*Am. J. Hum. Genet. 46:1082–1089, 1990*

# The Human Ryanodine Receptor Gene: Its Mapping to 19q13.1, Placement in a Chromosome 19 Linkage Group, and Exclusion as the Gene Causing Myotonic Dystrophy

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## Summary

**The recent cloning of cDNA encoding the $Ca^{++}$ release channel (ryanodine receptor) of human sarcoplasmic reticulum has enabled us to use somatic cell hybrids to localize the ryanodine receptor gene (RYR) to the proximal long arm of human chromosome 19. Studies with additional hybrids containing deletions or translocations in chromosome 19 enabled us to localize RYR to 19q13.1 in a region distal to GPI/MAG and proximal to D19S18/DNF11. On the basis that the myotonic dystrophy (DM) locus maps near this region and that myotonia could result from a defect in the ryanodine receptor, we examined the linkage between the DM locus and RYR. Our results, showing several DM-RYR recombinants, rule out an RYR defect as the cause of DM. However, localization of RYR to a region of human chromosome 19 which is syntenic to an area of pig chromosome 6 containing the HAL gene responsible for porcine malignant hyperthermia supports the candidacy of RYR for this disorder.**

## Introduction

In the course of induction of skeletal muscle contraction, the transverse-tubular (T-tubular) system conducts a depolarizing wave into the interior of the muscle cell. The $Ca^{++}$ release channel in the sarcoplasmic reticulum opens in response to an as yet unknown signal generated by the T-tubular depolarization, leading to an efflux of $Ca^{++}$ from the terminal cisternae of the sarcoplasmic reticulum into the myoplasm (Martonosi 1984). The resulting increase in myoplasmic $Ca^{++}$ leads to increased binding of the cation to troponin, which in turn facilitates the interaction of actin and myosin (Squire 1981).

Received December 21, 1989.

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0002-9297/90/4606-0008$02.00

The $Ca^{++}$ release channel of skeletal muscle sarcoplasmic reticulum is termed the ryanodine receptor because of its affinity for and modulation by the plant alkaloid ryanodine (Jenden and Fairhurst 1969). Recent work has shown that both the $Ca^{++}$ release channel and the foot structure bridging the gap between the transverse tubular system and the sarcoplasmic reticulum are composed of a homotetramer of a single 564,000-Da protein. (Campbell et al. 1987; Inui et al. 1987; Lai et al. 1988; Takeshima et al. 1989; Wagenknecht et al. 1989; Zorzato et al. 1990).

The cDNA encoding the ryanodine receptor from humans has been cloned and sequenced (Zorzato et al. 1990). We have used this cDNA to determine the sublocalization of the ryanodine receptor gene (RYR) to human 19q13.1, by means of high-resolution somatic cell hybrid analysis. This region is close to that which contains the gene responsible for myotonic dystrophy (DM; Brunner et al. 1989*b;* Korneluk et al. 1989*a*). Since DM is a disorder in which a fundamental derangement in excitation-contraction coupling leads to my-

otonia (Harper 1979), the possibility of an RYR defect causing DM was investigated. We present here the results of both two-point and multipoint linkage analyses between RYR and a chromosome 19 linkage group composed of seven loci including the DM locus. These data show that RYR is distinct from the DM locus and maps proximal to it.

## Material and Methods

### *Somatic Cell Hybrid Analysis*

The construction and cytogenetic characterization of the somatic cell hybrid lines containing intact chromosome 19, chromosome 19 translocation products, or der(19) segments derived by irradiation-selection is described in detail elsewhere (Mohandas et al. 1980; Brook et al. 1984; Bufton et al. 1986; Lusis et al. 1986; MacLennan et al. 1987 [and references therein]; Korneluk et al. 1989*b*; Schonk et al. 1989). Approximately 10 μg of genomic DNA were extracted from hybrid and control cells, digested to completion with *Eco*RI, and separated by electrophoresis for subsequent Southern blot analysis (Schonk et al. 1989). The probes pHRR-XH-1, a 1,001-bp *Xho*I-*Hin*dIII fragment consisting of bases 8550–9550 in the RYR cDNA sequence (Zorzato et al. 1990), and pHRR5, a 3.8-kb *Eco*RI RYR cDNA insert (bases 2381–6130; Zorzato et al. 1990) were used for Southern blot analysis. The insert DNAs were excised from Bluescript vector (Stratagene Inc.) by *Eco*RI digestion and were once or twice purified on low-melting-temperature agarose (Biorad) before being labeled with $^{32}$P-dCTP (Amersham Corp.) by random hexanucleotide primer extension to a specific activity of $2 \times 10^8$ dpm/μg.

