

families may share not only primary mutations but also many inherited and environmental modifiers.

Patrick T. Ellinor, M.D., Ph.D.

David J. Milan, M.D.

Calum A. MacRae, M.B., Ch.B.

Massachusetts General Hospital

Boston, MA 02114

cmacrae@partners.org

1. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. *N Engl J Med* 2003;348:1866-74.

THE AUTHORS REPLY: Dr. Ellinor and colleagues raise a host of relevant issues pertaining to the contribution of genotyping to risk stratification. We introduced into our model the factors that are currently considered important in the modulation of the clinical phenotype.^{1,2} When new clinical, inherited, or environmental modifiers are identified, they will be incorporated into a novel risk-stratification scheme. In the population we studied, a family history of cardiac events was not a significant predictor of risk. This finding is in agreement with previous data showing that symptoms in probands are not predictors of events among family members.^{3,4}

Our analysis could have been influenced by the presence of large families with several affected members. However, this problem is unlikely to have occurred, since 40 percent of the cases in the probands were sporadic, and the average number

of affected persons was three per mutation per family (3.3 with a mutation at the LQT1 locus, 3.1 with a mutation at the LQT2 locus, and 2.6 with a mutation at the LQT3 locus). Furthermore, the analysis among probands showed the same trend as in the entire population, but the size of the population was insufficient for the data to reach statistical significance.

Silvia G. Priori, M.D., Ph.D.

Istituto di Ricovero e Cura a Carattere

Scientifico Fondazione Maugeri

27100 Pavia, Italy

Peter J. Schwartz, M.D.

Istituto di Ricovero e Cura a Carattere

Scientifico Policlinico San Matteo

27100 Pavia, Italy

Carlo Napolitano, M.D., Ph.D.

Istituto di Ricovero e Cura a Carattere

Scientifico Fondazione Maugeri

27100 Pavia, Italy

1. Zareba W, Moss AJ, Schwartz PJ, et al. Influence of the genotype on the clinical course of the long-QT syndrome: International Long-QT Syndrome Registry. *N Engl J Med* 1998;339:960-5.

2. Locati EH, Zareba W, Moss AJ, et al. Age- and sex-related differences in clinical manifestations in patients with congenital long-QT syndrome: findings from the International LQTS Registry. *Circulation* 1998;97:2237-44.

3. Kimbrough J, Moss AJ, Zareba W, et al. Clinical implications for affected parents and siblings of probands with long-QT syndrome. *Circulation* 2001;104:557-62.

4. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Task Force on Sudden Cardiac Death of the European Society of Cardiology. *Eur Heart J* 2001;22:1374-450. [Erratum, *Eur Heart J* 2002;23:257.]

Mechanisms of Actions of Inhaled Anesthetics

TO THE EDITOR: Campagna et al. (May 22 issue)¹ provide a comprehensive review of the mechanisms of actions of inhaled anesthetics. I was surprised, however, by some of the information they provide in Table 2 of their article. First, the authors suggest that the channels coupled to ionotropic glutamate receptors are permeable to calcium and magnesium. However, these channels are permeable only to calcium and monovalent cations, especially in the case of N-methyl-D-aspartate (NMDA) receptors. Magnesium actually blocks NMDA channels in a voltage-dependent manner,² a characteristic that is the basis for its use as a noncompetitive NMDA antagonist in some clinical situations (e.g., excessive nociception). Second, there is no general agreement that serotonin type 3 receptors “[inhib-

it] resting potassium-leak currents.” These channels are permeable to monovalent cations and, in some cases, calcium and are directly excitatory.³

Table 3 might have been more positive about data concerning the opening of some background, two-pore-domain potassium channels by halogenated alkanes and ethers. This effect has been demonstrated with several agents (chloroform, halothane, isoflurane, and sevoflurane) by at least two groups^{4,5} in different preparations.

Vincent M. Seutin, M.D., Ph.D.

University of Liège

B-4000 Liège, Belgium

v.seutin@ulg.ac.be

1. Campagna JA, Miller KW, Forman SA. Mechanisms of actions of inhaled anesthetics. *N Engl J Med* 2003;348:2110-24.

2. Amino acid transmitters. In: Rang HP, Dale MM, Ritter JM, Gardner P. Pharmacology. 4th ed. New York: Churchill Livingstone, 2001:470-82.
3. Sanders-Bush E, Mayer SE. 5-Hydroxytryptamine (serotonin): receptor agonists and antagonists. In: Hardman JG, Limbird LE, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 10th ed. New York: McGraw-Hill, 2001:269-90.
4. Patel AJ, Honoré E, Lesage F, Fink M, Romey G, Lazdunski M. Inhalational anesthetics activate two-pore-domain background K⁺ channels. *Nat Neurosci* 1999;2:422-6.
5. Sirois JE, Lei Q, Talley EM, Lynch C III, Bayliss DA. The TASK-1 two-pore domain K⁺ channel is a molecular substrate for neuronal effects of inhalation anesthetics. *J Neurosci* 2000;20:6347-54.

