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## Genetics and Susceptibility to Malignant Hyperthermia

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# Genetics and Susceptibility to Malignant Hyperthermia

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## PRIME POINTS

- Learn about the effect of genetics on critical care nursing and why it is important to understand the impact genetics has on your practice.
- Malignant hyperthermia is a classic genetic aberration seen in critical care today—read about what genetic testing is available to determine which patients are at high risk for malignant hyperthermia.

## Background

Critical care nurses have seen the influences of genetics on their practice in many ways since the 1980s. These influences have been especially apparent since completion of the Human Genome Project in April 2003, leading to phenomenal advances in the practice of medicine in reference to genetics. Critical care nurses are seeing noticeable changes in patient care that will increase in the future. Because of these changes, understanding the science behind current advances is increasingly important so that the advances can be applied appropriately to critical care practice.

What must be more fully understood are the sciences of genetics and

## CE Continuing Education

This article has been designated for CE credit. A closed-book, multiple-choice examination follows this article, which tests your knowledge of the following objectives:

1. Discuss how advances in the study of genomics will affect the practice of critical care nurses in the future
2. Describe how genetic mapping can predict susceptibility to malignant hyperthermia
3. Discuss the pharmacological triggers for malignant hyperthermia reactions

genomics. *Genetics* is the study of single genes or groups of genes.<sup>1</sup> *Genomics* is the study of an organism's genome, which is all the DNA contained in an organism or a cell, which includes both the chromosomes within the nucleus and the DNA in mitochondria.<sup>2,3</sup> The study of the global properties of genomes of related organisms is usually referred to as genomics, which distinguishes it from genetics. The Human Genome Project provided a complete map of the human genome. This map identified genes that code for various proteins involved in the cellular workings of the human body.<sup>4</sup> This information has made it possible for researchers to begin to show links and correlates between environmental and genetic influences and how these interactions relate to health conditions.<sup>5</sup> Although, genetics will continue to play a role in the future of health care, genomics is where the bulk of the new advances will arise.<sup>6</sup> Studying interactions between the genome and the environment in humans potentially can lead to new ways to diagnose, prevent, and treat disease by altering assessment and

intervention strategies in health care. Currently, many investigators are examining the association between specific genes and disease processes, and much of this research will affect critical care nurses.

Genomics-related research will allow for individualized or person-

alized medicine,<sup>7-9</sup> with a more patient-specific care plan for each patient. Many of today's emerging advances in cancer are directed at determining the best treatment for individual patients on the basis of the genome of the tumor the patient has. For example, a patient

with breast cancer whose tumor is positive for the protein HER2 can be treated with the gene-specific drug herceptin. In patients with cardiovascular disease, genetic alterations are closely associated with medical conditions such as monogenic arrhythmia syndromes (eg, prolonged QT syndrome), as well as hypertension, familial hypertrophic cardiomyopathy, stroke, and elevated levels of low-density lipoprotein.<sup>6,10-14</sup> Other conditions with research potential are asthma and chronic obstructive pulmonary disease. Researchers are examining the genes associated with the causes of these disorders and the responses to

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## CASE STUDY

Mr F is a healthy 34-year-old man who is admitted to a local metropolitan hospital for a routine cholecystectomy. A preoperative assessment by the nurse anesthetist reveals no prior surgeries and a familial history of anesthetic complications, but Mr F is unsure of what the complications were called. During the surgery, no adverse effects are noted by the surgical team.

After successful removal of the gallbladder and an unremarkable anesthetic reversal, Mr F is transported to the postanesthesia care unit and monitored before transfer to a medical-surgical unit. Vital signs are as follows: heart rate, 75/min; blood pressure, 127/82 mm Hg; respiratory rate, 16/min; oxygen saturation, 100%; body temperature, 36.9°C. When Mr F arrives in the postanesthesia care unit, the receiving nurse notices an increase in his heart rate to 91/min and an increase in respirations to 21/min. After administering a 3-mg intravenous bolus of morphine sulfate for pain and increasing oxygen delivery to 4 L/min via Mr F's cannula, the nurse continues to see a gradual increase in heart rate and respirations as well as an increase in blood pressure. Mr F's vital signs are now as follows: heart rate, 114/min; blood pressure, 147/92 mm Hg; respirations, 25/min; oxygen saturation, 98%; and body temperature, 38.8°C. The nurse again treats Mr F with a 3-mg intravenous bolus of morphine sulfate and increases his oxygen to 5 L by mask.

