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Malignant Hyperthermia Genetic Testing in North America Working Group Meeting. Bethesda, Maryland. September 4–5, 2002

The Malignant Hyperthermia Working Group Meeting, sponsored by the Malignant Hyperthermia Association of the United States (MHAUS), was held September 4–5, 2002, in Bethesda, Maryland, to establish a consensus for genetic screening of malignant hyperthermia (MH) in North America.

MH is a potentially fatal pharmacogenetic disorder triggered by the administration of commonly used inhalational anesthetics and/or the muscle relaxant succinylcholine. A major obstacle in preventing the occurrence of MH is the difficulty of preoperative diagnosis. At present, the Caffeine Halothane Contracture Test (CHCT) is the only validated test available to phenotype MH-susceptible patients. Recent advances in identifying genes and their mutations causal for MH have helped to develop genetic testing. Gene linkage studies have shown that more than 50% of MH cases are associated with the ryanodine receptor 1 (RYR1, Ca^{2+} release channel of skeletal muscle) on chromosome 19q13.1–13.2. The European MH group has recently published guidelines for genetic testing for MH and listed 15 mutations in the RYR1 as potentially causative and diagnostic for MH.[1]

The meeting began with presentations by organizers Drs. Thomas Nelson, Ph.D., Professor, Wake Forest University, Winston-Salem, North Carolina, and Sheila Muldoon, M.D., Professor, Uniformed Services University of the Health Sciences, Bethesda, Maryland, updating clinical and genetic aspects of MH. Dr. Yoshitatsu Sei, M.D., Ph.D., Assistant Professor, Uniformed Services University of the Health Sciences, Bethesda, Maryland, presented an update of RYR1 gene screening in North America and discussed practical issues related to screening DNA samples from multiple centers in North America. Dr. Nyamkhishig Sambuughin, Ph.D, Assistant Professor, Barrows Neurological Institute, Phoenix, Arizona, discussed a strategy to screen the entire RYR1 gene. Dr. David MacLennan, M.D., Professor, Univeristy of Toronto, Toronto, Ontario, Canada, presented other candidate genes that are involved in calcium homeostasis in muscle cells. Dr. Henry Rosenberg, M.D., Professor, St. Barnabas Medical Center, Livingston, New Jersey, gave an overview of the current status of the Malignant Hyperthermia Association of the United States, and Dr. Barbara Brandom, M.D., Professor, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, gave an update of the North American MH Registry (NAMHR). Drs. Wayne Grody, M.D., Ph.D., Professor, University of California, Los Angeles Medical Center, Los Angeles, California; Sue Richards, Ph.D., F.A.C.M.G., Associate Professor, Baylor College of Medicine, Houston, Texas; Michael Watson, Ph.D., F.A.C.M.G., Adjunct Professor, Washington University, St Louis, Missouri; and Debra Leonard, M.D., Ph.D., Professor, University of Pennsylvania, Philadelphia, Pennsylvania, discussed their experience with the development of genetic testing for other genetic disorders, such as cystic fibrosis and familial adenomatous polyposis. The second day of the meeting was dedicated entirely to the development of a consensus statement and recommendations addressing the basic approaches to genetic studies of MH in North America, and the potential clinical uses of genetic testing for MH. This session, led by Dr. Leonard, produced a draft summary.

This article is accompanied by an Editorial View. Please see: Nelson TE, Rosenberg H, Muldoon SM: Genetic testing for malignant hyperthermia in North America (editorial). ANESTHESIOLOGY 2004; 100:000–000.

The consensus points formulated from the 2-day meeting are:

1. Genetic testing for MH can be developed and used with some limitations, including the low sensitivity of the test due to diversity of the mutations and genes.
2. At this time, the RYR1 gene is the focus for development of genetic testing. However, further genetic studies are required for more complete understanding of the relationship between mutations and MH susceptibility.
3. Guidelines should be developed for clinical testing in a Clinical Laboratory Improvement Act (CLIA)–certified laboratory.

Recommendations were formulated from two parts of the discussion. Part 1 focused on further genetic studies of the RYR1 gene in North America. Part 2 focused on clinical testing in a CLIA-licensed laboratory. A North American MH Mutation Panel 2002 was also established and agreed upon.

