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Dominant Hereditary Inclusion-Body Myopathy Gene (*IBM3*) Maps to Chromosome Region 17p13.1

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Summary

We recently described an autosomal dominant inclusion-body myopathy characterized by congenital joint contractures, external ophthalmoplegia, and predominantly proximal muscle weakness. A whole-genome scan, performed with 161 polymorphic markers and with DNA from 40 members of one family, indicated strong linkage for markers on chromosome 17p. After analyses with additional markers in the region and with DNA from eight additional family members, a maximum LOD score (Z_{max}) was detected for marker D17S1303 ($Z_{max} = 7.38$; recombination fraction (θ) = 0). Haplotype analyses showed that the locus (Genome Database locus name: *IBM3*) is flanked distally by marker *D17S945* and proximally by marker *D17S969*. The positions of cytogenetically localized flanking markers suggest that the location of the *IBM3* gene is in chromosome region 17p13.1. Radiation hybrid mapping showed that *IBM3* is located in a 2-Mb chromosomal region and that the myosin heavy-chain (MHC) gene cluster, consisting of at least six genes, co-localizes to the same region. This localization raises the possibility that one of the MHC genes clustered in this region may be involved in this disorder.

Introduction

Familial or hereditary inclusion-body myopathy (HIBM) constitutes a heterogeneous group of disorders histologically characterized by muscle fibers with rimmed vacuoles and inclusions consisting of filaments with a diameter of 15–21 nm (Griggs et al. 1995; Askanas and Engel 1998*a*). Autosomal recessive inheritance of HIBM (MIM 600737) has been described in quadriceps-sparing HIBM, with onset in early adulthood (Argov and Yarom 1984). This disorder has been linked to chromosome 9p1–q1 (Mitrani Rosenbaum et al. 1996; Argov et al. 1997). Autosomal dominant inheritance of HIBM has also been described (MIM 147420), but no chromosomal linkage has been presented to date. No unique clinical features, such as congenital joint contractures or ophthalmoplegia, were found in these patients, although the muscle weakness seemed to be predominantly proximal with a limb-girdle distribution (McKee et al. 1992; Neville et al. 1992; Sivakumar and Dalakas 1996). Similar histopathological changes have been reported in other hereditary myopathies, such as oculopharyngeal muscular dystrophy (Coquet et al. 1990), oculopharyngeal muscular dystrophy with distal myopathy (Fukuhara et al. 1982), Welander distal myopathy (Lindberg et al. 1991), tibial muscular dystrophy (Udd et al. 1993), and distal myopathy with rimmed vacuoles (DMRV; Nonaka et al. 1981). DMRV has recently been linked to chromosome 9 and is possibly allelic to quadriceps-sparing HIBM (Ikeuchi et al. 1997).

We recently described an autosomal dominant HIBM in a large Swedish family with 19 affected persons (Darin et al. 1998). Characteristic clinical features were congenital joint contractures that normalized during early childhood, external ophthalmoplegia, and predominantly proximal muscle weakness and atrophy. To identify a gene locus (HGM locus *IBM3*) for this disease, we performed linkage analysis by means of polymorphic DNA markers from 40 family members. A genomewide analysis showed linkage to chromosome 17p markers.

Subjects and Methods

Families

Data from the large multigeneration family (fig. 1) from western Sweden described elsewhere (Darin et al. 1998) were analyzed for myopathy inherited as an autosomal dominant trait. This familial disorder and the criteria for the diagnosis of myopathy have recently been reported (Darin et al. 1998). Characteristic clinical fea-

