Case Report

WHEN OBESITY IS HARD TO FIGHT: HOMOZYGOUS POMC MUTATION IN A HISPANIC MALE

Brianna Taylor[1], Gabriel Arevalo[1]

Author information: [1]Department of Pediatrics, Texas Tech University Health Sciences Center, 1400 Coulter Str, Amarillo, TX, USA

Received: 06-24-2021; Accepted: 07-04-2022; Published: 07-12-2022.

Abstract: *POMC* is a well-studied polypeptide that plays a key role in several crucial body functions. An error in this gene may lead to problems such as adrenal insufficiency, hypopigmentation, obesity, hypogonadotropic hypogonadism, and more. Since genetic testing has become more common, POMC has been targeted for therapeutic interventions that are now widely available for use as treatment. This report demonstrates how genetic testing was utilized to obtain several diagnoses early in life accurately and how that knowledge led to appropriate treatment. Genetic testing can be a powerful tool for physicians; accurate diagnosis directs available therapeutics, tremendously decreases comorbidities, and improves disease outcomes.

Keywords: genetic, adrenal insufficiency, hypopigmentation, hypogonadism, leptin, setmelanotide, obesity.

INTRODUCTION Some forms of obesity are genetically determined and can be difficult to manage with lifestyle modification or diet alone. The *POMC* protein plays a critical role in the production of adrenocorticotropic hormone (ACTH), responsible for blood glucose and arterial pressure control; it also participates in melanocyte-stimulating hormones (MSH) production and is responsible for the leptin signal pathway that controls appetite. Due to the disruption of these pathways, affected individuals often exhibit a congenital triad of symptoms consisting of hypocortisolism, red hair, and early-onset obesity. The FDA has recently approved melanocortin-4 agonist IMCIVREE™ (setmelanotide) for treating obesity due to defects in the *POMC, LEPR,* and *PCSK1* genes.

CASE PRESENTATION A 21-year-old Hispanic male presented to a nephrology clinic following his biopsy-proven IgA nephropathy and hypertension diagnosis. This patient was born at eight months gestation to a mother that suffered from pre-eclamptic complications. The mother noted that the patient's light skin complexion and red-tinted hair were noticeable at birth (Figures 1, 2). He has had a history of obesity since early childhood and, at this visit, weighed approximately 156 kg with a BMI of 49.3.

Early in the newborn period, he began having seizures that were controlled medically, and at six months of age, he began showing signs of uncontrollable, excessive weight gain. During these first few months of life, blood pressure and glycemic control were difficult to manage and ultimately led to the diagnosis of adrenal insufficiency before one year old. He was diagnosed with asthma at three years old, and at ten years old, he had renal insufficiency and hypertension. In addition to these diagnoses, he was later diagnosed with prediabetes and hypothyroidism.

Genetic testing was performed only when he reached early adulthood and revealed a homozygous mutation in the POMC gene. The specific mutation present in this patient is *POMC,* NM_000939.3:c20_21insGGGCCCTCGGGGGCCCCTCGGGTGG, pSer7Argfs*120; homozygous; it has only been reported once before in an individual with epilepsy (PubMed ID: 26795593).

The presented patient not only has several medical conditions directly related to his *POMC* mutation but also suffers from several comorbidities from the obesity caused by this defect. The patient has recently started treatment with IMCIVREE™ (setmelanotide) for weight control.

Corresponding Author: Brianna Taylor: Department of Pediatrics, Texas Tech University Health Sciences Center
Address for Authors: 1400 Coulter St S, Amarillo, TX 79106, USA
Brianna.Taylor@ttuhsc.edu

Figure 1 (left) shows the patient's obesity and hypopigmented skin.

Figure 2 (right) shows the red tint of the patient's hair.

DISCUSSION Since the Human Genome Project from 1990-2003, over 250 genes have been associated with obesity [1]. This is significant because in 2016, WHO estimated that "about 13% of the world's adult population (11% of men and 15% of women) were obese", defined as having a BMI>30 [2]. When diagnosing causes of obesity, physicians should be careful to complete detailed histories and physical examinations, including detailed family history, diet, activity, medications, and social history.

The *POMC* gene has since been known to be a key factor involved in genetically determined obesity as it plays a key role in weight regulation via the leptin signaling pathway. POMC is a precursor polypeptide that, when cleaved, forms a variety of peptides, including MSH, ACTH, lipotropin, and endorphins. These hormones have been found to stimulate different melanocortin (MC) receptors involved in processes such as skin pigmentation, adrenal regulation, and weight control. Receptors most related to this case are MC3 and MC4, two receptors associated with weight and energy stability [3].

