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Isolated erythrocytosis: study of 67 patients and identification of three novel germ-line mutations in the prolyl hydroxylase domain protein 2 (PHD2) gene

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Abstract

The oxygen sensing pathway modulates erythropoietin expression. In normal cells, intracellular oxygen tensions are directly sensed by prolyl hydroxylase domain (PHD)-containing proteins. PHD2 isozyme has a key role in tagging hypoxia-inducible factor (HIF)-α subunits for polyubiquitination and proteasomal degradation. Erythrocytosis-associated PHD2 mutations reduce hydroxylation of HIF-α. The investigation of 67 patients with isolated erythrocytosis, either sporadic or familial, allowed the identification of three novel mutations in the catalytic domain of the PHD2 protein. All new mutations are germ-line, heterozygous and missense, and code for a predicted full length mutant PHD2 protein. Identification of the disease-causing genes will be of critical importance for a better classification of familial and acquired erythrocytosis, offering additional insight into the erythropoietin regulating oxygen sensing pathway.