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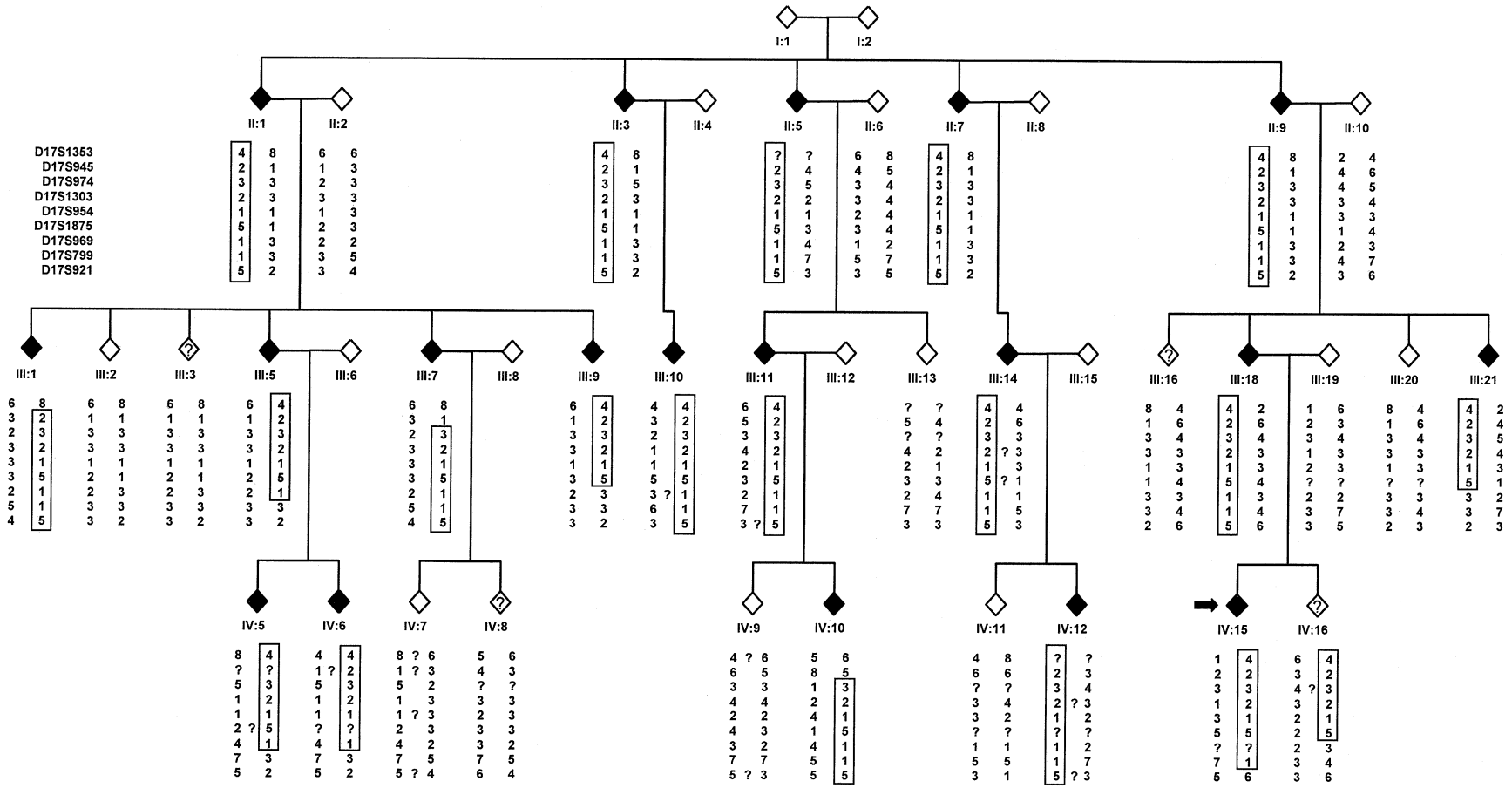

Figure 1 Pedigree of the investigated family and haplotype/recombination analysis of the analyzed family data. The data indicate the most likely paternal and maternal haplotypes for the region *D17S1353–D17S921* and a distal and a proximal border for the *IBM3* locus. Affected individuals are indicated by blackened symbols, unaffected individuals by unblackened symbols. The haplotype segregating with *IBM3* is boxed; uninformative loci are indicated by a question mark (?). Individuals III:7 and IV:10 display recombination events, giving a distal border for the *IBM3* locus, whereas recombinations for individuals III:9, III:21, and IV:16 indicate a proximal border. In summary, the haplotype/recombination data indicate that the *IBM3* locus is located in the region defined distally by marker *D17S974* and proximally by *D17S969*. The pedigree has been somewhat distorted and truncated to avoid identification.