### *Linkage Analysis*

A total of 440 individuals from 62 DM families were entered into the study. The clinical diagnosis of DM, as well as DNA extraction, restriction-enzyme digests, and Southern blot hybridization conditions for the linkage analysis were as described elsewhere (MacKenzie et al. 1989). The method of Feinberg and Vogelstein (1983) was used for probe labeling. The RYR probe pHRR-XH-1 as described in the previous section was used. The anonymous DNA markers utilized in the present study include p17.1 (D19S8; Shaw et al. 1986), pJSB11 (D19S16; Schepens et al. 1987), pα1.4P (D19S37; Korneluk et al. 1989*b*), and pEWRB1 (D19S50; Korneluk et al. 1989*a*). The apolipoprotein C2 (APOC2) genomic probe pSC11 (Wallis et al. 1984), a full-length APOC2 cDNA probe (Sharpe et al. 1984), and a genomic probe homologue to the 3′ end of the creatine kinase subunit M (CKMM) locus (Coerwinkel-Driessen et al. 1988; Brunner et al. 1989*a*) were also used. The enzymes used for RFLP analysis, as well as the frequencies and sizes of the various polymorphic alleles, are as described elsewhere (Korneluk et al. 1989*a*). The LINKAGE package of programs (Lathrop and Lalouel 1984, versions 4.7 and 5.03) was used for linkage analysis.

## Results

### *Somatic Cell Hybrid Analysis*

Analysis of a series of 13 somatic cell hybrids (MacLennan et al. 1987) revealed 100% concordance between the presence of chromosome 19 and hybridization of the RYR probe pHRR-XH-1 to a 15-kb *Eco*RI fragment (fig. 1 and table 1). Given that the degree of concordance for the remaining chromosomes ranged

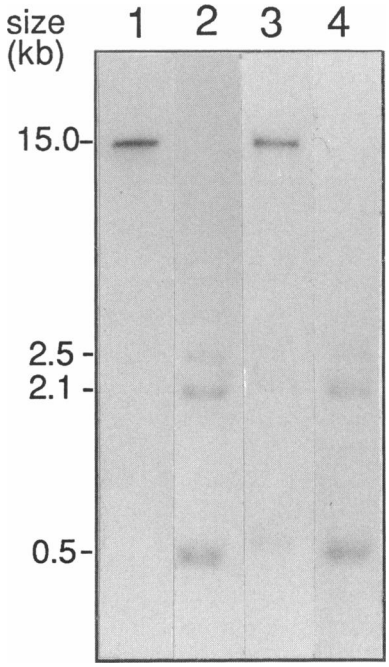


**Figure 1** Filter hybridization analysis of RYR. DNAs are from human (lane 1), mouse (lane 2), and mouse-human hybrids (lanes 3 and 4). DNAs were digested with *Eco*RI, and Southern blot analysis was performed with the probe pHRR-XH-1. The hybrid in lane 3 contained human chromosome 19; the hybrid in lane 4 did not. The 15-kb *Eco*RI band in human genomic DNA which hybridizes to pHRR-XH-1 is apparent. Cross-hybridization to mouse bands at 2.5, 2.1, and 0.5 kb was also observed.

**Table 1**

**Chromosomal Mapping of the Human Ryanodine Receptor Gene**

| Chromosome | Concordant | | Discordant | | Discordancy[a] (%) |
|---|---|---|---|---|---|
| | + / + | − / − | + / − | − / + | |
| 1 | 4 | 6 | 1 | 2 | 23 |
| 2 | 3 | 6 | 2 | 2 | 31 |
| 3 | 1 | 6 | 4 | 2 | 46 |
| 4 | 2 | 3 | 3 | 5 | 62 |
| 5 | 2 | 4 | 3 | 4 | 54 |
| 6 | 1 | 7 | 4 | 1 | 38 |
| 7 | 4 | 3 | 1 | 4 | 42[b] |
| 8 | 3 | 5 | 2 | 3 | 38 |
| 9 | 0 | 8 | 5 | 0 | 38 |
| 10 | 3 | 5 | 2 | 3 | 38 |
| 11 | 2 | 6 | 3 | 2 | 38 |
| 12 | 3 | 6 | 2 | 2 | 31 |
| 13 | 0 | 4 | 5 | 4 | 69 |
| 14 | 4 | 3 | 1 | 5 | 46 |
| 15 | 2 | 6 | 3 | 2 | 38 |
| 16 | 1 | 8 | 4 | 0 | 31 |
| 17 | 1 | 5 | 4 | 3 | 54 |
| 18 | 4 | 5 | 1 | 3 | 31 |
| 19 | 5 | 8 | 0 | 0 | 0 |
| 20 | 2 | 4 | 3 | 4 | 54 |
| 21 | 4 | 3 | 1 | 5 | 46 |
| 22 | 0 | 3 | 5 | 5 | 77 |
| X | 5 | 1 | 0 | 7 | 54 |
| Y | 0 | 7 | 5 | 1 | 46 |

