

Letter to the Editor

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Nomenclature for alleles of the cytochrome P450 oxidoreductase gene

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Recent focus on the cytochrome P450 oxidoreductase (*POR*) gene has resulted in the discovery of numerous new polymorphic alleles. Many of these were found [1–6] because of their association with steroidogenic 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 *POR* gene in normal unrelated individuals [8,9]. The association of *POR* variants with clinical phenotypes is the result of *POR* serving as the major electron donor for cytochrome P450 (*CYP*) enzymes with important endogenous functions in hormone biosynthesis. Consequently, defective *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, *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 *POR* to lanosterol 14- α -demethylase (*CYP51A1*) and squalene monooxygenase (*SQLE*). In addition, as *POR* is

equally important as an electron donor to *CYP* enzymes involved in the metabolism of drugs, *POR* variants may affect drug bioavailability. The effect of *POR* mutations on the activity of some drug-metabolizing *CYP* enzymes has been documented *in vitro* [12–14], but not yet *in vivo*. In addition, *POR* is an electron donor for heme oxygenase, cytochrome *b*₅, and several additional small molecules that can be directly metabolized by *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* allelic 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.

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