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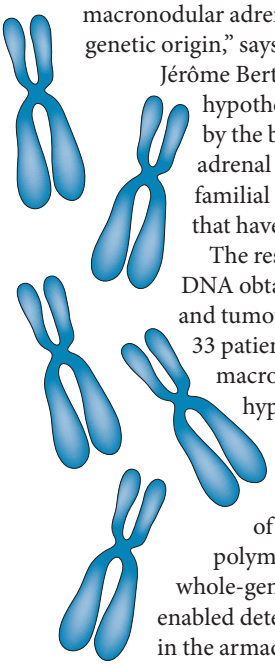
ADRENAL FUNCTION

Bilateral macronodular adrenal hyperplasia —new genetic and pathophysiological insights

Two recent studies on the genetics and pathophysiology of bilateral macronodular adrenal hyperplasia open new avenues for research on adrenal disorders.

Cushing syndrome, which results from exposure of the body to excess cortisol, can be caused by oversecretion of cortisol from adrenal tumours. Bilateral macronodular adrenal hyperplasia accounts for <2% of cases of Cushing syndrome. In individuals with this condition, hypersecretion of cortisol from enlarged adrenal glands leads to suppression of the release of adrenocorticotropic hormone (ACTH) from the pituitary gland and low plasma levels of ACTH. As such, the condition has also been called ACTH-independent macronodular adrenal hyperplasia.

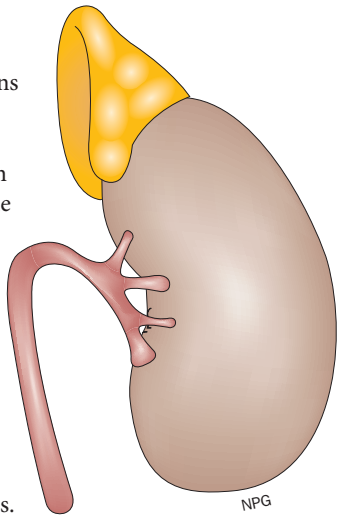
In the first study, Assié and co-workers identify a putative tumour suppressor gene involved in the development of bilateral macronodular adrenal hyperplasia. "We used a combined genomics approach to test the hypothesis that bilateral macronodular adrenal hyperplasia has a genetic origin," says senior investigator Jérôme Bertherat. "This hypothesis was supported by the bilateral nature of the adrenal tumours and rare familial cases of the condition that have been reported."



The researchers genotyped DNA obtained from blood and tumour samples from 33 patients with bilateral macronodular adrenal hyperplasia. The patients included 21 women and 12 men aged 30–73 years. Analysis of single nucleotide polymorphism arrays and whole-genome sequencing enabled detection of a mutation in the armadillo repeat-containing protein 5 (*ARMC5*) gene in tumours from 18 (55%) of the 33 patients. Interestingly, both alleles of *ARMC5* were mutated in all of the cases, including one germline mutation and one somatic mutation. This pattern of mutation suggested the 'two-hit' model of a tumour suppressor gene, in which a 'second hit', in addition to a germline inactivating mutation, leads to tumour development. In support of this hypothesis, in four patients with germline mutatons, different nodules from the hyperplastic adrenal glands had different secondary *ARMC5* mutations. In addition, *in vitro* functional studies of *ARMC5* demonstrated tumour suppressor protein properties, including effects on steroidogenesis and cell survival.

"The identification of *ARMC5* mutations in >50% of the patients clearly demonstrates the frequent genetic origin of the disease, which was speculated but not proven so far," comments Bertherat. "The findings raise the question of whether 'adrenal incidentalomas', which are seen in 4% of CT scans carried out for other reasons, represent mild forms of bilateral macronodular adrenal hyperplasia," says Ashley Grossman of the University of Oxford, who was not involved in the study. "So, adrenal disease may, similar to adrenomedullary disease, be much more a genetic disease than we ever suspected." Bertherat's team now plan to study the penetrance of the disease and whether familial screening could improve long-term clinical outcomes by enabling earlier treatment of the disease.

In the second study, Louiset *et al.* reveal why cortisol hypersecretion persists in bilateral macronodular adrenal hyperplasia despite the reduced plasma levels of ACTH that characterize the condition. "Our working hypothesis was that ACTH could be aberrantly expressed in some cortisol-secreting adrenocortical hyperplasias," explains senior researcher Hervé Lefebvre. The researchers examined the abnormal production of ACTH in specimens of hyperplastic macronodular adrenal tissue from 30 patients with the condition. The investigators found that a subpopulation of steroidogenic cells synthesized and released ACTH in adrenocortical hyperplastic tissues. Furthermore, the release of ACTH from these cells was triggered by ligands of aberrant membrane receptors. Importantly, the intra-adrenal ACTH appeared to stimulate cortisol secretion through a paracrine mechanism involving the melanocortin type 2 receptor, which suggests a role of this intra-adrenal ACTH in the pathogenesis of hypercortisolism.



Louiset *et al.* conclude that the term ACTH-independent for cases of bilateral adrenal macronodular hyperplasia is inappropriate, as the hypercortisolism is associated with ACTH ectopically produced in the adrenal glands. They suggest use of the term bilateral adrenal macronodular hyperplasia.

To Grossman, the insights from the two studies "show how important the clinical scientist still is." Research on this rare disease will shine a light on research into many adrenal disorders.

Carol Wilson

Original articles Assié, G. *et al. ARMC5* mutations in macronodular adrenal hyperplasia with Cushing's syndrome. *N. Engl. J. Med.* **369**, 2105–2114 (2013) | Louiset, E. *et al.* Intraadrenal corticotropin in bilateral macronodular adrenal hyperplasia. *N. Engl. J. Med.* **369**, 2115–2125 (2013)