NOTE.—Data are the number of hybrids in which the particular human chromosome and the hybridizing bands were either both present ( + / + ) or both absent ( − / − ) (concordant) or in which the human chromosome was absent and the hybridizing bands present ( + / − ) or in which the human chromosome was present and the bands absent ( − / + ) (discordant).

[a] Percentage of hybrids scores in which the indicated human chromosome and the hybridizing bands were discordant.

[b] Only 12 cell hybrids were scored for chromosome 7.

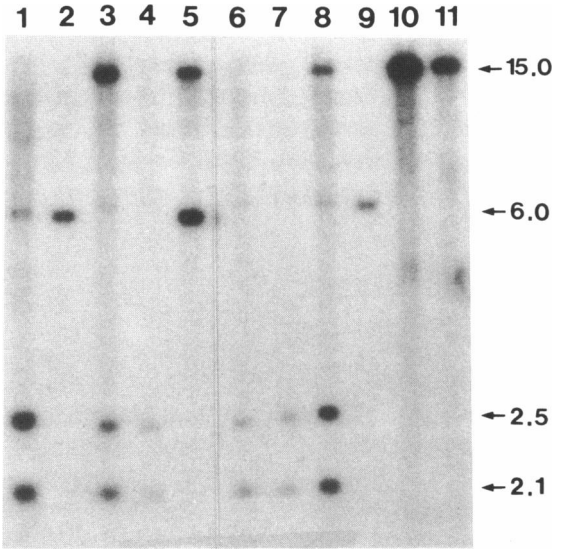


**Figure 2** Southern blot hybridization of the pHRR-XH-1 probe to *Eco*RI-digested DNA extracted from the following somatic cell hybrids: mouse A9 control (lane 1), hamster E36 control (lane 2), G24A9 (retains 19p13→19qter) (lane 3), G24B2TG (back-selected for the loss of 19p13→19qter) (lane 4), G35E4 (retains 19pter→19q13.3) (lane 5); B-9 (retains 19q13.2→19qter) (lane 6), GM89A99C7B (retains 19q13.3→19qter) (lane 7), CF104–19/6 (retains 19cen→qter) (lane 8), G89E5 (contains a normal human X chromosome only) (lane 9), normal human male (lane 10), and normal human female (lane 11). Cross-hybridization of the probe pHRR-XH-1 to hamster DNA sequences is seen at 6.0 kb, and cross-hybridization of this probe to mouse *Eco*RI fragments is seen at 2.5 and 2.1 kb.

from 23% to 73%, this result effectively mapped RYR to chromosome 19.

Somatic cell hybrid analysis with RYR probe pHRR-XH-1 was then conducted on a number of cell lines, each containing a different translocation-derived chromosome involving human chromosome 19. Figure 2 illustrates that the RYR probe hybridizes to genomic digests of human DNA from hybrids that retain the proximal 19q region but not to DNA from hybrids containing distal 19q regions. These results sublocalize RYR to 19qcen→q13.2.

Further map refinement was achieved with somatic cell hybrids (fig. 3) whose translocation products allowed the definition of five different intervals across 19q (Schonk et al. 1989). This mapping panel was extended with a series of cell hybrids containing der (19) irradiation products permitting discrimination between subsegments in the 19cen-q13.1 area (fig. 3). Hybridization of the pHRR5 *Eco*RI probe on *Eco*RI digests of cellular DNAs revealed the presence of genomic RYR sequences in somatic hybrids 908K1, 908K1A, 908K1B18, −B2, −B26, and ORIM7–1 and its absence in somatic hybrids 1219 G2, 908K1B15, −B17, −B19, and −B23. This localizes RYR to 19q13.1 distal to the genes for glucose phosphate isomerase (GPI) and myelin-associated glycoprotein (MAG; Schonk et al. 1989) and proximal to the anonymous marker pPM6.7 (D19S18; Smeets et al. 1987) and to the lymphocyte-specific cDNA DNF11 gene (Jandel et al. 1985).

