Understanding Rare Monogenic Melanocortin-4 Receptor (MC4R) Driven Obesity

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Obesity Is a Disease of Increased Fat Mass Associated With a Risk to Health

THE

Professionals Collaborating to Overcome Obesity

Obesity as a Disease:
The Obesity Society 2018 Position Statement

"Obesity is a multi-causal chronic disease recognized across the life-span resulting from long-term positive energy balance with development of excess adiposity that over time leads to structural abnormalities, physiological derangements, and functional impairments[1]"

Increased morbidity and mortality

- Increased risk of death[2]
- Long-term complications, including type 2 diabetes, hypertension, and CV disease[3,4]
- Increased risk of cancers[5]
- Obstructive sleep apnea and respiratory infections[6]
- Increased risk of mortality/complications following surgery[7,8]

Decreased HRQOL

- Stigma associated with obesity[9]
- Increased anxiety and depression in adults and children affected by obesity[10,11]
- Decreased physical HRQOL in children with obesity[11]
- Greater psychosocial impairment in children with obesity vs healthy-weight peers[11,12]

BMI, body mass index; CV, cardiovascular; HRQOL, health-related quality of life.

1. Jastreboff AM, et al. Obesity as a Disease: The Obesity Society 2018 Position Statement. *Obesity (Silver Spring)*. 2019 **2.** Calle EE, et al. *N Engl J Med*. 1999;341(15):1097-1105. **3.** Seidell JC, Halberstadt J. *Ann Nutr Metab*. 2015;66(suppl 2):7-12. **4.** Guh DP, et al. *BMC Public Health.* 2009;9:88. **5.** Renehan AG, et al. *Lancet.* 2008;371(9612):569-578. **6.** Zammit C, et al. *Int J Gen Med.* 2010;3:335-343. **7.** Ghanta RK, et al. *J Am Heart Assoc.* 2017;6(3):e003831. **8.** Terada T, et al. *J Am Heart Assoc.* 2016;5(6):e003282. **9.** Hilbert A, et al. *Obesity (Silver Spring)*. 2008;16(7):1529-1534. **10.** Nigatu YT, et al. *PLoS One.* 2016;11(2):e0148871. **11.** Wallander JL, et al. *Int J Obes (Lond).* 2013;37(7):920-925. **12.** Gibson LY, et al. *Eur J Pediatr.* 2017;176(7):925-933.

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Not All Obesity Is the Same

Obesity is a **multifactorial disease** with a variety of phenotypes, clinical presentations, and treatment responses[1]

Environmental Factors[2-4]

Diet

Lack of sleep

Increased stress

Overeating

Physical inactivity

Medications

Genetic Factors[5,6]

Common genetic variants

Impairment of gene expression or function

Rare genetic variants

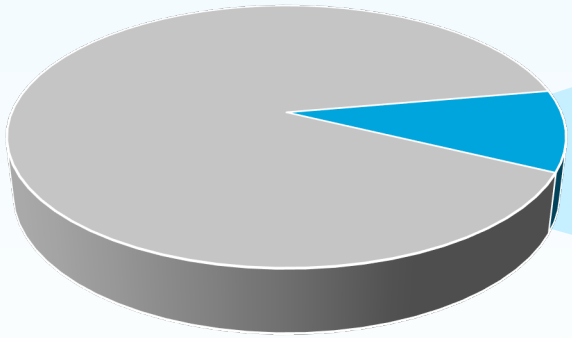
Acquired Factors[7]

Hypothalamic injury

1. Haqq et al. *Child Obes.* 2021;17:229-240. **2.** Muñoz Yáñez et al. *Austin Journal of Nutrition and Metabolism*. 2017;4:1052. **3.** Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/obesity/symptoms-causes/syc-20375742. Updated September 2, 2021. Accessed October 12, 2021. **4.** Domecq et al. *J Clin Endocrinol Metab*. 2015;100:363-370. **5.** Speliotes et al. *Nat Genet*. 2010;42:937-948. **6.** Huvenne et al. *Obes Facts*. 2016;9:158-173. **7.** Rose et al. *Obesity (Silver Spring)*. 2018;26:1727-1732.

