Mass General Brigham

Monogenic & Polygenic Obesity in Children

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Disclosures

I have no disclosures

Pediatric Obesity

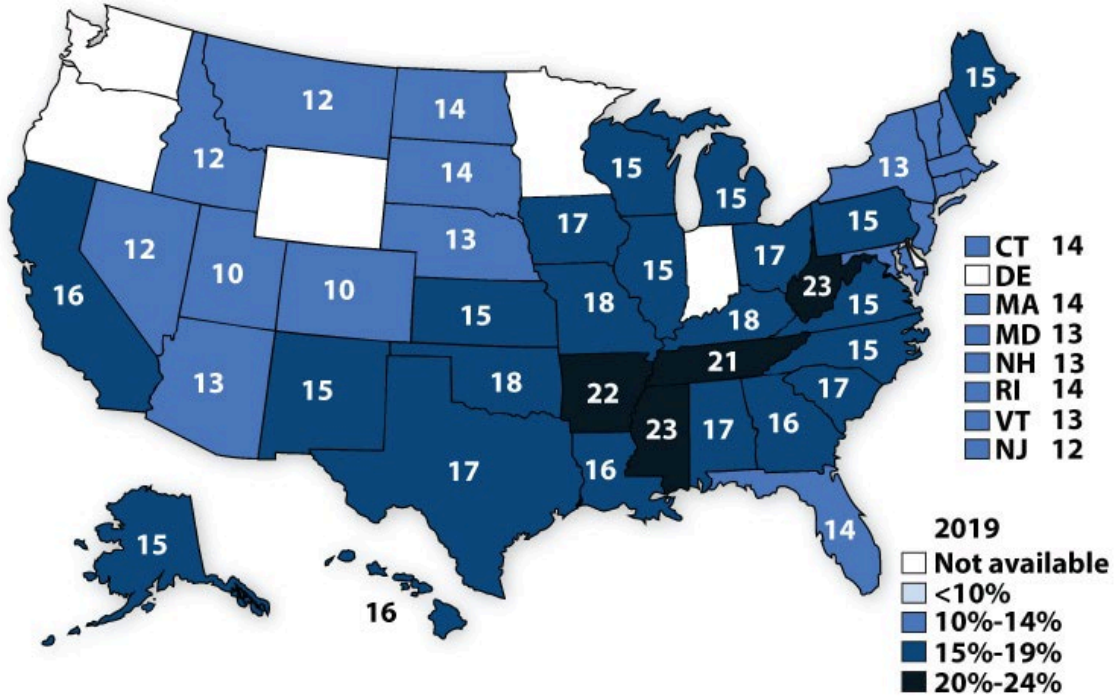
Obesity results from complex interactions between environment & genetics

Treatment methods in early childhood obesity tend to address environmental and lifestyle factors, but heritable factors are also vital

Differences in obesity prevalence between ethnic populations, familial transmission and twin concordance support a substantial genetic component

The heritability for variation in BMI ranges from approximately 40 to 70% in multiple studies

Adolescent Obesity Prevalence 2019 (CDC)



Monogenic Obesity

Several forms of non-syndromic monogenic childhood obesity exist, although they are observed in less than 1% of children evaluated in tertiary level pediatric clinics

Monogenic obesity = a mutation occurring in just a single gene involved in regulation of body weight

Obesity is such a highly heterogeneous disease, severe cases presenting with an early age of onset are typically driven by highly penetrant rare genetic variants

Most genes implicated in this form of childhood obesity are involved in the leptin-melanocortin signaling pathway

5 genes causing some of the most prevalent forms of non-syndromic monogenic childhood obesity: MCR4, LEP, LEPR, POMC, PCSK1

MC4R

In 1998, Melanocortin 4 receptor (MCR4) variants were reported to be associated with dominantly inherited human obesity