### *Linkage Analysis*

The proximity of RYR to the DM locus in this region of chromosome 19 led us to carry out a study of the linkage between the two loci. A two-allele RYR

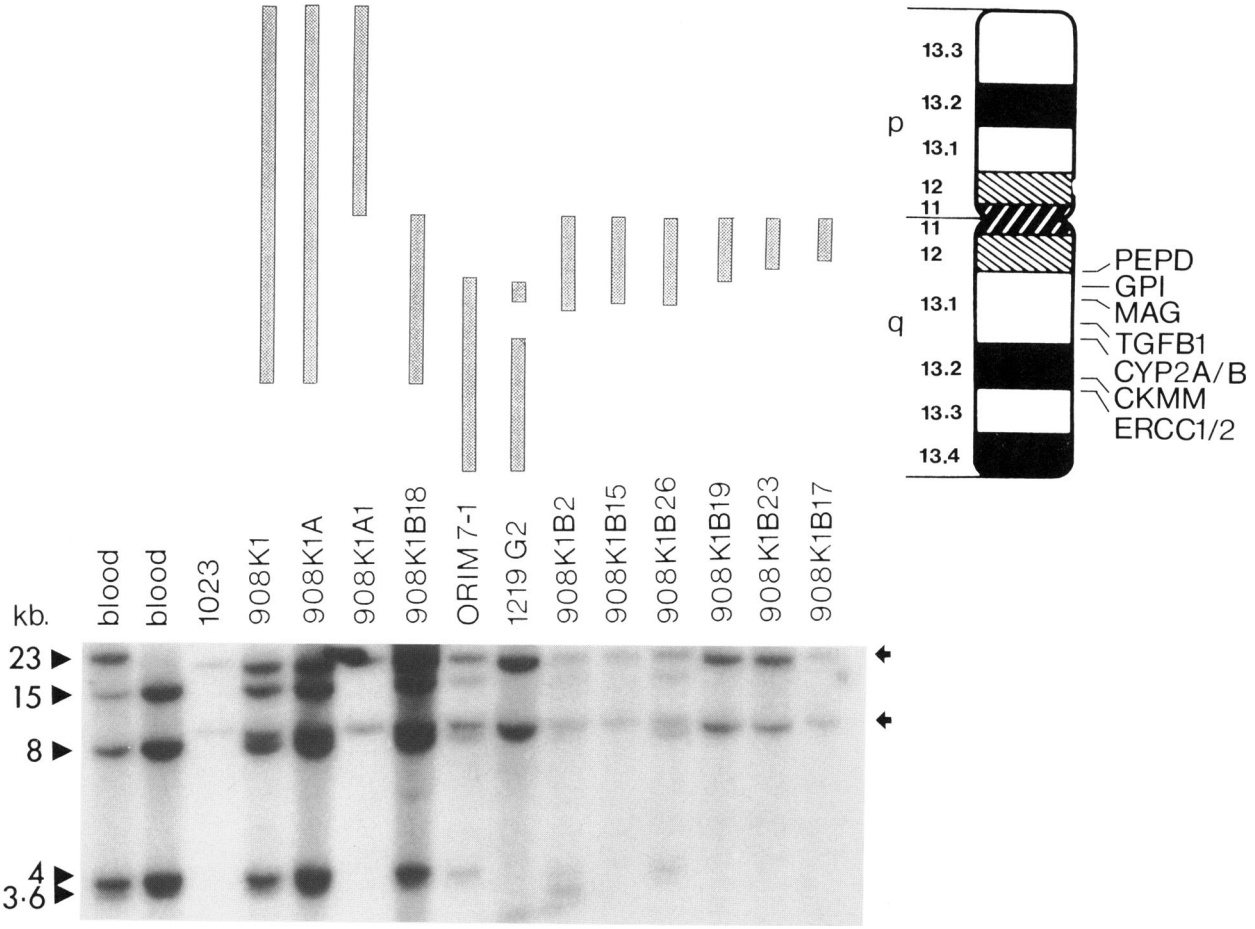


**Figure 3** Schematic representation of the chromosome 19 content in various human-hamster somatic cell hybrids (*left*) and the positions of relevant genes on chromosome 19q (*right*). The hybrid 908K1 contains a single der (X;19) (q24;q13.2) chromosome with a rearranged 19p arm. Cell lines 908K1A, 908K1A1, and 908K1B18 contain chromosome regions 19pter→q13.2, 19pter→cen, and 19cen→q13.2, respectively. Irradiation-derivative cell hybrids, designated 908K1B 1–26, contain unique human chromosomal segments beginning at 19cen and terminating in the region 19q12-q13.2, as shown in the diagram. In addition to other human chromosomes, the somatic cell hybrid ORIM 7–1 contains a t(X;19) (Xqter;19q13.1) chromosome. Cell line 1219 G2 contains a der(19) 19q13.1-qter::12pter-12q15 product, a small region containing the GPI and MAG loci proximal to the 19q13.1 breakpoint, and chromosomes 5, 6, 17, 18, and 20–22 (Schonk et al. 1989). Hybridization analysis of an RYR cDNA probe to *Eco*RI-digested DNAs from the somatic cell hybrids are shown in the lower panel. The DNA content of each lane is indicated above the autoradiogram. In lanes 1 and 2, the 23-kb or 15+8-kb alleles detected by the probe pHRR5 are evident, while lane 3, containing hamster cell line 1023 DNA, shows the 19- and 9-kb background hamster signals.