THE AUTHORS REPLY: We appreciate Dr. Seutin's close reading of our review. We agree that the physiologic roles of 5-hydroxytryptamine type 3 channels remain unclear. Adding to the complexity in this area, recent data indicate that, depending on the agent, inhaled anesthetics can enhance or inhibit the function of 5-hydroxytryptamine type 3A receptors.¹ The effects of inhaled anesthetics on channels that conduct background potassium-leak currents are also fascinating, complex, and difficult to summarize briefly. The findings of Patel et al.² and others do not suggest that the various background potassium channels have a common role in anesthetic actions. A reasonable inference is that they may influence the side-effect profiles of different agents. In revising and condensing Table 2, we truncated the entry for NMDA-sensitive glutamate channels, which should read, "Cation conductance for

calcium and magnesium inhibition." The entry for α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid and kainate should read, "Cation conductance for calcium," which is subunit-dependent.³

It has been brought to our attention that the structure of sevoflurane shown in Figure 1 is erroneous. The formula for the correct structure is $\text{CH}(\text{CF}_3)_2\text{-O-CH}_2\text{F}$. To our embarrassment, the structures for methoxyflurane ($\text{CH}_3\text{-O-CF}_2\text{-CHCl}_2$) and enflurane ($\text{CHF}_2\text{-O-CF}_2\text{-CHFCl}$) are also incorrect. Regarding nitrous oxide, some sources suggest that the oxygen atom is bound to both nitrogen atoms in a cyclic triangle, but in fact the arrangement is linear. The structure is best represented as a resonant hybrid of $\text{N}\equiv\text{N}^+\text{-O}^-$ and $\text{N}^=\text{N}^+=\text{O}$.

Jason A. Campagna, M.D., Ph.D.

Keith W. Miller, D.Phil.

Stuart A. Forman, M.D., Ph.D.

Massachusetts General Hospital
Boston, MA 02114
saforman@partners.org

1. Suzuki T, Koyama H, Sugimoto M, Uchida I, Mashimo T. The diverse actions of volatile and gaseous anesthetics on human-cloned 5-hydroxytryptamine₃ receptors expressed in *Xenopus* oocytes. *Anesthesiology* 2002;96:699-704.
2. Patel AJ, Honoré E, Lesage F, Fink M, Romey G, Lazdunski M. Inhalational anesthetics activate two-pore-domain background K⁺ channels. *Nat Neurosci* 1999;2:422-6.
3. Kohler M, Burnashev N, Sakmann B, Seeburg PH. Determinants of Ca²⁺ permeability in both TM1 and TM2 of high affinity kainate receptor channels: diversity by RNA editing. *Neuron* 1993;10:491-500.

Breast-Cancer Genomics

TO THE EDITOR: In Figure 1 of their article, Wooster and Weber (June 5 issue)¹ ignore an important paradox by dismissing mutations in the ATM (ataxia-telangiectasia mutated) gene as not contributing to breast cancer. Current theories propose that ATM senses DNA damage and then signals BRCA1. For example, ATM phosphorylates BRCA1, signaling it to arrest the cell cycle after DNA damage due to ionizing radiation. Pathogenic BRCA1 mutations markedly increase the risk of breast cancer. The dependence of BRCA1 on ATM thus makes it logical that mutations in the ATM gene would also increase the risk of breast cancer. Similarly, mutations in the CHEK2 gene increase the risk of breast cancer, and CHEK2 may have functional links with ATM.^{2,3} The authors accept the idea of a "BRCA3" gene with little

hesitation, although such a gene has not yet been identified. ATM could actually represent BRCA3, according to claims that heterozygotes for ATM mutations may account for up to 20 percent of cases of breast cancer. Stipulations to these claims are required because of data that do not support the presence of excess truncating ATM mutations in early-onset breast cancer.⁴ However, a clearer discussion of at least the proposed relations among ATM, CHEK2, and BRCA1 would facilitate clinical application and help resolve this confusing paradox.

Bernard Friedenson, Ph.D.

University of Illinois—Chicago College of Medicine
Chicago, IL 60612

1. Wooster R, Weber BL. Breast and ovarian cancer. *N Engl J Med* 2003;348:2339-47.