Genetic Contributions to Obesity and Examples of Rare Genetic Diseases of Obesity

Types of Obesity[1-6]



Multiple gene variants: not rare

(chart not drawn to scale for prevalence of the types of obesity)

Rare genetic diseases of obesity:
MC4R pathway dysfunction

Monogenic Obesity

POMC deficiency
LEPR deficiency
PCSK1 deficiency
MC4R deficiency
SRC1 deficiency
SH2B1 deficiency

Syndromic Obesity

Bardet-Biedl syndrome
Alström syndrome
Prader-Willi syndrome
Smith-Magenis syndrome

LEPR, leptin receptor; MC4R, melanocortin-4 receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; SH2B1, Src homology 2 B adapter protein 1; SRC1, steroid receptor coactivator 1.

1. Huvenne H, et al. *Obes Facts*. 2016;9(3):158-173. **2.** Hinney A, et al. *Eur Child Adolesc Psychiatry*. 2010;19(3):297-310. **3.** Kostovski M, et al. *Pril (Makedon Akad Nauk Umet Odd Med Nauki)*. 2017;38(3):121-133. **4.** Bays H, Scinta W. *Curr Med Res Opin*. 2015;31(11):2059-2069. **5.** Lu Q, et al. *J Mol Endocrinol.* 2019;62(1):37-46. **6.** Burns B, et al. *Hum Mol Genet.* 2010;19(20):4026-4042.

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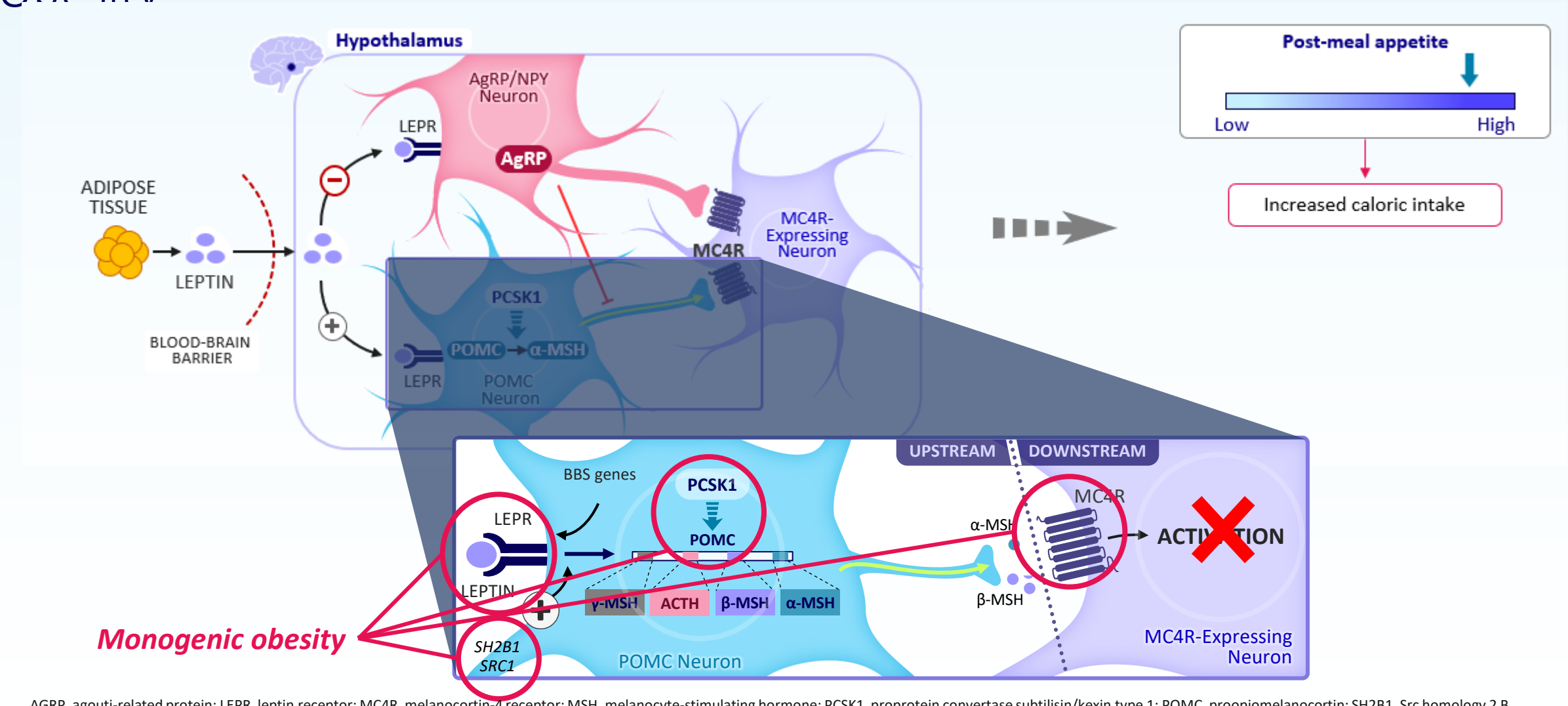
Rare Variants in Key MC4R Pathway Genes Are Associated With Genetic Obesity