*Bam*HI RFLP was identified utilizing pHRR-XH-1 (fig. 4). The (+) allele containing the *Bam*HI site had an observed frequency of .25, and the (−) allele had an observed frequency of .75. The results of two-point linkage analysis between RYR and seven chromosome 19 loci including the DM locus are shown in table 2. RYR is closely linked to D19S16 (maximum lod score [$Z_{max}$] = 5.71, recombination fraction [$\theta$] = .00). Moderate linkage is seen between RYR and D19S8 ($Z_{max}$ = 8.61, $\theta$ = .04), between RYR and CKMM ($Z_{max}$ = 12.36, $\theta$ = .05), and between RYR and the DM locus ($Z_{max}$ = 5.02, $\theta$ = .07). Weaker linkage ($Z_{max}$ = 5.73, $\theta$ = .11) is seen in the RYR/APOC2 pairing. Both lod score characterizing the linkage between RYR and D19S37 ($Z_{max}$ = 2.28, $\theta$ = .11) and that characterizing the linkage between RYR and pEWRB1 ($Z_{max}$ = 1.96, $\theta$ = .22) were <3.

A list of the recombinant chromosomes involving RYR and the two loci, D19S16 and D19S8, which show the tightest linkage to RYR is depicted in figure 5. These recombinant events, specifically those observed in individuals with recombinant chromosomes 1 and 2, iden-

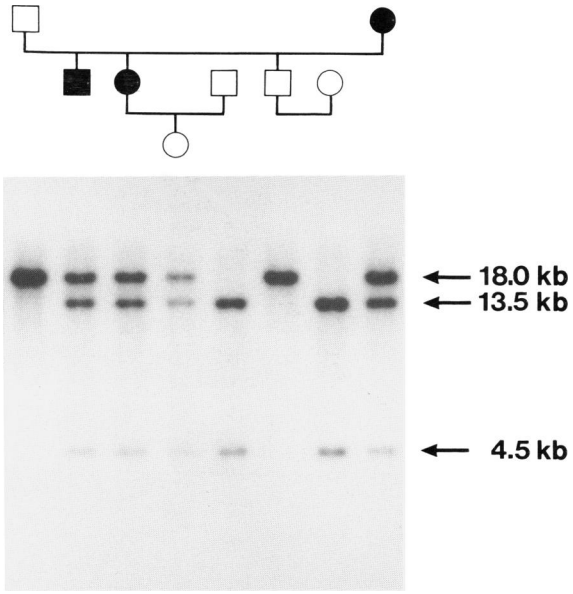


**Figure 4** Segregation analysis of the *Bam*HI polymorphism detected by the probe pHRR-XH-1 in a DM family. Clinically affected individuals are designated by solid symbols. In this family, the DM phenotype segregates with the grandmaternal 13.5+4.5-kb (+) allele.

