

A Guide to Monogenic Obesity

This is a practical guide for healthcare professionals who work with children living with obesity. It explains what monogenic obesity is and why recognising monogenic obesity is important within healthcare, along with actionable recommendations and the ethical, legal and social implications related to this topic. It should be used in conjunction with specialist advice, national guidelines and genetics/endocrinology services where indicated.

Recommendations for Practice



Consider genetic causes in children with very early and severe obesity



Ensure treatment is centred on the child, not solely on their obesity diagnosis



Reduce shame, blame and weight-based stigma in every clinical interaction

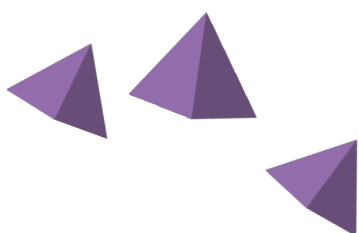
Obesity and Genetics: What's the Link?

Obesity is a complex chronic disease influenced by a wide interplay of environmental, biological and behavioural factors. While environmental influences play a substantial role, a significant proportion of an individual's susceptibility to obesity is genetically determined.

Over the past two decades, research has established a robust evidence base showing how genetic factors contribute to obesity risk, such as genetic mutations, normal variations in DNA sequences and changes to gene expression (the process by which information encoded in a gene is turned into a function). In most cases, this genetic influence is **polygenic**, involving many genes with small additive effects.



However, there is a rare form of obesity caused by variants in a single gene: **monogenic obesity**. Although uncommon, it is clinically important. Recognising monogenic obesity enables healthcare professionals to provide more accurate diagnoses, avoid stigma, ensure compassionate care and identify patients who may benefit from targeted or precision treatments.



What is Monogenic Obesity?

Monogenic obesity is a rare type of obesity caused by a change in one single gene that has a major impact on how the body regulates appetite and weight.

This is different from the far more common form of obesity, which usually results from small effects of many different genes combined with environmental and lifestyle factors (polygenic obesity).

In monogenic obesity, the condition usually follows a Mendelian inheritance pattern, meaning the genetic change can be passed down through families. Most of the genes involved are part of the leptin-melanocortin pathway, a system in the brain that helps control hunger, fullness, and energy balance.

Key Genes Involved in the Leptin-Melanocortin Pathway

LEP and LEPR allow the body to produce leptin and sense the leptin signal (the hormone that signals fullness).

POMC and PCSK1 create the signal to activate MCR4 and therefore work in tandem to reduce hunger.

MC4R is the brain's 'satiety switch'. It receives signals about the body's energy stores, leading to reduced appetite when stores are sufficient.



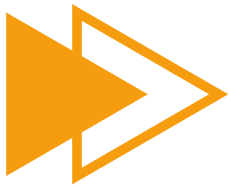
Monogenic obesity almost always starts very early in life, typically before age five. Children affected often show rapid and severe weight gain, intense hunger (hyperphagia) and weight that does not improve despite usual lifestyle interventions. Depending on which gene is affected, some individuals may also have additional hormone or developmental problems - for example, adrenal insufficiency in *POMC* or *PCSK1* deficiency. To date, more than 85 distinct forms of monogenic obesity have been identified.

In some children, their brain's appetite-control system does not receive the correct signals to feel full after eating. This is caused by a fault in a single gene that affects how hunger is regulated.



Why is it Important to Understand Monogenic Obesity as a Healthcare Professional?

Understanding monogenic obesity is crucial for healthcare professionals, both to improve patient care and to advance precision medicine.



Accurate Diagnosis and Early Intervention

Recognising monogenic forms of obesity helps clinicians distinguish them from the much more common polygenic or lifestyle-related obesity. Severe, rapid weight gain beginning in early childhood, especially when accompanied by marked hyperphagia,, should raise suspicion of a genetic cause. Early genetic testing can confirm the diagnosis and prevents families from being directed toward repeated, ineffective lifestyle-only interventions. It also enables timely referral to specialist services and consideration of targeted treatments where appropriate.



Monogenic obesity should be considered in children with **severe obesity before age five**, intense **hyperphagia**, a **family history** of early-onset obesity, or features suggestive of **endocrine or developmental abnormalities**.

