Letters to the Editor

Metabolic Gene Allele Nomenclature

Letter

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The interest in human genetic diversity for understanding disease etiology, toxicology, and response to therapy has grown in recent years into an active field of research. For example, in cancer epidemiology, and especially in the field of molecular epidemiology, a great deal of attention has been paid to the role of common population polymorphisms in genes controlling carcinogen metabolism. These genes have low penetrance with respect to cancer risk, and their precise role with respect to interactions with environmental agents is under intensive investigation. An international collaborative project on Genetic Susceptibility to Environmental Carcinogens (1) has been established to address many of the questions related to these polymorphisms by pooling data from different studies conducted in the field.

Among the effects of the most recent technological advances in molecular biology had been a tremendous simplification in techniques of analysis of specific gene sequence polymorphisms. High-throughput PCR methods now allow for rapid and low-cost detection of known sequence variants, as well as for the discovery of unknown variants such as the large number of single nucleotide polymorphisms that are known to exist throughout the human genome.

As research into the function of metabolic gene polymorphisms began to expand over the past 3–5 years, it became clear that the lack of a common nomenclature for these allelic variants could become a major stumbling block for future progress. New polymorphisms were given names by their discoverers in a fairly random fashion, and it became quite common for a single allele to be called by different names in different publications. Attempts to clarify genotype designations were even more awkward.

In 1995 and 1996, two papers were published in Pharmacogenetics that were critically important in beginning to resolve these problems. Each paper was authored by a group of molecular geneticists who had specialized in the genes concerned, *N-acetyltransferase 1* and *2* (2) and *CYP2D6* (3). In 1996, a similar proposal was published for *CYP1A1* nomenclature (4). A recent paper has summarized the importance of a logical nomenclature strategy for human gene alleles (5).

In 1999, a systematic review on metabolic cancer susceptibility genes (6) was published, which represented an important contribution to define the epidemiological and public health aspects of these genetic risk factors on human cancer and other diseases. This book included a proposal on nomenclature for many of the genes discussed in the book (7). This chapter uses the nomenclature systems previously published for *NAT1*, *NAT2*, *CYP2D6* (2, 3), and with some modifications, *CYP1A1* (4). For other genes such as *CYP2E1*, no viable nomenclature system had yet been proposed at the time of the preparation of the chapter.

As might have been expected, during the interval between completion and review of this chapter and its final publication in the fall of 1999, other groups, particularly in the field of human genetics, were also struggling to bring some order to the nomenclature of allelic variants of metabolic genes. One such group, composed of leaders in the field of human CYP genetics, published a proposal for a nomenclature system for most of the human CYP gene alleles (8). At the same time, this group initiated a Web site (http://www.imm.ki.se/CYPalleles), which is described in a recent letter (9) and in the accompanying letter in this issue (10), wherein the current name for each *CYP* allele may be found.

The advantages of using a Web-based format, as opposed to a publication format, for nomenclature systems are clear. New alleles may be added quickly and names assigned unambiguously. Simultaneous publication by different authors using different designations for the same allele are easily avoided, and any investigator may be certain of using the most up to date, standardized, and universally accepted name for whatever alleles are used in his/her research. Other Web sites currently exist for the *NAT* genes (http://www.louisville.edu/medschool/pharmacology/NAT.html) and other genes.

Unfortunately, there are some points of difference between the allele designations in the CYP Web site (9) and those of the proposal published in the book *Metabolic Polymorphisms and Susceptibility to Cancer* (7). The differences concern particular nomenclature for *CYP1A1* and *CYP2E1*. The reasons for these differences are partially related to differences in perspective between the fields of molecular epidemiology and molecular genetics, and to a lesser extent because of differences in interpretation of the frequencies of certain alleles. However, these differences are neither substantive nor important, especially when compared with the very disturbing possibility of the existence of two noncompatible nomenclature systems for *CYP* alleles. For example, a recent review lists the two different nomenclatures for *CYP1A1* in a table (11).

As the author of the 1999 nomenclature chapter (7) in the book *Metabolic Polymorphisms and Susceptibility to Cancer*, as well as senior editors of that book, we believe, as do our colleagues on the CYP Web site nomenclature committee, that universal acceptance and usage of one single system for all metabolic gene alleles is a critically important goal for the present and future success of this area of research. We therefore urge all researchers in the field, including epidemiologists and others who may have found the book nomenclature chapter to be useful in comparison to the previous chaotic situation, to hence forward follow the Web-based nomenclature systems for all *CYP*, *NAT*, and other genes.

Although there is presently no single Web site that gives

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nomenclatures for all the metabolic gene classes, and also because new genes and polymorphisms are continuously described, investigators interested in this field may see the Web site for the International collaborative project on Genetic Susceptibility to Environmental Carcinogens (www.gsec.net), which has links to all the existing relevant nomenclature Web sites.

The future of research in pharmacogenetics, genetic susceptibility, and related fields promises to be an exciting and challenging one, and it is to be hoped that with a single well-defined system of allele nomenclature, we will be in a better position to tackle the challenges that lie ahead.

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