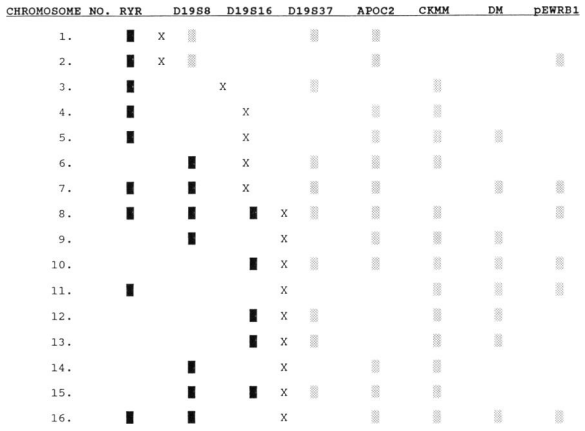


**Figure 5** List of 16 recombinant chromosomes involving RYR, D19S8, and D19S16 that were observed in our DM pedigrees. Centromeric loci are represented by a black rectangle (■); telomeric markers which show recombination with the centromeric markers are indicated by a stippled rectangle ( ▒ ). Uninformative loci have been left blank. X = the region containing the crossover site.

tify RYR as the most centromeric marker of the chromosome 19 linkage group recently generated by Korneluk et al. (1989*a*). Consequently, the following ordering on the proximal long arm of chromosome 19 can be made: 19qcen–RYR–D19S8–D19S16–D19S37–APOC2–CKMM–DM–pEWRB1–19qter.

Three- and four-point linkage analyses were used to calculate the odds against placement of RYR in the various interlocus spaces (fig. 6). These multipoint results clearly support the centromeric localization of RYR with respect to the linkage group, as the odds against proposed telomeric localizations of the gene are considerably higher than those against a centromeric mapping.

## Discussion

The four recombinations between RYR and the DM locus, depicted in figure 5 and reflected in the DM-RYR recombinant fraction of .07, demonstrate the nonidentity of the DM locus and RYR. The pattern of observed recombinants, the two-point linkage results, and multipoint linkage analysis all strongly suggest a mapping of RYR considerably centromeric to the DM locus. This interpretation is corroborated by our somatic cell hybridization mapping data. One of the cell lines utilized

**Table 2**

**Lod Scores Characterizing Linkage of RYR to Various Chromosome 19 Loci**

| Locus | Lod Scores at θ of | | | | | | | | | | $Z_{max}$ | $\theta_{max}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | .001 | .01 | .02 | .03 | .04 | .05 | .1 | .2 | .3 | .4 | | |
| pERWB1 ..... | −29.97 | −14.10 | −9.45 | −6.82 | −5.02 | −3.69 | −.05 | 1.89 | 1.62 | .63 | 2.05 | .17 |
| DM ..... | 1.94 | 3.97 | 4.47 | 4.73 | 4.89 | 4.97 | 4.98 | 4.03 | 2.58 | 1.05 | 5.04 | .07 (.01–.20) |
| CKMM ..... | 5.80 | 10.63 | 11.64 | 12.09 | 12.29 | 12.35 | 11.73 | 8.77 | 5.16 | 1.81 | 12.36 | .05 (.02–.12) |
| APOC2..... | −5.90 | 1.18 | 2.94 | 3.89 | 4.51 | 4.89 | 5.72 | 4.94 | 3.14 | 1.21 | 5.73 | .11 (.04–.21) |
| D19S37 ..... | −2.36 | −0.36 | 1.09 | 1.49 | 1.75 | 1.91 | 2.27 | 1.96 | 1.17 | .34 | 2.28 | .11 |
| D19S16 ..... | 5.70 | 5.59 | 5.48 | 5.36 | 5.24 | 5.14 | 4.51 | 3.20 | 1.84 | .58 | 5.71 | .00 (.00–.08) |
| D19S8 ..... | 6.21 | 8.10 | 8.45 | 8.58 | 8.61 | 8.58 | 8.01 | 6.03 | 3.63 | 1.26 | 8.61 | .04 (.00–.12) |

Note.—Numbers in parentheses are the 1-lod-unit confidence intervals for θ's associated with $Z_{max} > 3$.

