Diagnosing different obesity

Not all obesity is the same. Insatiable hunger and early-onset obesity can be distinct signs of melanocortin-4 receptor (MC4R) pathway impairment.[1]

The melanocortin-4 receptor (MC4R) pathway in the hypothalamus plays a critical role in energy balance and body weight regulation. Some gene variants that cause rare diseases can cause impairment of the MC4R pathway, resulting in monogenic obesity.[1]

Hunger and weight in monogenic obesity

The MC4R pathway is responsible for regulating hunger, satiety, and energy expenditure and subsequently plays a critical role in body weight regulation. While there are a variety of symptoms to look for in patients with rare genetic diseases that cause obesity, impairment of the MC4R pathway due to genetic variants can lead to 2 key features.[1-3]

Two key features

Hyperphagia

Early-onset obesity

Hyperphagia (a chronic, pathological condition characterized by insatiable hunger, impaired satiety, and persistent abnormal food-seeking behaviors) and early-onset obesity due to MC4R pathway impairment require **distinct diagnosis and management** compared with the management of general obesity.[4]

Additional symptoms associated with monogenic obesity

Symptoms associated with monogenic obesity can vary and may include additional clinical characteristics, like neurological, growth, and endocrine abnormalities, as well as significant weight disparity among family members.[2,3]

These diseases can be complex to diagnose based solely on clinical manifestations but can be confirmed through genetic testing.

Monogenic obesity can be caused by[1,5-7]:

- POMC deficiency
- PCSK1 deficiency
- LEPR deficiency
- SH2B1 deficiency
- SRC1 deficiency

The importance of genetic testing

Clinical guidelines recommend genetic testing to inform diagnosis and appropriate interventions for patients.

> "If hyperphagia and/or a family history of extreme obesity is present, genetic testing is recommended."
>
> **— Obesity Medicine Association**

Genetic testing may offer new information for your management plan:

Clinical trial eligibility

Diagnosis

Disease management

Genetic testing through the Uncovering Rare Obesity® program is available for eligible patients. For more information about the genetic testing program, visit **UncoveringRareObesity.com**.

Monogenic obesity— Distinguishing the signs and symptoms

Signs & Symptoms of Select Genetic Diseases That Cause Monogenic Obesity[1-13]					
	POMC deficiency	**PCSK1 deficiency**	**LEPR deficiency**	**SH2B1 deficiency**	**SRC1 deficiency**
Hyperphagia	✓	✓	✓	✓	✓
Early-onset obesity	✓	✓	✓	✓	✓
Endocrine disorders/ dysfunction	Hypothyroidism, hypogonadotropic hypogonadism, ACTH deficiency	Hypothyroidism	Hypogonadotropic hypogonadism		
Metabolic dysfunction	Diabetes, hypocortisolism, hypoglycemia	Diabetes, hypocortisolism, hypoglycemia, hyperinsulinemia, metabolic acidosis	Diabetes, hyperinsulinemia	Diabetes, hyperinsulinemia, leptin resistance	Hyperinsulinemia, hyperleptinemia
Growth abnormalities		Failure to thrive in infancy		Reduced height	
Other clinical characteristics	Liver disease, red hair and light skin pigmentation, delayed puberty	Gastrointestinal symptoms, polydipsia/ polyuria	Delayed puberty		

This table does not include all possible signs and symptoms associated with each deficiency. Genetic testing can inform the diagnosis of these conditions.

Learn more about rare genetic diseases that cause obesity. Visit HCP.DifferentObesity.com/Monogenic-Obesity for more information.

Helpful resources for your practice

A diagnosis of a rare genetic disease that causes monogenic obesity may be suspected based on clinical presentation and confirmed via genetic testing.

Learn about genetic testing

Uncovering Rare Obesity® can help support a diagnosis. Genetic testing is available for your eligible patients.

Visit **UncoveringRareObesity.com**

Know the genes

Genetic testing through the Uncovering Rare Obesity® program is available for eligible patients.

Download the **Gene Panel Handout**

Connect with a Rhythm Representative

Find resources and get further information about rare genetic diseases that cause obesity.

Connect With a Rep

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