tures were congenital joint contractures that normalized during early childhood, external ophthalmoplegia, and predominantly proximal muscle weakness and atrophy. Hand tremor was frequently associated. The clinical course was nonprogressive in childhood, although most adult patients experienced deterioration of muscle function starting at ~40 years of age. Focal disorganization of myofilaments occurred in childhood, whereas adults with progressive muscle weakness showed dystrophic changes and rimmed vacuoles with cytoplasmic and intranuclear inclusions of 15–21-nm filaments. Occasional congophilic inclusions, accumulations of ubiquitin, and inclusions that showed immunoreactivity with an antibody to hyperphosphorylated tau (SMI-31) were additional features suggesting that this myopathy should be grouped with the HIBMs.

The family members were diagnosed as affected or unaffected by one of us (N.D.), who applied a standardized questionnaire and a clinical examination form. Informed consent was given by each individual. Forty-eight family members were examined. The probands were classified as definitely affected if they had symptoms and clinical signs of myopathy in addition to external ophthalmoplegia. They were considered unaffected if they were without definite symptoms and had normal muscle findings. Muscle biopsy findings were not used as inclusion criteria. Those cases in which family members did not fulfill these criteria were considered "unclear." Obstetric, pediatric, child health clinic, and other relevant medical files were reviewed. A follow-up interview and clinical examination were performed 4 years after the first examination. In the initial total-genome scan, data from 40 family members were used. After linkage to chromosome 17 markers had been detected, data from an additional set of eight family members were analyzed for markers in this region only.

DNA Isolation, Genotyping, and Linkage Analysis

DNA was isolated from venous blood samples anticoagulated with EDTA and extracted according to standard procedures. PCR was performed according to standard procedures. In brief, amplifications were done in a 20-μl volume containing 125 ng of genomic DNA; 15 pmol of each primer; 10 mM Tris HCl (pH 8.3); 50 mM KCl; 1.5 mM $MgCl_2$; 0.001% (w/v) gelatin; 4.4 nmol of each dATP, dCTP, dGTP, dTTP; 0.66 μCi $\alpha[^{32}P]$-dCTP; and 0.55 U *Taq* DNA polymerase (Perkin-Elmer). Amplifications were done in a Hybaid Omnigene Temperature Cycler. Simple-sequence-repeat polymorphisms (SSRPs) were determined by the length of amplified PCR products on a 6% polyacrylamide/7 M urea sequencing gel. After drying, the gel was exposed to a Fuji X-ray film overnight at room temperature.

Two-point linkage analyses were performed with the MLINK and the ILINK programs from the LINKAGE 5.1 package (Lathrop et al. 1984). The model used for analyses was an autosomal dominant inheritance with full penetrance (1.0) and a disease allele frequency of .0001.

A screen of the genome was done by means of primer pairs set denoted "CHLC [Cooperative Human Linkage Center] Human Screening Set/Weber version 6a," which consists of 161 markers spaced over the genome (Cooperative Human Linkage Center). The primers were synthesized through the Nordic Genetic Marker Repository (C. Wadelius, personal communication). After the initial gene localization, additional markers from the chromosome 17p gene region were used. These were from the Généthon (Dib et al. 1996) and the Cooperative Human Linkage Center (Murray et al. 1994) linkage maps. The recently published integrated maps (Broman et al. 1998; Marshfield Medical Research Foundation) were used for estimation of distances between markers of different groups.

