# ‘Developmental role of PHD2 in the pathogenesis of pseudohypoxic pheochromocytoma’

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**Abstract**

Despite a general role for the HIF hydroxylase system in cellular oxygen sensing and tumour hypoxia, cancer-associated mutations of genes in this pathway, including *PHD2*, *PHD1*, *EPAS1* (encoding *HIF-2α*) are highly tissue-restricted, being observed in pseudohypoxic pheochromocytoma and paraganglioma (PPGL) but rarely, if ever, in other tumours. In an effort to understand that paradox and gain insights into the pathogenesis of pseudohypoxic PPGL, we constructed mice in which the principal HIF prolyl hydroxylase, *Phd2*, is inactivated in the adrenal medulla using TH-restricted Cre recombinase. Investigation of these animals revealed a gene expression pattern closely mimicking that of pseudohypoxic PPGL. Spatially resolved analyses demonstrated a binary distribution of two contrasting patterns of gene expression amongst adrenal medullary cells. *Phd2* inactivation resulted in a marked shift in this distribution towards a *Pnmt*$^{-}$/*Hif-2α*$^{+}$/*Rgs5*$^{+}$ population. This was associated with morphological abnormalities of adrenal development, including ectopic TH$^{+}$ cells within the adrenal cortex and external to the adrenal gland. These changes were ablated by combined

inactivation of *Phd2* with *Hif-2α* but not *Hif-1α*. However, they could not be reproduced by inactivation of *Phd2* in adult life, suggesting that they arise from dysregulation of this pathway during adrenal development. Together with the clinical observation that pseudohypoxic PPGL manifests remarkably high heritability, our findings suggest that this type of tumour likely arises from dysregulation of a tissue-restricted action of the PHD2/HIF-2α pathway affecting adrenal development in early life and provide a model for the study of the relevant processes.