Dysregulation of the HIF pathway due to VHL mutation causing severe erythrocytosis and pulmonary arterial hypertension

Hereditary erythrocytosis can be caused by mutations in genes involved in the hypoxia-inducible factor (HIF) pathway.1-3 For example, Chuvash polycythemia is caused by an R200W substitution in the von Hippel–Lindau protein (VHL).1 There is increasing evidence linking VHL-HIF dysregulation to altered vascular physiology, and a mouse model of Chuvash polycythemia develops evidence of pulmonary arterial hypertension (PAH) who is a compound heterozygous mutation causing severe erythrocytosis and pulmonary arterial hypertension.

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stability of each protein. We measured the rate of reduction in protein level after inhibition of translation with cycloheximide. This was consistently increased in the D126N and S183L clones compared with clones expressing WT (Figure 1E-F). This instability is unlikely to contribute to impaired ability to regulate HIF in the complementation assays described above, in which the VHL proteins are expressed at much higher levels than in normal cells. However, we postulate that decreased stability of VHL in EPO-producing cells in vivo is the most likely explanation for the severity of the phenotype.
Now 8 years old, this patient undergoes regular phlebotomy to maintain an Hb of less than 16 g/dL. Pulmonary vascular measurements remain stable, with no evidence of ventricular dysfunction. He remains under surveillance for classic features of VHL disease, though has developed none to date.

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