Estimation of Distances between DNA Markers with a Radiation Hybrid Panel

Relevant markers in the chromosome 17 region (*D17S969, D17S1303, D17S974,* and *D17S945*), together with sequence-tagged sites (STSs) for two candidate genes, were tested versus the Stanford Human Genome Center G3 radiation hybrid mapping panels (Research Genetics). The two STSs for genes tested were *PMP22* exon 3 (primers: PMPex3F: 5′-CCA TGG CCA GCT CTC CTA AC-3′ and PMPex3R 5′-CAT TCC GCA GAC TTT GAT GC-3′; 59°C) and myosin, heavy polypeptide 2, skeletal muscle, adult (Genome Database locus: *MYH2*; primers: LL120: 5′-TCA AGC TTC TTC CTC CTC CTC AGC TCT TTC AG-3′ and LL77: 5′-TTA AGC CCC TCC TCA AGA GTG CA-3′; 60°C). The STS primers for the *MYH2* and the *PMP22* genes were derived from the Genome Database. Data were analyzed by means of both the RH-map software package (Boehnke et al. 1991) and electronic submission to the RH-server (Stanford Human Genome Center). Markers were mapped versus the 1000:1 bins map from the G3 RH-map 2.0 of the Stanford Human Genome Center.

Results

Linkage Analysis

Data from 40 individuals in the family were used in the analyses (for pedigree, see fig. 1). Linkage analyses were performed by means of microsatellite polymorphisms from the Cooperative Human Linkage Center Human Screening Set/Weber version 6a, which contain 161 markers spaced over the genome. The data were

analyzed by means of the MLINK and ILINK programs (data available on request) in the LINKAGE 5.1 package. One region in chromosome region 17p gave a strong indication of linkage. Additional markers in this region were subsequently analyzed with DNA from eight additional family members. We found a region ranging from marker *D17S1353* to marker *D17S921* that was strongly linked to the *IBM3* locus. Pairwise LOD scores for these markers are shown in table 1. Four markers (*D17S974, D17S1303, D17S954,* and *D17S1875*) had a combined LOD score that was maximal (Z_{max}) at a recombination fraction (θ) of zero (θ at Z_{max} = .00). For four markers in the region, the maximal LOD score was >4, with a peak at *D17S1303* (Z_{max} = 7.38 at θ = .00.)

Recombination Analysis

To further narrow the region of the *IBM3* gene locus, we performed a family haplotype analysis for the region *D17S1353* to *D17S921* (fig. 1). Several recombination events were detected between markers *D17S945* and *D17S974*—for example, from individuals II:1 to III:7 and from individuals III:11 to IV:10. These findings place *D17S945* distal to the *IBM3* locus. Furthermore, recombination events were detected between markers *D17S1875* and *D17S969*—for example, from individuals II:1 to III:9 and from individuals II:9 to III:21. These findings place *D17S969* proximal to the *IBM3* locus. Taken together, the findings from the family recombination analyses indicate that the *IBM3* gene is located in a region defined distally by marker *D17S945* and proximally by marker *D17S969* (fig. 2). On a recently published integrated map, this region is estimated at ~6 cM (Broman et al. 1998).

Radiation Hybrid Data for 17p

Four polymorphic markers (*D17S969, D17S1303, D17S974,* and *D17S945*) in the *IBM3* gene region were analyzed by means of the Stanford Human Genome Center G3 radiation hybrid mapping panel. In addition, STS markers for one of the myosin heavy-chain (MHC) gene family members, MYH2, and for the PMP22 gene (involved in Charcot-Marie-Tooth disease, used as a control) were included in the analysis. The PCR patterns of the four polymorphic markers used were found to be very similar (data not shown). The most-likely deviant clones, markers *D17S969* and *D17S945,* had a calculated distance of ~2 Mb (separated by ~80–100 cR), whereas markers *D17S1303* and *D17S974* were found to map between these markers. This is also corroborated by the Stanford Human Genome Center RH-map, version 2.0, where the markers *D17S945, D17S974, D17S1303,* and *D17S969* were found to map to the