During the nurse's assessment, she notices that Mr F's body temperature is increasing. As the surgeon and the certified registered nurse anesthetist are called to report Mr F's condition, the patient begins to experience muscle rigidity of the trunk. At this point, vital signs are as follows: heart rate, 127/min; blood pressure, 167/101 mm Hg; respirations, 31/min; oxygen saturation, 89%; and body temperature, 39.5°C. Mr F's electrocardiogram begins to show ventricular ectopy. A possible diagnosis of malignant hypertension is made by the nurse anesthetist, the malignant hyperthermia cart is brought in, and Mr F is immediately treated with 2.5 mg/kg of dantrolene intravenously and 2 mEq/kg of bicarbonate and is reintubated. Serial blood gas analyses are started, along with coagulation studies, a complete blood cell count, and measurements of electrolyte, creatine kinase, lactate, and myoglobin levels. Sequential samples are also collected from the urinary catheter to monitor myoglobin levels in the urine. Mr F is covered with a cooling blanket and ice packs.

Laboratory studies reveal the following: pH, 7.21; Pco<sub>2</sub>, 75 mm Hg; Po<sub>2</sub>, 85 mm Hg (oxygen saturation); and potassium level, 7.2 mEq/L. Mr F is given 10 units of regular insulin intravenously, 50 mL of 50% dextrose in water intravenously, and 10 mg/kg of calcium chloride. He is transferred to the intensive care unit for further evaluation. His vital signs upon transfer are as follows: heart rate, 115/min; blood pressure, 150/92 mm Hg; respiratory rate, 26/min; oxygen saturation, 93%; body temperature, 38°C.

treatment.<sup>15-23</sup> Other areas of research in genetics and genomics include, but are not limited to, type 2 diabetes, sepsis, transfusion medicine, kidney disease, and wound healing.<sup>24-32</sup>

In this article, we explore genetics and genomics in the context of the pathophysiology of malignant hyperthermia. In addition, we provide a glimpse of advances being made in genetic testing and application of pharmacogenetics to practice, specifically in patients with genetic susceptibility to malignant hyperthermia.

hyperthermia.<sup>36</sup> Mutations at this locus account for 80% of all cases of susceptibility to malignant hyperthermia. Most *RYR1* mutations occur in the areas of amino acid residues 35 to 614 (N-terminal region), 2117 to 2458 (central region), and 3916 to 4973 (C-terminal region). To date, approximately 42 mutations linked to this gene have been found. Most of these mutations are called *missense* mutations,<sup>33</sup> meaning the mutation alters a single base within the section of DNA that codes for a certain amino acid; the mutation can result in an amino

volatile inhalation agents and/or succinylcholine, a depolarizing muscle relaxant, are used. The volatile agents identified as triggers of malignant hyperthermia are halothane, isoflurane, enflurane, sevoflurane, and desflurane. The combination of succinylcholine and a potent volatile anesthetic agent triggers a more rapid reaction than does a volatile agent alone or succinylcholine alone.<sup>1</sup> No evidence indicates that intravenous anesthetics such as opioids induce malignant hyperthermia.

## The advantages of genetic testing over the contracture test are reduced invasiveness, lower cost, and the lack of morbidity associated with muscle biopsy.

