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Nomenclature for alleles of the cytochrome P450 oxidoreductase gene

Sarah C. Sim[a], **Walter L. Miller**[b], **Xiao-Bo Zhong**[c], **Wiebke Arlt**[d], **Tsutomu Ogata**[e], **Xinxin Ding**[f], **C. Roland Wolf**[g], **Christa E. Flück**[h], **Amit V. Pandey**[i], **Colin J. Henderson**[j], **Todd D. Porter**[k], **Ann K. Daly**[l], **Daniel W. Nebert**[m], and **Magnus Ingelman-Sundberg**[a]

[a] Department of Physiology and Pharmacology, Section of Pharmacogenetics, Karolinska Institutet, Stockholm, Sweden [b] Department of Pediatrics, University of California, San Francisco, California, USA [c] Department of Pharmacology, Toxicology, and Therapeutics, University of Kansas Medical Center, Kansas City, Kansas, USA [d] Centre for Endocrinology, Diabetes and Metabolism, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, UK [e] Department of Endocrinology and Metabolism, National Research Institute for Child Health and Development, Tokyo, Japan [f] Wadsworth Center, New York State Department of Health, and School of Public Health, State University of New York at Albany, New York, USA [g] Cancer Research UK Molecular Pharmacology Unit, Biomedical Research Institute, Ninewells Hospital and Medical School, Dundee, UK [h] Pediatric Endocrinology and Diabetology, University Children's Hospital Bern, Bern, Switzerland [i] Department of Clinical Research, Pediatric Endocrinology Unit, University of Bern, Bern, Switzerland [j] Cancer Research UK Molecular Pharmacology Unit, Biomedical Research Institute, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK [k] Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, Kentucky, USA [l] Institute of Cellular Medicine, Newcastle University Medical School, Framlington Place, Newcastle upon Tyne, UK [m] Department of Environmental Health and Center for Environmental Genetics (CEG), University of Cincinnati Medical Center, Cincinnati, Ohio, USA

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-alpha-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.

Correspondence to Dr Sarah C. Sim, PhD, Karolinska Institutet, Nanna Svartz väg 2, Stockholm 171 77, Sweden Tel: +46 8 5248 77 54; fax: +46 8 33 73 27; e-mail: sarah.sim@ki.se.

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.

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