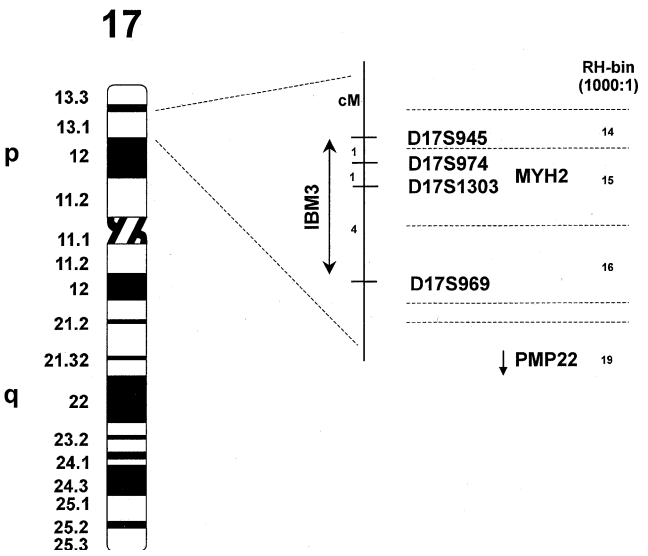

Figure 2 Summary of radiation hybrid data from the *IBM3* gene region on 17p13.1. The *MYH2* gene was found to localize in close proximity to markers *D17S974* and *D17S1303* in the *IBM3* gene region, whereas the control gene *PMP22,* although localized to 17p, clearly mapped outside the *IBM3* critical region. Genetic distances are derived from Broman et al. (1998) and the RH-bin information is derived from RH-server (Stanford Human Genome Center).

Table 1

Two-Point LOD Score Values for Linkage between *IMB3* and Chromosome 17 Markers

	LOD Score at θ =								
Marker	0	.01	.05	.1	.2	.3	.4	Z_{max}	θ at Z_{max}
D17S1353	−∞	-1.02	.78	1.30	1.39	1.02	.46	1.39	.2
D17S945	−∞	3.95	4.85	4.80	4.01	2.83	1.39	4.85	.05
D17S974	2.05	2.01	1.83	1.61	1.14	.67	.27	2.05	0
D17S1303	7.38	7.25	6.74	6.07	4.66	3.12	1.48	7.38	0
D17S954	2.37	2.33	2.15	1.93	1.46	.97	.47	2.37	0
D17S1875	4.76	4.68	4.35	3.92	3.00	1.99	.90	4.76	0
D17S969	−∞	3.95	4.85	4.80	4.01	2.83	1.40	4.85	.05
D17S799	−∞	-.12	1.63	2.08	2.01	1.47	.71	2.08	.1
D17S921	−∞	-2.46	.01	.79	1.09	.82	.36	1.09	.2

1000:1 bins 14, 15, 15, and 16, respectively, of the 87 bins on chromosome 17. The MYH2 gene had a pattern of positive clones most similar to markers *D17S1303* and *D17S974*. MYH2 could be shown to link strongly (LOD score = 9.87) to markers in bin 15, whereas PMP22 had a pattern very different from the other five markers and linked strongly (LOD score 12.38) to markers in bin 19 (fig. 2).

Discussion

We have shown, by means of linkage analysis, that the *IBM3* gene is linked to polymorphic DNA markers on chromosome 17p. By means of recombination/haplotype analysis, the gene could be mapped to the region between markers *D17S969* on the proximal side and *D17S945* on the distal side in 17p13.1. This region is ~6 cM, on a recently published integrated map. To further characterize the region on the physical map, four microsatellite markers were tested versus the Stanford Human Genome Center G3 radiation hybrid map, together with one of the MHC genes known to cluster to the region. The most likely order of the polymorphic markers in the radiation hybrid analysis is 17pter–*D17S945*–*D17S974*–*D17S1303*–*D17S969*–17cen (fig. 2). Two interesting features of the analysis were that (1) *MYH2* clearly mapped close to the central markers *D17S974* and *D17S1303* and thus locates within the *IBM3* critical region, and (2) the distance between the markers flanking the *IBM3* gene region, such as *D17S945* and *D17S969,* is most likely ~2 Mb and thus smaller than the distance indicated by the genetic map, which is ~6 cM. A group of five to six MHC genes are known to cluster to the 17p13.1 gene region (Leinwand et al. 1983; Yoon et al. 1992; Soussi Yanicostas et al. 1993). Considering the nature of the disorder, these genes are likely candidates for being the *IBM3* locus.

