Medical Xpress

Cushing's syndrome: A genetic basis for cortisol excess

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An international team of researchers led by an endocrinologist at Ludwig-Maximilians-Universitaet (LMU) in Munich has identified genetic mutations that result in uncontrolled synthesis and secretion of the stress hormone cortisol.

Cortisol is a hormone that is produced by the adrenal gland in response to stressful events, and modulates a whole spectrum of physiological processes. An international research collaboration has now identified genetic mutations that lead to the production and secretion of cortisol in the absence of an underlying stressor.

The discovery emerged from the genetic characterization of benign tumors of the adrenal gland which produce cortisol in excess amounts. Patients who develop such tumors suffer from weight gain, muscle wasting, osteoporosis, diabetes and hypertension. This condition, known as Cushing's syndrome, can be successfully treated by surgical removal of the affected adrenal gland.

Overproduction of cortisol

The team, which included researchers from Germany, France and the US and was led by Professors Felix Beuschlein and Martin Fassnacht of the LMU Medical Center, were able to show that in one-third of a patient population with such adrenal tumors, a mutation in the gene for the enzyme phosphokinase A was specifically associated with the

continuous production of cortisol. This mutation had occurred in the adrenal gland and is therefore restricted to the tumor cells. The results have just appeared in the prestigious *New England Journal of Medicine*.

"The gene for phosphokinase A plays a key role in the regulation of adrenal gland function, and the newly identified mutation causes it to become irreversibly activated, which results in the unrestrained production of cortisol," says Felix Beuschlein. In collaboration with a group at the US National Institutes of Health, the team was also able to identify patients who carry similar genetic alterations in their germline DNA. In these families, Cushing's syndrome occurs as a heritable genetic disease.

The elucidation of the genetic mechanism responsible for a significant fraction of cases of Cushing's syndrome provides a new diagnostic tool, and may also lead to new approaches to treatment. To enable further investigations towards this end, the German Cushing Register, which is maintained by Professor Martin Reincke at the LMU Medical Center, has received a grant of 400,000 euros from the Else Kröner-Fresenius Foundation. A recently initiated European research consortium devoted to the study of Cushing's syndrome, of which Professors Beuschlein and Fassnacht are members is supported by a grant of 700,000 euros from the ERA-NET program administered by the Federal Ministry for Education and Research.

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