### Genes

Susceptibility to malignant hyperthermia is an inherited genetic disorder that is manifested as an autosomal dominant pharmacogenetic trait.<sup>33</sup> Identification of this disorder was based on a family in Australia and was first reported in the early 1960s.<sup>34</sup> Genetic incidence is estimated to be 1 in 10 000.<sup>35</sup>

In genetic studies, 6 loci within the human genome that are linked with susceptibility to malignant hyperthermia have been identified. Of these loci, 3 have been mapped and the genes identified; the other 3 loci have been mapped, but the genes have not been identified. Studies during the early 1990s revealed MHS1, a locus that is associated with mutations in the gene *RYR1*, which codes for ryanodine receptor 1 on band 19q13.1. MHS1 is a primary site where mutation occurs, resulting in susceptibility to malignant

acid change and an altered protein.<sup>37</sup> Another locus identified was MHS3, associated with mutations in the gene *CACNA2D1*, which codes for the  $\alpha_2\delta$  subunit of a dihydropyridine-sensitive L-type calcium channel. This specific mutation has been reported in only a few persons and accounts for 1% of all cases of susceptibility to malignant hyperthermia.

The last identified locus is MHS5, which is associated with mutations in *CACNA1S*, the gene that codes for skeletal muscle calcium channels. Mutations in MHS5 also account for 1% of all cases of susceptibility to malignant hyperthermia. The other 3 loci (MHS2, MHS4, and MHS6) have been mapped, but the specific genes have not been clearly identified yet.

### Pharmacogenetics

Malignant hyperthermia is a rare reaction and usually occurs when

Results of multiple studies have suggested links between susceptibility to malignant hyperthermia, the use of potent volatile anesthetics, and mutation of *RYR1*. In North America, 10 mutations account for 22% of the population susceptible to malignant hyperthermia.<sup>33</sup> In Australia and New Zealand, a unique mutation was found in the malignant hyperthermia/central core disease region I of the *RYR1* gene specific to 9 families.<sup>38</sup>

Mutations in *RYR1* affect skeletal muscle, leading to the sustained release of calcium from the sarcoplasmic reticulum, causing a hypermetabolic state to occur within the muscle tissue. The mutated area of the ryanodine receptor is the site of action for the inhaled agents and/or succinylcholine. The mutation changes the receptor from one of regulation to one with an excitatory function that results in the abnormal release of intracellular

calcium and causes the malignant hyperthermia cascade. The drastic and uncontrolled increase in skeletal muscle oxidative metabolism increases carbon dioxide production and causes a 3- to 5-fold increase in oxygen consumption. Other signs include muscle rigidity, rhabdomyolysis, and marked elevation in body temperature (see "Case Study"). This series of events can cause skeletal muscle damage as well as hypermetabolic states of crisis, such as cardiac arrhythmias, that if untreated result in death.

Research studies support the link between genetic mutation of the ryanodine receptor and pharmacological effects of halothane that cause malignant hyperthermia. Evidence from studies with the contracture test, in which halothane, caffeine, and ryanodine challenges are used, supports a similar individual pharmacogenetic effect among the 3 agents rather than a specific, different pharmacological action for each.<sup>33</sup> Tammaro et al<sup>33</sup> clearly found a connection between the use of halothane as a potent inhaled volatile anesthetic and its interaction with the mutated ryanodine receptor to directly induce malignant hyperthermia.

## Genetic Testing

Genetic testing is used to detect whether someone has a genetic condition or is likely to acquire a disease. Generally, persons are tested if they

have a familial history for a certain disease, they have signs or symptoms of a genetic disorder, or they are concerned about their children inheriting a genetic disorder (see "Case Study").

Genetic testing for malignant hyperthermia has only recently been developed and implemented.<sup>39-42</sup> According to the June 2006 newsletter of the Malignant Hyperthermia Association of the United States<sup>43</sup> and the September 2005 newsletter of the American Society of Anesthesiologists,<sup>44</sup> PreventionGenetics, LLC, a company in Wisconsin, has begun offering molecular genetic testing for malignant hyperthermia, as has the University of Pittsburgh Medical Center for Medical Genetics.<sup>39</sup> Genetic testing, which requires only a small sample of blood, is less invasive than the muscle contracture test, the previously used reference standard. The contracture test requires a biopsy specimen of muscle tissue, which is then exposed to halothane and caffeine through various techniques. Although the contracture test is sensitive, it is more invasive, expensive, and inconvenient to patients than is genetic testing.