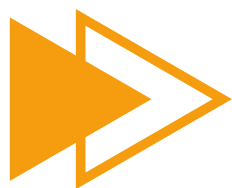


Clinical Features That May Point to Monogenic Obesity in Children

Signs that a child's weight pattern may not be driven by environment or lifestyle include:

- Rapid weight gain beginning in infancy or early childhood
- Strong, persistent hunger that appears out of the child's control
- Limited response to well-delivered dietary advice or physical activity programmes
- Presence of hormonal, developmental, or behavioural features that do not quite fit the 'typical' obesity picture
- A family history of early-onset severe obesity





Personalised Treatment and Better Outcomes

Not all cases of monogenic obesity can be targeted with drug therapy, but where possible, targeted treatment can make a real difference. Research is moving fast and new targeted treatments are emerging. Confirming the specific gene involved in monogenic obesity can guide access to targeted treatments that address the underlying biological pathway:

- **Recombinant leptin** is an effective treatment for individuals with leptin deficiency.
- **Setmelanotide**, an MC4R pathway agonist, has proven benefit in patients with deficiencies in genes of the leptin-melanocortin pathway, including POMC, PCSK1, and LEPR.
- **Diazoxide choline** for patients with Prader-Willi syndrome.





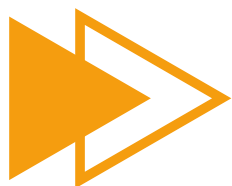
These targeted approaches can significantly improve satiety, weight trajectories, metabolic outcomes, and quality of life. These results are not achievable through lifestyle interventions alone.

Bariatric surgery is a common treatment for polygenic obesity; however, many physicians consider that obesity surgery should not be prescribed for patients with monogenic obesity. Patients with Prader-Willi syndrome face higher complication risks¹, and individuals carrying monoallelic pathogenic MC4R variants (a single harmful mutation) show

more major complications than those carrying the non-mutated version of the gene, independent of age, baseline BMI, sex, operation type, and weight loss².

Carriers of monoallelic pathogenic MC4R variants have been shown to experience greater weight regain at 60 months after Roux-en-Y gastric bypass compared to controls and showed reduced weight loss following sleeve gastrectomy during the first year of follow-up³. Therefore, surgery may not be appropriate treatment for this form of obesity and should be considered carefully.

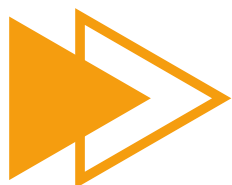




Genetic Counselling for Families

Understanding the inheritance pattern (autosomal recessive or dominant) allows clinicians to:

- Provide genetic counselling to families.
- Inform parents about recurrence risks and options for prenatal or preimplantation diagnosis.
- Identify at-risk relatives who may benefit from early screening or intervention.

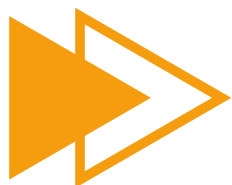


Reducing Psychological Burden and Stigma

Children with monogenic obesity are frequently misinterpreted as being 'undisciplined' or overeating by choice. Recognising that their condition has a biological cause helps healthcare professionals:

- Reduce blame and stigma experienced by patients and families.
- Support psychological well-being by validating the child's experience.
- Encourage adherence with treatment by building trust and empathy.





Broader Insights into Obesity Mechanisms

Research into monogenic obesity has helped uncover the key biological mechanisms that regulate appetite and energy balance, particularly the leptin-melanocortin pathway. Understanding these mechanisms helps healthcare professionals appreciate that obesity is not simply about willpower; rather, it is strongly influenced by underlying biology. These insights are also shaping the development of precision-medicine approaches, which may eventually benefit a wider range of patients beyond those with rare genetic forms.

Types of Obesity		
	Polygenic	Monogenic
Age of obesity onset	Any age	Early onset (before five years old)
Feeding behaviour	Phenotypic variability (e.g., poor satiety, increased hunger)	Hyperphagia
Efficacy of lifestyle-based management strategies	Partially effective	Not effective
Response to medical or surgical management strategies	Heterogenous responses	Limited research

Adapted from Fitch et al. (2024)⁴

Ethical, Legal and Social Implications

Recognising monogenic obesity in children carries important ethical and social responsibilities that should guide clinical practice. While a genetic diagnosis can be reassuring and reduce blame, it must be communicated and managed with care.



Communicate Sensitive

The diagnosis should be explained clearly and compassionately to ensure families feel supported, not judged



Acknowledge relief, guilt or anxiety that may be felt by families



Balanced Framing

Help families recognise that, even with a genetic contribution, they can make positive choices that support their child's long-term health, confidence, and quality of life



Emphasise genes influence appetite and weight regulation, whilst supporting healthy lifestyle habits and psychological wellbeing



Family Implications

The diagnosis may affect siblings and wider family members. Discussions around possible risks, testing, and family planning should be handled gently



Offer access to genetic counselling



Reduce Stigma

Healthcare professionals should actively counter weight stigma and reinforce that the child's experience of hunger and weight is not a behavioural failing



A genetic explanation should help shift the narrative from blame to biology



Child Autonomy

As children age, they should be included in conversations about their condition in a manner appropriate to their understanding, promoting agency and trust



