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Mouse model for bilateral adrenal hyperplasia

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Primary pigmented nodular adrenocortical disease (PPNAD) is a rare form of bilateral hyperplasia leading to high morbidity due to pituitary-independent hypercortisolism and Cushing's syndrome. PPNAD may be either sporadic or regarded as the most frequent endocrine manifestation of Carney's complex (CNC), an autosomic dominant multiple neoplasia syndrome characterized by cardiac myxomas, spotty skin pigmentation and endocrine overactivity [1]. Both isolated PPNAD and CNC have been associated with null mutations in *PRKARIA*, a gene encoding the type 1 α regulatory subunit (RI α) of the cAMP-dependent protein kinase (PKA) [2 and 3]. Tumor-specific loss of heterozygosity within the chromosomal region harboring *PRKARIA* is observed in CNC patients and isolated PPNAD suggesting that *PRKARIA* is a potential tumor suppressor gene [4]. Because general homozygous loss of *Prkar1a* is lethal in early mouse embryos [5], adrenal-specific knockout was required to demonstrate tumor suppressor activity. Therefore, we produced mice with *Prkar1a* gene inactivation in adrenocortical cells by mating *Prkar1a* floxed mice with the *Akr1b7*-Cre mouse line, a novel Cre expressing line we developed to allow specific gene ablation in the steroidogenic lineage of the adrenals without affecting the gonads [6]. Adrenal cortex-specific *Prkar1a* knockout mice (AdKO) develop pituitary-independent Cushing's syndrome and evident signs of deregulated adrenocortical cells differentiation and proliferation. These defects lead to improper maintenance and expansion of foetal adrenal cells in adult adrenals and establishment of pretumoral conditions. Our data provide the first in vivo evidence that the absence of RI α subunit of PKA is sufficient to explain autonomous adrenal hyperactivity and bilateral hyperplasia observed in PPNAD. They also strongly suggest that deregulated PKA activity positively affects the maintenance of foetal characters in adult glands.

References

1. Carney JA, Gordon H, Carpenter PC, Shenoy BV, Go VL. The complex of myxomas, spotty pigmentation and endocrine overactivity. *Medicine (Baltimore)*. 1985; 64:270–283. [PubMed: 4010501]
2. Kirschner LS, Carney JA, Pack SD, et al. Mutations of the gene encoding the protein kinase A type I-alpha regulatory subunit in patients with the Carney's complex. *Nat Genet*. 2000; 26:89–92. [PubMed: 10973256]

3. Casey M, Vaughan CJ, He J, et al. Mutations in the protein kinase A R1alpha regulatory subunit cause familial cardiac myxomas and Carney's complex. *J Clin Invest.* 2000; 106:R31–R38. [PubMed: 10974026]
4. Groussin L, Jullian E, Perlemoine K, et al. Mutations of the *PRKARIA* gene in Cushing's syndrome due to sporadic primary pigmented nodular adrenocortical disease. *J Clin Endocrinol Metab.* 2002; 87:4324–4329. [PubMed: 12213893]
5. Amieux PS, Howe DG, Knickerbocker H, et al. Increased basal cAMP-dependent protein kinase activity inhibits the formation of mesoderm-derived structures in the developing mouse embryo. *J Biol Chem.* 2002; 277:27294–27304. [PubMed: 12004056]
6. Lambert-Langlais S, Val P, Guyot S, et al. A transgenic mouse line with specific Cre recombinase expression in the adrenal cortex. *Mol Cell Endocrinol.* 2009; 300:197–204. [PubMed: 19041690]