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Adrenal

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Loss of KDM1A in Bilateral Macronodular Adrenal Hyperplasia With GIP-Dependent Cushing's Syndrome and in Acromegaly With Paradoxical GH Response to Oral Glucose

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Context: Primary bilateral macronodular adrenal hyperplasia (PBMAH) with glucose-dependent insulinotropic polypeptide (GIP)-dependent Cushing's syndrome is caused by ectopic expression of GIP receptor (GIPR) in the adrenal lesions. Such ectopic expression of GIPR was also reported in other endocrine neoplasm, notably in somatotroph pituitary adenomas from acromegalic patients with paradoxical increase of GH after oral glucose load, suggesting a common molecular pathogenesis. We aimed to identify the driver event responsible for GIP-dependent PBMAH with Cushing's syndrome and ectopic GIPR expression in somatotropinomas.

Methods: We conducted an international, multicenter, cohort study. We collected blood and adrenal samples from patients who had undergone unilateral or bilateral adrenalectomy for GIP-dependent PBMAH with Cushing's syndrome. Adrenal samples from patients with PBMAH and Cushing's syndrome without food-dependent cortisol production were used as controls. We further collected somatotropinoma specimens from acromegaly patients followed at two expert endocrine centers in France.

Results: 17 patients with familial or sporadic GIP-dependent PBMAH with Cushing's syndrome were studied. We identified germline heterozygous mutations in the lysine demethylase 1A (KDM1A) gene in all 17 patients. We further identified a recurrent deletion of the short arm of chromosome 1 harboring the KDM1A locus in the adrenal lesions of affected patients. None of the 25 patients in the control group had KDM1A germline or somatic alterations. Concomitant genetic inactivation of both KDM1A alleles resulted in loss of KDM1A expression in the adrenal lesions. RNA-sequencing revealed the global impact of KDM1A loss in adrenal tissue on gene transcription and identified differentially regulated genes including those encoding for GIPR and other G-Protein-Coupled Receptors that may be involved in adrenal tumorigenesis and regulation of steroidogenesis. In vitro pharmacologic inhibition, silencing and knock-out by CRISPR-Cas9 genome editing of KDM1A led to an increase in GIPR transcripts and protein in human adrenocortical H295R cells. Somatotropinoma samples from 78 patients with acromegaly were studied. 24% of these patients presented with a paradoxical rise of GH after oral glucose load and expressed ectopically GIP-receptor in their somatotropinoma. None of the somatotropinomas harbored KDM1A pathogenic variants, but those from patients with paradoxical GH response displayed a recurrent chromosome 1p loss.

Discussion: We identified germline inactivating KDM1A mutations and loss of heterozygosity as a genetic predisposition to GIP-dependent PBMAH with Cushing's syndrome following a tumor suppressor gene model of tumorigenesis. We currently perform genetic screening in first-degree relatives of patients with GIP-dependent PBMAH with Cushing's syndrome and clinical examination with biochemical testing in asymptomatic KDM1A variant carriers. We did not identify somatic KDM1A mutations in somatotropinomas expressing GIPR ectopically, however their recurrent 1p chromosome loss suggests that KDM1A haploinsufficiency may contribute to GIPR expression in those tumors.

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