A POMC defect can result in early-onset obesity, amongst other classic findings such as red-tinted hair, hypopigmentation of the skin, and adrenal insufficiency. Very few children have been reported to have this condition, and even fewer have been reported with a homozygous *POMC* mutation rather than heterozygous, as in the presented case. Hyperphagia, cholestasis, severe weight gain, and adrenal insufficiency are common findings within the first few months of infancy, with exponential weight gain typically occurring by the end of the first year of life [4]. As seen in this report, this patient was diagnosed with adrenal insufficiency shortly after birth and began showing excessive weight gain by six months of age. Later in life, hypopigmentation of the skin due to lack of MSH, signs of hypothyroidism due to lack of TSH, and hypogonadotropic hypogonadism due to insufficient luteinizing hormone and the follicle-stimulating hormone may become evident [5]. The presented patient did not have hypogonadotropic hypogonadism but displayed hypopigmented skin and hypothyroidism, suggesting impaired signaling of MSH and

thyrotropin-releasing hormone. These findings highlight the importance of routine surveillance for skin cancer and hypothyroid-related symptoms, such as constipation, weight gain, cold intolerance, and depression in these patients.

Genetic testing for obesity started to play a significant role in patient management after treatment was introduced for mutations in three specific genes: *POMC, LEPR,* and *PCSK1* in 2020 [6].

This patient is a prime example of how genetic testing led to a fast and precise diagnosis with the proper treatment of his disease. By identifying this early, years of costly doctor visits and investigation were avoided, as well as potential complications secondary to untreated disease.
It is also important to be cognizant of syndromic obesity, such as Prader-Willi syndrome and Cohen syndrome [1], especially in the pediatric population, because they each carry important pathology individually. For cases of genetic obesity, there are now two FDA-approved drugs available – Setmelanotide (MC4R agonist) and Metreleptin (leptin analog) [6].

CONCLUSION Genetically determined, early-onset obesity due to a *POMC* mutation is difficult to treat despite modification of lifestyle and eating habits. The patient, in this case, is amongst many individuals with genetic mutations associated with comorbidities due to obesity [https://www.ncbi.nlm.nih.gov/books/NBK573068/].

Therefore, this case highlights the importance of understanding the underlying processes between *POMC* and steady weight to improve these patients' lifelong care. It is critical to optimize treatment options, such as lifestyle modifications and medications, early in the disease process. Early management may help prevent or slow the progression of obesity and decrease rates of comorbidities, including hypertension, heart disease, diabetes, and various cancers, improving overall outcomes for this patient population.

Acknowledgements: We would like to acknowledge and thank the patient's mother who provided us with a detailed history of the patient.

REFERENCES:

1. Tirthani E, Said MS, Rehman A. Genetics and Obesity. In: StatPearls [Internet]. StatPearls Publishing; 2021.
2. Obesity and overweight [Internet]. Who.int. [cited 2022 Jul 8]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
3. Biebermann H, Kühnen P, Kleinau G, Krude H. The neuroendocrine circuitry controlled by POMC, MSH, and AGRP. Handb Exp Pharmacol [Internet]. 2012 [cited 2022 Jul 8];(209):47–75. Available from: https://pubmed.ncbi.nlm.nih.gov/22249810/.
4. Çetinkaya S, Güran T, Kurnaz E, Keskin M, Sağsak E, Savaş Erdeve S, et al. A patient with proopiomelanocortin deficiency: An increasingly important diagnosis to make. J Clin Res Pediatr Endocrinol [Internet]. 2018 [cited 2022 Jul 8];10(1):68–73. Available from: http://dx.doi.org/10.4274/jcrpe.4638.
5. Gregoric N, Groselj U, Bratina N, Debeljak M, Zerjav Tansek M, Suput Omladic J, et al. Two cases with an early presented proopiomelanocortin deficiency-A long-term follow-up and systematic literature review. Front Endocrinol (Lausanne) [Internet]. 2021;12:689387. Available from: http://dx.doi.org/10.3389/fendo.2021.689387
6. FDA approves first treatment for weight management for people with certain rare genetic conditions [Internet]. U.S. Food and Drug Administration. FDA; [cited 2022 Jul 8]. Available from: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-treatment-weight-management-people-certain-rare-genetic-conditions