

Documents

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Loss of KDM1A in GIP-dependent primary bilateral macronodular adrenal hyperplasia with Cushing's syndrome: a multicentre, retrospective, cohort study

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^a Université Paris-Saclay, INSERM, Physiologie et Physiopathologie Endocrinienne, Le Kremlin-Bicêtre, France

^b Division of Endocrinology, Department of Medicine and Research Center, Centre hospitalier de l'Université de Montréal, Montréal, QC, Canada

^c Department of Neurosciences, Centre hospitalier de l'Université de Montréal, Montréal, QC, Canada

^d Department of Endocrinology, Diabetes, and Nutrition, Hôpital Haut Lévêque, Centre Hospitalier Universitaire de Bordeaux, Pessac, France

^e Endocrinology Unit, Department of Medicine, Hospital-University of Padua, Padua, Italy

^f Department of Neuroscience, Hospital-University of Padua, Padua, Italy

^g Université Claude Bernard Lyon 1, UMR INSERM 1052, CNRS 5286, Centre de Recherche de Cancérologie de Lyon, Lyon, France

^h Service d'Histologie, Embryologie et Cytogénétique, Assistance Publique-Hôpitaux de Paris, Hôpital Antoine Bécère, Clamart, France

ⁱ Service d'Anatomie et Cytologie Pathologiques, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

^j Service de Chirurgie Digestive et Endocrinienne, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

^k Service de Génétique Moléculaire et d'Hormonologie, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

^l Service d'Endocrinologie et des Maladies de la Reproduction, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

^m UMS 44, Institut Biomédical du Val de Bièvre, Le Kremlin-Bicêtre, France

ⁿ U1016 INSERM, Institut Cochin, Paris, France

^o US12 Centre d'immunophénomique, Parc Scientifique et Technologique de Luminy, Marseille, France

^p Department of Endocrinology, Diabetes, and Metabolism, Evangelismos Hospital, Athens, Greece

^q Department of Endocrinology and Nutrition, Université catholique de Louvain, Cliniques Universitaires Saint-Luc, Brussels, Belgium

^r Department of Endocrinology, Diabetes and Metabolic Diseases, Normandie Univ, Rouen University Hospital, Rouen, France

^s CHR Orleans, Service d'Endocrinologie, Diabète et Nutrition, Orleans, France

^t Department of Endocrinology, Diabetes, and Nutrition, and PériTox, UMR-I 01 INERIS, Université de Picardie Jules Verne, Amiens, France

^u Service d'Endocrinologie, Hôpital Larrey, Toulouse, France

^v Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, Netherlands

^w Service de Chirurgie Générale et Endocrinienne, Univ Lille, Institut Pasteur de Lille, INSERM U1190, Translational Research Laboratory for Diabetes, CHU Lille, Lille, France

Abstract

Background: GIP-dependent primary bilateral macronodular adrenal hyperplasia with Cushing's syndrome is caused by aberrant expression of the GIP receptor in adrenal lesions. The bilateral nature of this disease suggests germline genetic predisposition. We aimed to identify the genetic driver event responsible for GIP-dependent primary bilateral macronodular adrenal hyperplasia with Cushing's syndrome. Methods: We conducted a multicentre, retrospective, cohort study at endocrine hospitals and university hospitals in France, Canada, Italy, Greece, Belgium, and the Netherlands. We collected blood and adrenal samples from patients who had undergone unilateral or bilateral adrenalectomy for GIP-dependent primary bilateral macronodular adrenal hyperplasia with Cushing's syndrome. Adrenal samples from patients with primary bilateral macronodular adrenal hyperplasia who had undergone an adrenalectomy for overt or mild Cushing's syndrome without evidence of food-dependent cortisol production and those with GIP-dependent unilateral adrenocortical adenomas were used as control groups. We performed whole genome, whole exome, and targeted next generation sequencing, and copy number analyses of blood and adrenal DNA from patients with familial or sporadic disease. We performed RNA sequencing on adrenal samples and functional analyses of the identified genetic defect in the human adrenocortical cell line H295R. Findings: 17 patients with GIP-dependent primary bilateral macronodular adrenal hyperplasia with Cushing's syndrome were studied. The median age of patients was 43.3 (95% CI 38.8–47.8) years and most patients (15 [88%]) were women. We identified germline heterozygous pathogenic or most likely pathogenic variants in the KDM1A gene in all 17

patients. We also identified a recurrent deletion in the short p arm of chromosome 1 harboring the KDM1A locus in adrenal lesions of these patients. None of the 29 patients in the control groups had KDM1A germline or somatic alterations. Concomitant genetic inactivation of both KDM1A alleles resulted in loss of KDM1A expression in adrenal lesions. Global gene expression analysis showed GIP receptor upregulation with a log2 fold change of 7.99 (95% CI 7.34–8.66; $p=4.4 \times 10^{-125}$), and differential regulation of several other G protein-coupled receptors in GIP-dependent primary bilateral macronodular hyperplasia samples compared with control samples. In vitro pharmacological inhibition and inactivation of KDM1A by CRISPR-Cas9 genome editing resulted in an increase of GIP receptor transcripts and protein in human adrenocortical H295R cells. Interpretation: We propose that GIP-dependent primary bilateral macronodular adrenal hyperplasia with Cushing's syndrome results from a two-hit inactivation of KDM1A, consistent with the tumour suppressor gene model of tumorigenesis. Genetic testing and counselling should be offered to these patients and their relatives. Funding: Agence Nationale de la Recherche, Fondation du Grand défi Pierre Lavoie, and the French National Cancer Institute. © 2021 Elsevier Ltd

Correspondence Address

Kamenicky P.; INSERM U1185, France; email: peter.kamenicky@universite-paris-saclay.fr

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