AGRP, agouti-related protein; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; SH2B1, Src homology 2 B adapter protein 1; SRC1, steroid receptor coactivator 1.

1. Yazdi et al. *PeerJ*. 2015;3:e856. **2.** Krashes et al. *Nat Neurosci.* 2016;19:206-219. **3.** Cone. *Endocr Rev*. 2006;27:736-749. **4.** da Fonseca et al. *J Diabetes Complications.* 2017;31:1549-1561. **5.** Yang et al. *Nat Commun*. 2019;10:1718. **6.** Seo et al. *Hum Mol Genet.* 2009;18:1323-1331. **7.** Heydet et al. *Dev Neurobiol.* 2013;73:1-13. **8.** Davenport et al. *Curr Biol.* 2007;17:1586-1594.

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Monogenic Obesity Driven by MC4R Pathway Impairment by Rare Genetic Variants Are Likely Underdiagnosed

The true prevalence of MC4R pathway diseases caused by rare genetic variants is unknown because genetic testing is not often done in individuals with obesity[1,2]

	Biallelics	Biallelics	Heterozygotes	Heterozygotes
Gene	**URO Yield**	**US Prev. Est.**	**URO Yield**	**US Prev. Est.**
MC4R	0.33%	17,587	3.03%	161,484
LEP	0.01%	533	0.16%	8,527
PCSK1	0.12%	6,395	1.73%	92,200
POMC	0.09%	4,797	1.93%	102,859
LEPR	0.11%	5,862	2.17%	115,650
NCOA1	0.04%	2,132	2.09%	111,387
SH2B1	0.06%	3,198	2.47%	131,639

[a]Numbers reflect individuals appearing in detailed case histories from published literature or conference proceedings and do not include those appearing in reports such as genomic analyses or population screening studies. Analysis performed in June 2019.[3] [b]A list of loss-of-function variants in *LEPR*, *POMC*, and *PCSK1* was compiled from published literature and supplemented with computationally predicted deleterious missense variants. The frequency of carriers, homozygotes, and compound heterozygotes for each gene was calculated using data from gnomAD sequencing data and the number of individuals with loss-of-function variants of interest was estimated using Hardy-Weinberg proportions. Prevalence was estimated using a US population size of 300 million.[2]
MC4R, melanocortin-4 receptor

1. Heymsfield et al. *Obesity (Silver Spring)*. 2014;22(suppl 1):S1-S17. **2.** Ayers et al. *J Clin Endocrinol Metab*. 2018;103:2601-2612. **3.** Data on file, Rhythm Pharmaceuticals.

