Nomenclature for alleles of the cytochrome P450 oxidoreductase gene

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Recent focus on the cytochrome P450 oxidoreductase (\textit{POR}) gene has resulted in the discovery of numerous new polymorphic alleles. Many of these were found [1–6] because of their association with steriodogenic disorders and congenital skeletal malformations resembling the phenotype of Antley-Bixler syndrome [7], whereas other alleles have been found as a consequence of sequencing the \textit{POR} gene in normal unrelated individuals [8,9]. The association of \textit{POR} variants with clinical phenotypes is the result of \textit{POR} serving as the major electron donor for cytochrome P450 (CYP) enzymes with important endogenous functions in hormone biosynthesis. Consequently, defective \textit{POR} alleles can be the cause of abnormal glucocorticoid, mineralocorticoid, and sex steroid synthesis [10], thus leading to a form of congenital adrenal hyperplasia. In addition, \textit{POR} deficiency can cause skeletal defects, the mechanism of which is yet unknown but has been suggested to result from impaired sterol synthesis [11] because of decreased electron flow from \textit{POR} to lanosterol 14-alpha-demethylase (CYP51A1) and squalene monoxygenase (SQLE). In addition, as \textit{POR} is equally important as an electron donor to CYP enzymes involved in the metabolism of drugs, \textit{POR} variants may affect drug bioavailability. The effect of \textit{POR} mutations on the activity of some drug-metabolizing CYP enzymes has been documented \textit{in vitro} [12–14], but not yet \textit{in vivo}. In addition, \textit{POR} is an electron donor for heme oxygenase, cytochrome \textit{b}_5, and several additional small molecules that can be directly metabolized by \textit{POR} without CYP enzymes.
Thus, an increasing focus on the importance of POR in drug response and adverse drug reactions is to be expected.

Until now, no systematic guidelines have been proposed for the naming of POR alleles. To standardize POR allelic nomenclature, the Human CYP Allele Nomenclature Chair and Committee have taken the initiative to devise a system for the designation of POR alleles that follows the guidelines for CYP allelic star (CYP*) nomenclature (http://www.cypalleles.ki.se/criteria.htm). The POR allele nomenclature web page (http://www.cypalleles.ki.se/por.htm) was launched in September 2008, listing 35 different alleles. On this POR web page, the alleles are presented together with their corresponding nucleotide and amino acid changes, and the phenotypic consequences observed by in vitro and in vivo studies. Among the more important POR variants are POR*2 and *5 (Arg457His and Ala287Pro, respectively), the former being the most frequent mutation in Japanese and Chinese POR-deficient patients [5,15], whereas the latter is the POR mutation most frequently found in Caucasians. Alleles with frameshift mutations (POR*9, *10, and *20–24), deletions, insertions, and several of the alleles that result in amino acid substitutions are also associated with in vivo phenotypes, as is a splice defect in the POR*3 allele.

To maintain a common nomenclature system within the field, fellow scientists investigating POR polymorphisms are highly recommended to submit novel POR allelic variants to the Human CYP Allele Nomenclature Committee (http://www.cypalleles.ki.se/criteria.htm) by contacting the Webmaster for designation and reservation of novel POR allele names.

The authors of this Letter, a number of whom have identified the novel POR alleles, are supportive of this new nomenclature system, and will use this system in their future work.

References