Part 1. Genetic Studies of the RYR1 Gene. Full RYR1 mutation analysis of patients in the North American MH Registry who have strongly positive phenotypic MH is recommended. The analysis includes (1) mutation screening using the consensus of the 2002 North American MH Mutation Panel (table 1), (2) screening exons in the mutation hot spots of the RYR1 gene using a gene scanning approach, and (3) full-sequence analysis. For this study, the selection criteria of patients in the North American MH Registry must be determined by a history of the clinical episode (D5 and D6) and positive CHCT results. For patients negative for full RYR1 mutation analysis, additional analysis (*e.g.*, analyses for gross alterations and mutations in promoter regions) is recommended. There are also recommendations for evaluation of new sequence variants by using American College of Medical Genetics guidelines, database searches, studies of "wild type" (*i.e.*, normal individuals), transfection studies, and family studies. Finally, further broad population studies using the consensus MH mutation panel are recommended.

Part 2. Clinical Testing in a CLIA-licensed Laboratory. The Working Group listed conditions for using clinical genetic testing:

1. Request from a physician at an approved MH Diagnostic Center with informed consent is needed.
2. Indications for genetic testing are (a) diagnostic testing for proband with positive CHCT or unknown CHCT (if genetic results are negative, CHCT is recommended); (b) presymptomatic testing for family members with an identified mutation, and for family members with an absence of an identified mutation when proband is unavailable for testing; and (c) confirmation of research testing.
3. At a minimum, the laboratory should test for the current consensus MH mutation panel (table 1). All samples, including those having no mutation, will be banked and used in future research on RYR1 and other genes that may be associated with MH.
4. A negative result without a known familial mutation will be reported, with a statement that this result does not rule out the risk of MH.
5. Results will be reported to MH Diagnostic Center referring physicians. Genetic counseling by qualified individuals should be provided.
6. The ideal setting for genetic testing would be a CLIA-certified laboratory with a genetic counseling program. Genetic counseling may be provided in the context of the MH Centers.

Finally, the Working Group recommended that the following actions should begin immediately:

- identification and selection of well-characterized MH patients by the North American MH Registry
- establishment of the RYR1 database
- education of MH biopsy centers about genetic testing

Table 1. North American MH Mutation Panel 2002

Exon	Mutation	RYR1 Amino Acid Change	No. of Families in North America*	Estimated Incidence in Europe (%)	Phenotype
6	C487T	R163C	2	2–7	MHS, CCD
9	G742A	G248R	2	2	MHS
11	G1021A	G341R	1	6–17	MHS
17	C1840T	R614C	6	4–45	MHS
39	C6487T	R2163C	2	4	MHS
39	G6488A	R2163H	0	1	MHS, CCD
39	G6502A	V2168M	1	8	MHS, CCD
40	C6617T	T2206M	2	One family	MHS
44	Deletion	G2347	2	0	MHS
44	G7048A	A2350T	2	0	MHS
45	G7300A	G2434R	9	4–10	MHS
45	G7307T	R2435H	1	2.5	MHS, CCD
46	G7361A	R2454H	4	One family	MHS
46	C7372T	R2458C	0	4	MHS
46	G7373A	R2458H	0	4	MHS
101	G14582A	A4861H	NA	Multiple families	CCD
102	T14693C	I4898T	NA	Multiple families	MHS, CCD

Includes individuals from the United States and Canada. Selection criteria of the 17 mutations are (1) the mutations are seen in more than one family in North America or Europe, and (2) previous testing of a sequence variant to rule out a polymorphism.

* Data collaboration of the Uniformed Services University of the Health Sciences, Bethesda, Maryland; Thomas Jefferson University, Philadelphia, Pennsylvania; Wake Forest University, Winston-Salem, North Carolina; University of California Davis, Davis, California; Barrow Neurological Institute, Phoenix, Arizona; and University of Toronto, Toronto, Ontario, Canada.

CCD = central core disease; MH = malignant hyperthermia; MHS = malignant hyperthermia susceptibility; NA = not available at the time of the meeting.

- production of educational materials for patients and physicians by the Malignant Hyperthermia Association of the United States
- searches for potential funding sources Conclusion

The ultimate goal of genetic research is to elucidate the mechanisms leading to MH at the molecular level. The ability to identify genetic mutations associated with MH creates the possibility of using DNA testing to make predictive statements regarding reactions to anesthetics that trigger MH. This is the first meeting that has produced recommendations and a consensus for genetic screening of MH in North America. These recommendations are based on current scientific understanding, as well as the prevailing legal and social contexts in the United States. Revisions and expansions of this work are expected in the near future. We gratefully acknowledge the support of the Malignant Hyperthermia Association of the United States.

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Reference

1. Urwyler A, Deufel T, McCarthy T, West S: Guidelines for molecular genetic detection of susceptibility to malignant hyperthermia. Br J Anesth 2001; 86: 283–7

(Accepted for publication August 12, 2003)