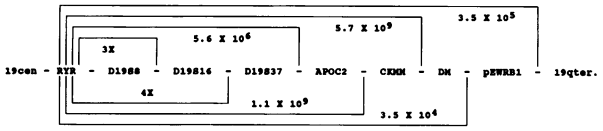


**Figure 6** Odds against placement of RYR in various map intervals, vs. the proposed centromeric mapping as determined by multipoint linkage analysis.

in the present study was B-9, which contains as its sole chromosome 19 component that portion of the long arm lying distal to D19S37 (Korneluk et al. 1989*a*). Consequently, this hybrid cell line effectively bisects our linkage group. The absence of binding of an RYR cDNA probe to B-9 DNA maps RYR centromeric to D19S37, whereas the DM locus lies telomeric to D19S37 (Korneluk et al. 1989*a*). The probes p17.1 (D19S8) and pJSB11 (D19S16) have both been mapped to 19q13.1 (Schonk et al. 1989) The close linkage between these loci and RYR suggests a mapping of RYR to 19q13.1. This is supported by the high-resolution mapping utilizing the hybrid cell lines containing der(19) irradiation products which maps RYR to 19q13.1 between GPI/MAG and D19S18/DNF11 (fig. 3).

It has been difficult until now to discriminate between the chromosome 19 content in cell hybrids 908K1B15 and -B26. The detection of RYR DNA in 908K1B26 but not in 908K1B15, however, indicates that the breakpoint in 908K1B26 is slightly distal to that in 908K1B15. As the intervals between the various endpoints in the 908K1B derivatives are most likely small, this result may indicate that RYR maps close to a breakpoint in these cell lines. Probes from the 5′ and 3′ ends of RYR, used in combination with long-range restriction analysis, may help establish both the chromosomal orientation of RYR and the physical distances between the 908K1B26 breakpoint and the various neighboring genes.

Although a defect in RYR clearly does not cause DM, such a defect could be responsible for malignant hyperthermia (MH). MH is an autosomal dominant disorder in which exposure to an inhalational anaesthetic precipitates diffuse muscle contracture and elevated body temperature, findings consistent with the sustained release of $Ca^{++}$ into muscle cells (Britt 1979; Gronert 1980). Biochemical evidence implicates a defect in the ryanodine receptor as a possible cause of MH (Casson and Downes 1977; Endo et al. 1983; Nelson 1983; Kim et al. 1984; O'Brien 1986; Rousseau et al. 1987; Mickelson et al. 1988). The halothane sensitivity gene (HAL), which causes MH in the pig, is located on chromosome 6 (Davies et al. 1988) and is linked to and bracketed by the phosphohexose isomerase gene (PHI; GPI in humans) and by the serum post albumin2 locus (Po2), which map to human 19q (Hojny et al. 1985; Juneja et al. 1987; Eiberg et al. 1989). Thus physiological and biochemical data combined with our mapping of RYR to a region of chromosome 19 syntenic to that which contains the HAL gene in pigs, suggest the possibility that a defect in RYR may cause MH in both humans and pigs. This contention is strengthened by a recent study demonstrating genetic linkage between MH and an RYR polymorphism (MacLennan et al. 1990). Direct structural analysis of RYR in humans and pigs affected with MH is currently underway.

## Acknowledgments

The excellent technical assistance of Heather MacLeod, Donelda Lahey, Vijay Khanna, and Stella de Leon is gratefully acknowledged. We wish to thank James Blustein, Melanie Mahtani, and Donald Federberg for help with computer programming and linkage analysis. We are grateful to Dr. A. Hunter and his numerous clinical colleagues for identification of DM families, clinical assessment, and arrangement of blood taking. The excellent neurologic assessments of Drs. P. Jacob and P. Humphries, upon which much of this work rests, is gratefully acknowledged. We are grateful to Dr. D. Schonk and to P. van Dijk for the hybrid cell lines and for maintenance of tissue culture and to Professor H. H. Ropers for helpful suggestions. This work is supported by Muscular Dystrophy Association of Canada (MDAC) grants to R.G.K., R.G.W., and D.H.M.; by a Medical Research Council of Canada (MRC) grant to H.F.W., R.G.K., R.G.W., and D.H.M.; by Muscular Dystropy Association (USA) grants to R.G.K., R.G.W., and B.W.; and by a Dutch Praeventiefonds, Dutch Beatrixfonds, and Deutsche Forschungsgemeinschaft grant to B.W. F.Z. is a postdoctoral fellow of the Canadian Heart Foundation, A.E.M. is a postdoctoral fellow of the MRC, and J.F. is a postdoctoral fellow of the MDAC. Inquiries regarding RYR probes should be directed to D.H.M. at the address given for him on the first page of this article.

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