the 7q breakpoint found in the fetus reported by Benzacken *et al.*[1] This observation reinforces the suggestion that disruption of a gene or separation from its regulatory sequences by the translocation breakpoint in 7q21.2 could be responsible for the occurrence of holoprosencephaly.

JEAN-PIERRE FRYNS
Centre for Human Genetics, University of Leuven, Herestraat 49, B-3000 Leuven, Belgium

1 Benzacken B, Siffroi JP, Le Bourhis C, *et al.* Different proximal and distal rearrangements of chromosome 7q associated with holoprosencephaly. *J Med Genet* 1997;34:899-903.

BOOK REVIEW

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Gene Therapy for Neurological Disorders and Brain Tumours. Editors E Antonio Chiocca, Xandra Breakfield. (Pp 550; $135.00.) Totowa, NJ: Humana Press. 1997. ISBN 0-89603-507-7.

This book looks at neurological and neuro-oncological gene therapy through a series of reviews of current understanding and practice and not as a recipe book of protocols and procedures. Readers will certainly have a better understanding of the relevant biology of the vectors discussed and their applications and limitations but would not be in a position to design experiments based on the contents. The book is divided into three parts: Vectors and Promoters, Neuro-oncology, and Neurological Disorders.

The chapters on the different types of vectors review the life cycles and genome structures of the various viruses as well as describing the development of the vectors for therapeutic use. The exception is the chapter on Epstein-Barr virus which is limited to reviewing the pathogenesis and biology of primary CNS lymphoma (PCNSL) and the use of EBV in the treatment of this disorder. Throughout the chapters, the enthusiasm of the authors for their chosen vector is continually tempered with acknowledgment of the current limitations of each virus. After reading these chapters, however, the reader is left with the feeling that "some day this will be useful". As the editors comment, "the unrealistic perception of gene therapy as a "cure" or as "a failed treatment", created by premature and exaggerated news reports, is likely to disappear". The area where real therapeutic gains are first likely to come is the focus of the second part of the book, neuro-oncology. This begins with a comprehensive review of current treatment modalities for brain tumours and their deficiencies and is followed by chapters on gene therapies and specifically tumour suppressor therapy and cytokine based gene therapy (with 410 references!). The review on delivering therapeutic genes to the brain discusses direct inoculation and blood brain barrier disruption and the reader is left with the feeling that for the disorders discussed in the final part of the book, neurological disorders, only the latter approach is likely to suffice. The chapter on CNS regeneration is followed by specific chapters on Parkinson's disease, ischaemic stroke, lysosomal storage diseases, and Huntington's disease. They are of necessity largely theoretical (from a human perspective) but do show how the basic science of gene therapy is rapidly advancing on areas of clinical utility. There are a few niggling errors, such as the reference to the Huntington's disease gene as ITIS on two occasions (including the first sentence of the chapter on HD) and automatic spell check generated word substitutions ("transpose"' for "transgenic").

Overall the book makes interesting reading for those looking for reviews of the current standing of gene therapy in the CNS. It would not, however, be high on my list of "must haves" for a genetics departmental library and I doubt whether it would find a place with colleagues actively working in the field.

JOHN MACMILLAN