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Rare MC4R Monogenic Diseases Present With a Variety of Clinical Characteristics, but Early-Onset, Severe Obesity and Hyperphagia Are Common Features

Disease	Early-onset, severe obesity	Hyperphagia	Growth	Endocrine abnormalities	Other possible characteristics
POMC deficiency[1-4]	✓	✓	Accelerated growth during childhood	Adrenocorticotropic hormone deficiency, mild hypothyroidism	Red/orange hair, light or pale skin
LEPR deficiency[5,6]	✓	✓	Normal linear growth with reduced adult height	Hypogonadotropic hypogonadism, hypothyroidism, hyperinsulinemia	Severe bacterial infections due to defective T-cell immunity
PCSK1 deficiency[2,7,8]	✓	✓	Typically normal height	Hypoglycemia, hypothyroidism, adrenocorticotropic hormone deficiency	Intestinal malabsorption, diarrhea in early infancy
SRC1 deficiency[10-13]	✓	✓	Typically normal height	Insulin resistance	Adipose tissue fibrosis, liver fibrosis
SH2B1 deficiency[14]	✓	✓	Reduced adult height	Hyperinsulinemia	Early speech and language delays, behavioral problems (ie, aggression and social isolation)
MC4 deficiency	✓	✓	Accelerated linear growth in childhood; tall stature	Hyperinsulinemia	Early spontaneous onset of puberty; Advanced reproductive age in females and erectile dysfunction in males

LEPR, leptin receptor; MC4R, melanocortin-4 receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; SH2B1, Src homology 2 B adapter protein 1; SRC1, steroid receptor coactivator 1.

1. Coll AP, et al. *J Clin Endocrinol Metab.* 2004;89(6):2557-2562. **2.** Styne DM, et al. *J Clin Endocrinol Metab.* 2017;102(3):709-757. **3.** Mendiratta MS, et al. *Int J Pediatr Endocrinol.* 2011;2011(1):5. **4.** Argente J, et al. *Endocr Abstr.* 2019;63:P976. **5.** Farooqi IS, O'Rahilly S. *J Endocrinol.* 2014;223(1):T63-T70. **6.** Thaker VV. *Adolesc Med State Art Rev.* 2017;28(2):379-405. **7.** Stijnen P, et al. *Endocr Rev.* 2016;37(4):347-371. **8.** Martin MG, et al. *Gastroenterology.* 2013;145(1):138-148. **9.** Huvenne H, et al. *Obes Facts.* 2016;9(3):158-173. **10.** Cacciottolo TM, et al. *QJM.* 2019;112(9):724-729. **11.** Lu Q, et al. *J Mol Endocrinol.* 2019;62(1):37-46. **12.** Yang Y, et al. *Nat Commun.* 2019;10(1):1718. **13.** Cacciottolo TM, et al. *J Clin Endocrinol Metab.* 2022 **14.** Doche ME, et al. *J Clin Endocrinol.* 2012;122(12):4732-4736.

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LEPR deficiency[5,6]	✓	✓			
PCSK1 deficiency[2,7,8]	✓	✓			
SRC1 deficiency[10-13]	✓	✓			
SH2B1 deficiency[14]	✓	✓			
MC4 deficiency	✓	✓			

However, **early-onset obesity** and **hyperphagia** are key clinical features common to many rare MC4R pathway diseases

LEPR, leptin receptor; MC4R, melanocortin-4 receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; SH2B1, Src homology 2 B adapter protein 1; SRC1, steroid receptor coactivator 1.