Complete age appropriate and inclusive conversations



Equity of Access

Healthcare systems should work to prevent disparities in who receives genetic evaluation or emerging therapies



All children, regardless of background, should have fair access to assessment and treatment



Privacy and Protection of Genetic Information

Children's genetic data must be stored securely and shared only when necessary for clinical care



Share the minimum necessary, with documented consent and an audit trail

The Leptin-Melanocortin Pathway Explained

How It Normally Works



Fat tissue releases the hormone leptin when energy stores are sufficient

Leptin travels to the appetite control centre in the hypothalamus of the brain, binds to its receptor LEPR and tells the brain 'we have enough energy'

This switches on POMC neurons which activates the MCR4 receptor putting 'the brakes' on appetite

Result: hunger goes down, fullness goes up and energy expenditure rises

What Happens in Monogenic Obesity

Depending on the gene affected you will see differing impacts



The body can't make leptin

No leptin signal is produced so the brain thinks the body needs energy



Leptin can't reach or activate the receptor (LEPR defects)

Signal is made, but the brain never 'hears' it



The POMC pathway can't activate

Leptin signal arrives, but the 'brake' neurons cannot turn on

Regardless of the mutation the brain interprets the body as being in an energy deficit, resulting in intense hunger, rapid weight gain and low energy expenditure

Figure 1. How the leptin-melanocortin pathway regulates appetite and what happens when monogenic obesity occurs

Recommendations for Practice



Consider genetic causes in children with very early and severe obesity

Recommendation: Healthcare professionals should consider referral for genetic assessment when a child shows rapid weight gain early in life, intense hunger, and limited response to standard lifestyle-based treatment.

Why this matters: This ensures children receive the correct diagnosis and appropriate pathway of care.



Ensure treatment is centred on the child, not solely on their obesity diagnosis

Recommendation: Management should be personalised and may include behavioural support, nutritional guidance, psychological support, and where appropriate specialised medical treatment related to the child's genetic profile.

Why this matters: A one-size-fits-all obesity approach is often ineffective for these children and may worsen emotional distress.



Reduce shame, blame and weight-based stigma in every clinical interaction

Recommendation: Professionals should actively use language and explanations that reinforce that monogenic obesity is a biological condition, not a failure of parenting, lifestyle, or self-control.

Why this matters: This improves family engagement, supports mental well-being, and creates a more compassionate clinical environment.

Glossary

Term	Definition
Inheritance pattern	How a genetic trait or disorder is passed down through generations. <ul style="list-style-type: none"> • Autosomal Dominant: A single faulty gene from one parent causes the condition, it often appears in every generation. • Autosomal Recessive: Two faulty gene copies (one from each parent) are needed, the condition may skip generations.
Leptin	A hormone primarily produced by fat cells that tells your brain you're full, helping regulate appetite, energy balance, and long-term weight by signalling satiety (fullness) controlling food intake and energy expenditure.
Leptin-melanocortin pathway	A signalling system in the brain that regulates appetite, body weight, and energy balance by telling the body when it is full. It works when the hormone leptin, released from fat cells, binds to receptors on neurons in the hypothalamus, triggering a chain reaction that leads to the production of melanocortins. These melanocortin hormones then signal to decrease food intake, promoting a feeling of satiety.
Melanocortins	A family of hormones that are involved in regulating bodily functions such as skin and hair pigmentation, inflammation, appetite and energy balance.
Mendelian inheritance pattern	Traits controlled by a single gene are passed from one generation to the next in a simple, predictable way.
POMC and PCSK1 deficiency	Rare genetic disorders that cause severe, early-onset obesity due to a disruption in the brain's hunger and satiety (fullness) signals.
Prader-Willi syndrome	A rare genetic condition that causes a wide range of physical symptoms, learning difficulties and behavioural challenges. Symptoms include restricted growth and an excessive appetite and overeating, which can lead to dangerous weight gain.
Preimplantation genetic testing	A specialised in-vitro fertilisation (IVF) procedure that allows for the genetic testing of embryos before they are implanted in the uterus.
Roux-en-Y gastric bypass	A procedure to create a small pouch at the top of the stomach. A section of intestine is 'plumbed' into this pouch so that the food bypasses the rest of the stomach and enters the intestine lower down. It works by limiting the amount you can eat at each mealtime but also by altering the hormone levels produced by the gut to improve diabetes and make you less hungry.
Sleeve gastrectomy	An operation to remove approximately 80% of the stomach, leaving a thin tube or sleeve in order to restrict the volume of food you can eat. It also removes some stomach cells that produce a hormone that controls hunger, so patients often don't feel as hungry after the procedure.

Find Out More

Bonnefond, A., Bruner, W.S., Grant, S.F.A. et al. The genetics of obesity: aetiology, prevention and therapy. *Nat Metab* (2026).

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