The Malignant Hyperthermia Association of the United States Web site states that genetic testing detects only about 30% of persons at risk. The genetic test is very specific, however, so those with a positive test are almost certainly at risk for malignant hyperthermia. Sequence analysis, which is complete sequencing of the *RYR1* gene, may detect mutation at a rate of up to 70%.<sup>39-42</sup> The Malignant Hyperthermia Association of the United States<sup>42</sup> also advises the following types of persons be considered for genetic testing:

- Persons who have tested positive on the contracture test

- Relatives of persons who have tested positive on the contracture test
- Persons shown by a research protocol to have a mutation that causes malignant hyperthermia

- Relatives of persons with a known mutation for malignant hyperthermia
- Persons with a very high likelihood of having experienced an episode of malignant hyperthermia.

As mentioned earlier, the advantages of genetic testing over the contracture test are reduced invasiveness, lower cost, and the lack of morbidity associated with muscle biopsy. In time, the sensitivity of the genetic test most likely will improve markedly.<sup>42</sup>

## Conclusion

The completion of the Human Genome Project has changed the practice of medicine and will soon affect all facets of health care. Critical care nurses must understand the implications of genomics so that they can provide the safest and most patient-specific care available. The incidence of malignant hyperthermia is 1 in 10 000, so most likely most anesthesia providers and critical care nurses will be directly involved in at least one case of the disorder during their careers.<sup>1</sup> Critical care nurses will be able to use genetic information to improve patients' outcomes in several ways. Perhaps the most effective application of genetic information is in preventing malignant hyperthermia altogether. To do so, critical care nurses must be able to access a patient's genomic information through genetic testing. Identifying patients and family members who are at high risk for malignant hyperthermia is critical to reducing adverse health conditions related to this disorder. Critical care nurses must also become



To learn more about genetics, read "ECG Characteristics of a Genetic Disorder" by Michele M. Pelter et al in the *American Journal of Critical Care*, 2007;16:621-622. Available at [www.ajconline.org](http://www.ajconline.org).

knowledgeable about the pharmacogenomic implications related to the interaction of current anesthetic agents that will trigger malignant hyperthermia in susceptible patients. Finally, prompt assessment and recognition of postsurgical complications related to malignant hyperthermia can decrease the frequency of skeletal muscle damage, cardiac arrhythmias, and even death. At this time, researchers are focusing on the ryanodine receptor gene and its link to malignant hyperthermia.<sup>3</sup> With the achievement of an inexpensive, noninvasive, genetically specific test available to all preoperative patients (see [www.genetests.org](http://www.genetests.org)), malignant hyperthermia may be eliminated sooner rather than later. **CCII**

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### Financial Disclosures

None reported.

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**CE Test** Test ID C0862: Genetics and Susceptibility to Malignant Hyperthermia

**Learning objectives:** 1. Discuss how advances in the study of genomics will affect the practice of critical care nurses in the future 2. Describe how genetic mapping can predict susceptibility to malignant hyperthermia 3. Discuss the pharmacological triggers for malignant hyperthermia reactions