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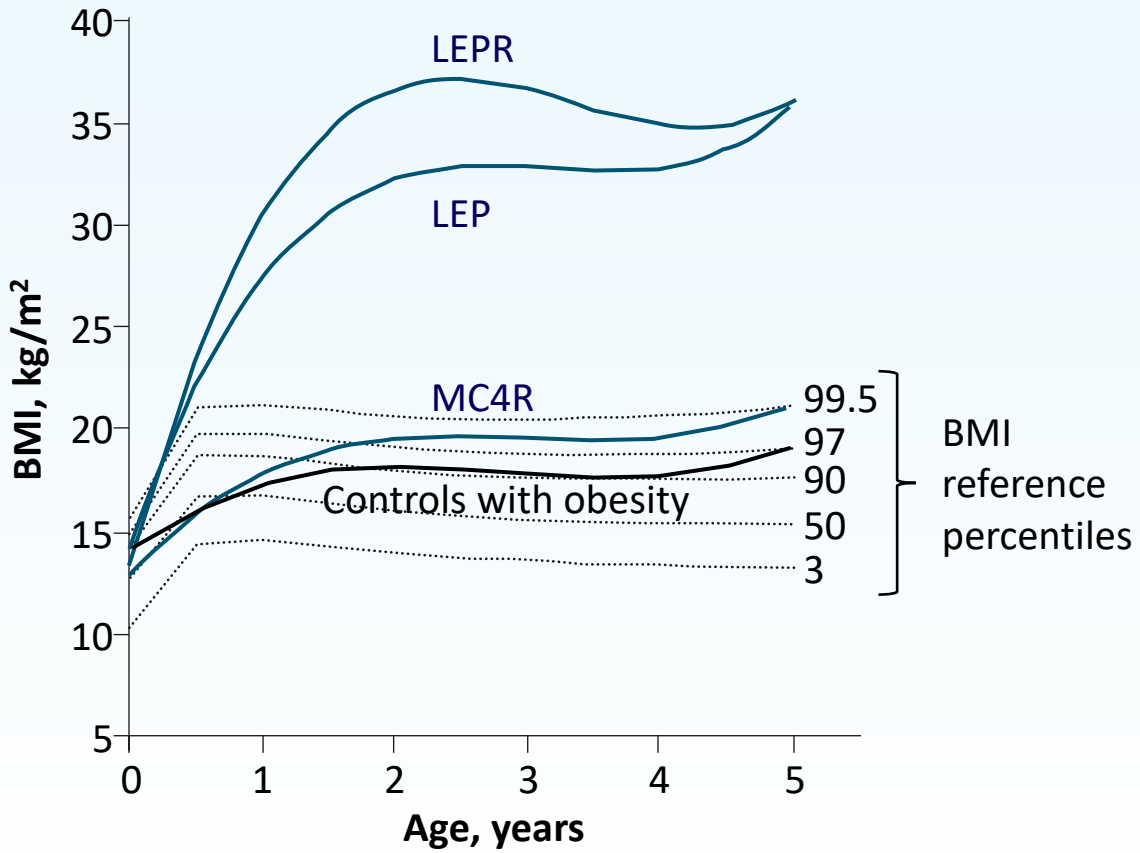
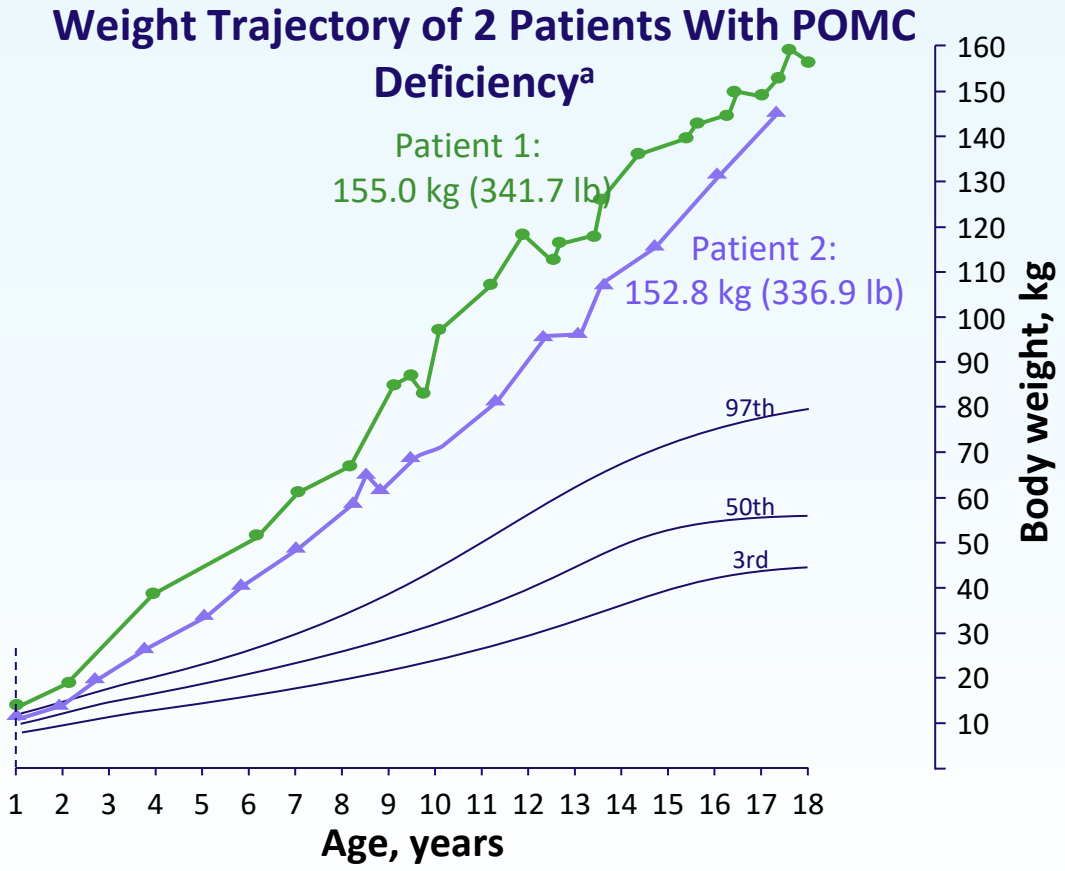
Range of BMI in Children With Obesity Due to Monogenic Variants in the MC4R Pathway





