## THE GENETICS OF FAMILIAL ADRENAL TUMORS

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For a tumor type, the concept of «familial tumors» encompasses germline mutations predisposing either directly to this tumor, or to a syndrome to which the tumor type belongs. This general concept applies to adrenal tumors, and will be developed here. Adrenal tumors gather a broad range of diseases, scattered on two main categories depending on whether they are arising from adrenal cortex or medulla. From adrenal cortex, the dreadful adrenocortical carcinoma is in a large majority of cases sporadic and non syndromic. A germline mutation is found in less than 5% of cases, mainly related to Li Fraumeni syndrome (*TP53* mutations), or to Lynch syndrome (mutations in mismatch-repair genes). A vast majority of adrenocortical adenomas are sporadic, related to sporadic mutations — mainly *PRKACA* and *CTNNB1*. In terms of germline predisposition, adrenocortical adenomas seem more common in rare tumor predisposition syndromes such as Multiple Endocrine Neoplasia type 1 (mutations of *MENIN*) and Gardner syndrome (mutatons of *APC*). Primary macronodular adrenocortical hyperplasia is related to germline *ARMC5* mutations in $^1/_3$ of cases. Pigmented primary nodular adrenal dysplasia are often syndromic, part of the Carney complex (mutations of *PRKAR1A*). Other adrenocortical hyperplasias/dysplasias are rare, and several mutated genes have been reported. Tumors arising from adrenal medulla are called pheochromocytoma. These tumors are parented to paragangliomas, of extra-adrenal location. Approximately $^1/_3$ of pheochromocytoma and paragangliomas are related to germline mutations. The most commonly mutated genes are part of succinate deshydrogenase complex (mutations of *SDHB*, *C* and *D* mainly). Syndromic forms of pheochromocytoma include Multiple Endocrine Neoplasia type 2 (mutations of *RET*), Von-Hippel-Lindau syndrome (mutations of *VHL*) and neurofibromatosis type 1. Mutations in >10 other genes have been reported so far. An up-to-date catalogue of these mutations will be presented for each of this disease, with a special emphasis of their pathophysiological and clinical consequences.

KEYWORDS: familial adrenal tumors, genetics, mutations, multiple endocrine neoplasia.

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## HYPERALDOSTERONISM

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Primary aldosteronism is the most common cause of secondary hypertension with the estimated prevalence of around 5—10% in hypertensive patients and up to 20% in those with refractory hypertension. However, it is still underdiagnosed in clinical practice. The disease is characterized by autonomous aldosterone overproduction, independent of renin-angiotensin system, which is caused by bilateral adrenal hyperplasia or aldosterone-producing adenoma in more than 90% of cases. Several studies have demonstrated that primary aldosteronism is associated with high cardiovascular, cerebrovascular and renal morbidity and mortality. Although hypokalemia is the hallmark of the disease, most of the patients are actually normokalemic. Recommended diagnostic evaluation involves measurement of plasma aldosterone and renin with subsequent calculation of aldosterone to renin ratio (ARR) which serves as the screening test for primary aldosteronism. In patients with elevated ARR this is followed by one of the four available confirmatory tests; oral salt loading, saline infusion, captopril challenge or fludrocortisone suppression test. If confirmatory testing is positive, further diagnostic investigations are directed toward identification of the primary aldosteronism subtype as the treatment differs between aldosterone producing adenoma and bilateral adrenal hyperplasia. Selective adrenal venous sampling for aldosterone is recommended as the only reliable way to separate unilateral from bilateral disease. Patients with unilateral disease are candidates for surgery whereas those with bilateral hyperplasia are treated with mineralocorticoid receptor antagonists. Early detection and appropriate treatment of primary aldosteronism could reduce morbidity and mortality to the levels seen in patients with essential hypertension.

KEYWORDS: hyperaldosteronism, secondary hypertension, aldosterone-producing adenoma, hypokalemia.

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## MANAGEMENT OF PHEOCHROMOCYTOMA

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The report focuses on catecholamine-secreting tumors that develop from chromaffin cells of adrenal medulla and sympathetic ganglia, which are referred to as pheochromocytomas and catecholamine-secreting paragangliomas. Catecholamine-secreting tumors are rare, with an annual incidence of two to eight cases per a million people. There are 6—8% of pheochromocytomas among incidentally discovered adrenal tumors. Nevertheless, it is important to suspect, confirm, localize, and remove these tumors because associated hypertension is treated with surgical removal of a tumor. There is mortality risk (especially when the diagnosis is unknown). At least 5—6% of tumors are malignant; up to 30—35% of tumors are familial. Thus, detection of these tumors in the proband may result in early diagnosis in other family members. The report summarizes epidemiological data; pathogenesis; laboratory, genetic and topical diagnostic