1. Which one of the following is the study of DNA contained in an organism?
  - a. Genetic mapping
  - b. Genomics
  - c. Cytology
  - d. Genetics
2. What is an important benefit of genomics-related research?
  - a. Saves money on health care costs
  - b. Allows for a more individualized plan of care for patients
  - c. Provides cookbook medical care
  - d. Allows insurance companies to save money by refusing care to high-risk patients
3. How is the genetic expression of malignant hyperthermia manifested?
  - a. As an autosomal dominant pharmacogenetic reaction
  - b. As an autosomal recessive pharmacogenetic trait
  - c. As an autosomal dominant pharmacogenetic trait
  - d. As an autosomal enzymatic pharmacogenetic reaction
4. Surgical patients exhibit malignant hyperthermia when exposed to which classes of drugs?
  - a. Neuromuscular blocking agents and volatile inhalation agents
  - b. Neuromuscular blocking agents and antibiotics
  - c. Antibiotics and sedating agents
  - d. Steroids and antibiotics
5. The hypermetabolic state of the mutated skeletal muscle in the malignant hyperthermia response is due to the sustained release of which of the following?
  - a. Calcium
  - b. Potassium
  - c. Sodium
  - d. Magnesium
6. Testing for genetic disorders is performed when patients have all of the following except which one?
  - a. Signs and symptoms of the disorder
  - b. Familial tendencies of the disorder
  - c. Concerns that children will inherit the disorder
  - d. Concerns about the sex of their children
7. According to the Malignant Hyperthermia Association of the United States, genetic testing can identify what percentage of the persons at risk for malignant hyperthermia reactions?
  - a. 60%
  - b. 70%
  - c. 80%
  - d. 90%
8. Genetic mapping has made it possible for scientist to discover correlation links between which two influences?
  - a. Environmental and genetic influences
  - b. Environmental and chemical influences
  - c. Environmental and geometric influences
  - d. Environmental and generic influences
9. The genetic incidence of malignant hyperthermia is estimated to be which of the following?
  - a. 1: 1000
  - b. 1:10 000
  - c. 1:100 000
  - d. 1:1 000 000
10. How do mutations in RYR1 change the ryanodine receptor's function?
  - a. From the excitatory function to regulation function
  - b. From the regulation function to excitatory function
  - c. From the regulation function to deregulation function
  - d. From the excitatory function to oxidative function
11. Mutations at the MHS1 site account for what percentage of patients with susceptibility to malignant hyperthermia?
  - a. 80%
  - b. 70%
  - c. 60%
  - d. 50%

Test answers: Mark only one box for your answer to each question. You may photocopy this form.

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| Objective 2 was met  | <input type="checkbox"/> | <input type="checkbox"/> |
| Objective 3 was met  | <input type="checkbox"/> | <input type="checkbox"/> |
| Content was relevant to my nursing practice  | <input type="checkbox"/> | <input type="checkbox"/> |
| My expectations were met   | <input type="checkbox"/> | <input type="checkbox"/> |
| This method of CE is effective for this content  | <input type="checkbox"/> | <input type="checkbox"/> |
| The level of difficulty of this test was:  |                          |                          |
| <input type="checkbox"/> easy <input type="checkbox"/> medium <input type="checkbox"/> difficult |                          |                          |
| To complete this program, it took me _____ hours/minutes.  |                          |                          |

Name \_\_\_\_\_ Member # \_\_\_\_\_

Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ ZIP \_\_\_\_\_

Country \_\_\_\_\_ Phone \_\_\_\_\_

E-mail \_\_\_\_\_

RN Lic. 1/St \_\_\_\_\_ RN Lic. 2/St \_\_\_\_\_

Payment by:  Visa  M/C  AMEX  Discover  Check

Card # \_\_\_\_\_ Expiration Date \_\_\_\_\_

Signature \_\_\_\_\_

The American Association of Critical-Care Nurses is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. AACN has been approved as a provider of continuing education in nursing by the State Boards of Nursing of Alabama (#ABNP0062), California (#01036), and Louisiana (#ABN12). AACN programming meets the standards for most other states requiring mandatory continuing education credit for relicensure.

## Corrections

In the December 2008 issue, the article “Genetics and Susceptibility to Malignant Hyperthermia” (2008;28:32-36) omitted the following 3 authors in the byline: Tracy D. Mill, RN, BSN, CCRN, Michael Dore, RN, BSN, CCRN, and Gordon McSherry, RN, BSN, CCRN.

In the February 2009 issue, Figure 10 on page 72 in the article by Baranchuk et al titled “Electrocardiography Pitfalls and Artifacts: The 10 Commandments” (2009;29:67-73) should have the following caption: “Reversal of left arm and right leg electrodes.”

In the February 2009 issue, CE tests C0912 (page 47) and C0913 (page 58) are incorrect. To take the correct CE tests, please go to the *Critical Care Nurse* Web site at [www.ccnonline.org](http://www.ccnonline.org).