Disequilibrium of porphobilinogen synthase assemblies accounts for ALAD porphyria.

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Porphobilinogen synthase (PBGS) catalyzes the first common reaction in the biosynthesis of the tetrapyrrole pigments, which are essential for respiration, photosynthesis, and methanogenesis. A rare inborn error of metabolism, ALAD porphyria, is caused by human PBGS dysfunction. PBGS can participate in an equilibrium of architecturally distinct homomeric assemblies. An octamer contains intersubunit interactions that support high activity by allowing proper gating of active site access. A hexamer does not have these interactions and activity is low. The equilibrium between octamer and hexamer is governed by pH, and in some species by an allosteric activator that binds to an octamer-specific site. In the case of human PBGS, the ratio of octamer to hexamer is very sensitive to the protein sequence. Thus, we designed single amino acid variants that dramatically alter the human PBGS quaternary structure equilibrium to allow direct investigation of the interchange of structural isoforms. Of consequence to inborn errors of metabolism, all eight ALAD porphyria-associated variants favor the hexamer relative to wild type human PBGS. These variants occur throughout the sequence (F12L, E89K, C132R, G133R, V153M, R240W, A274T, and V275M); octamer destabilization can be rationalized only for three of the eight variants (C132R, G133R, and R240W). Inexplicably, homomeric F12L assembles only to hexamer, though it can form a heteromeric octamer with wild-type PBGS. Had it not been for the stabile hexameric assembly of F12L, it is unlikely that we would have obtained a crystal structure for the PBGS hexamer, whose structure could not have been predicted from first principals nor homology.

Key References:

1. Jaffe EK (2016) The Remarkable Character of Porphobilinogen Synthase. *Acc Chem Res* 49(11):2509-2517.
2. Jaffe EK & Stith L (2007) ALAD porphyria is a conformational disease. *American Journal of Human Genetics* 80(2):329-337.