BMI may be a useful indicator that children should undergo genetic screening

[a]Controls with obesity have a BMI >30 kg/m² by age 14-16 years and do not have a homozygous or compound heterozygous mutation in *LEPR*, *LEP*, or compound heterozygous or heterozygous mutation in *MC4R*.

BMI, body mass index; LEP, leptin; LEPR, leptin receptor; MC4R, melanocortin-4 receptor.

Kohlsdorf K, et al. *Int J Obes (Lond)*. 2018;42(9):1602-1609.

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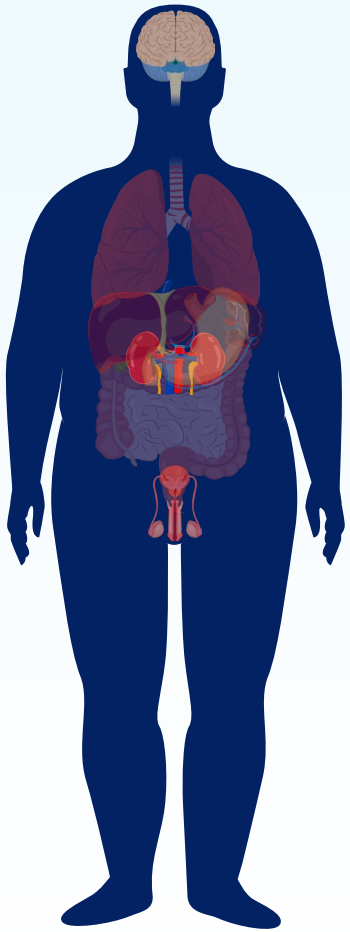
Guidelines and Expert Recommendations for Diagnosing Rare MC4R Pathway Diseases[1-4]



Identify patients

- Early-onset,[a] severe obesity
- Hyperphagia
- Other clinical characteristics of rare MC4R pathway diseases (ie, neurological abnormalities, growth abnormalities, endocrine abnormalities)
- Family history of notable weight differences between family members

Genetic testing can aid in the diagnosis of rare MC4R pathway diseases

Genetically identifiable, nonsyndromic	Clinically identifiable, syndromic
• POMC deficiency • LEPR deficiency • PCSK1 deficiency • SRC1 deficiency • SH2B1 deficiency	• Bardet-Biedl syndrome

[a]Before 5 years of age.
LEPR, leptin receptor; MC4R, melanocortin-4 receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; SH2B1, Src homology 2 B adapter protein 1; SRC1, steroid receptor coactivator 1.

1. Styne DM, et al. *J Clin Endocrinol Metab*. 2017;102(3):709-757. **2.** van der Valk ES, et al. *Obes Rev*. 2019;20(6):795-804. **3.** Huvenne H, et al. *Obes Facts*. 2016;9(3):158-173. **4.** Smith ACM, et al. https://www.ncbi.nlm.nih.gov/books/NBK1310/. Accessed July 16, 2021.

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