Myosin consists of two MHC and two pairs of nonidentical myosin light chains. The human MHC genes in striated muscle are organized in two chromosomal clusters. The alpha and slow/beta cardiac MHC genes are located on chromosome 14q (Saez et al. 1987). The other five to six MHC skeletal muscle genes, including embryonic, perinatal, the adult fast gene (2A, 2X, and probably 2B), and an unidentified gene that probably corresponds to the MHC-extraocular, are clustered on a 300–600-kb segment on chromosome 17p13.1 (Leinwand et al. 1983; Yoon et al. 1992; Soussi Yanicostas et al. 1993).

Mutations in MHC genes have only rarely been associated with disease. Mutations in the beta cardiac myosin (*MYH7*) gene on chromosome 14q have been shown to cause familial hypertrophic cardiomyopathy (FHC; Towbin 1998), a disorder that may present with an associated central-core pathology in skeletal muscle (Fananapazir et al. 1993). Mutations in several other genes that encode sarcomere-associated proteins have recently been identified as causes of FHC (Towbin 1998), and mutations of cardiac actin have been associated with dilated cardiomyopathy (Olson et al. 1998). Alpha tropomyosin slow (*TPM3*) mutations are associated with rare cases of autosomal dominant and recessive nemaline myopathy (Laing et al. 1995), and myosin light chain mutations are associated with a rare myopathy in human heart and skeletal muscle (Poetter et al. 1996).

A mutation in one of the MHC genes may be responsible for the morphological and clinical findings presented here. In addition to autosomal dominant cardiomyopathy, the *MYH7* gene also causes various degrees of myopathic changes in skeletal muscle with central cores (Fananapazir et al. 1993). This is similar to the focal disorganization of myofilaments with minicores found in the disorder described elsewhere (Darin et al. 1998). Because the MHC genes are expressed in different fiber types and at different times during development (Whalen et al. 1981; Wieczorek et al. 1985), a mutation in an MHC gene might be responsible for the characteristic external ophthalmoplegia and the peculiar course of our disorder with congenital joint contractures that normalize during early childhood and then deteriorate in middle adulthood.

The relation of myosin with rimmed vacuoles is not clear. Rimmed vacuoles are considered to be autophagic in nature (Fukuhara et al. 1980). In DMRV, it has been hypothesized that myosin and other sarcomere-associated proteins, after a partial degradation by extralysosomal processes, stimulate lysosome formation and induce autophagic rimmed vacuoles (Kumamoto et al. 1982). Rimmed vacuoles and filamentous inclusions have also been described in tibial muscular dystrophy (Udd et al. 1993), in which another sarcomere-associated protein, titin, is a possible candidate gene (Haravuori et al. 1998). Further identification of the gene and gene product responsible for the phenotype in this family will be important for understanding the molecular background and the pathogenesis of HIBM. Such will also permit studies on the relationship between these disorders and clinically and morphologically related diseases such as certain hereditary congenital and distal myopathies.

The characteristic filamentous inclusions, congophilic inclusions, and several of the pathologically accumulating proteins that have been described in HIBM were originally described in a sporadic inflammatory myopathy named inclusion-body myositis (IBM), which has been considered the most common muscle disease that begins at >50 years of age (Askanas and Engel 1998*b*). The identification of genes associated with HIBM may, therefore, give new insights into the pathogenesis of the

progressive and debilitating sporadic IBM. The large sizes of the MHC genes located on 17p13.1 and the fact that information is incomplete on the gene structure for most of them are factors that will make the identification of the mutation difficult. Nevertheless, analyses for mutations in the MYH genes in the family presented here are in progress.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Cooperative Human Linkage Center, http://www.chlc.org (for linkage analyses and for information on genetic markers)

Généthon, http://www.genethon.fr (for information on genetic markers)

Genome Database, http://www.gdb.org (for STS primers)

Marshfield Medical Research Foundation, http://www.marshmed.org/genetics (for estimation of distances between markers of different groups)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for autosomal recessive inheritance of HIBM [MIM 600737] and for autosomal dominant inheritance of HIBM [MIM 147420]

Stanford Human Genome Center, http://www-shgc.stanford.edu/RH/ (for marker analysis)

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