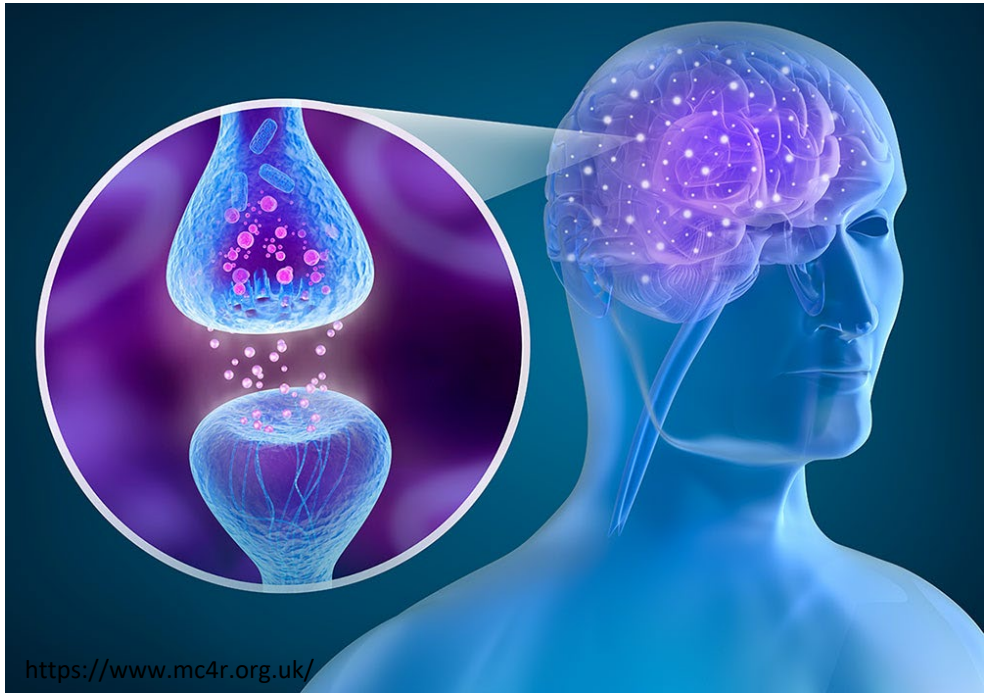
The MCR4 gene plays an important role in food intake, energy balance, and weight control

Melanocortin 4 receptor is mainly found in the hypothalamus, responsible for appetite and satiety

In murine models, MC4 receptors have been found to be involved in the feeding behavior, regulation of metabolism, sexual behavior, and male erectile function

In animal models, deletion of *MC4R* also results in hyperphagia and increased body fat, ultimately leading to hepatic steatosis without atherogenic diet

Homozygous variants are rare, cause earlier/severe obesity



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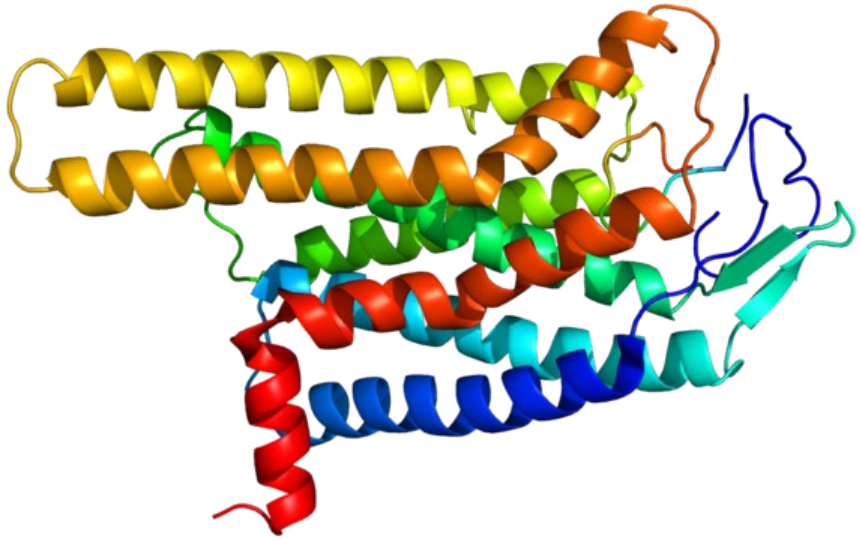
MCR4

MC4R variants seem to have an incomplete penetrance and some degree of codominance

Individuals that carry pathogenic variants have a 4.5X risk of developing obesity vs noncarriers

More than 200 variants have been identified to date, primarily heterozygous dominant acting missense variants

Heterozygous variants have been found in 2–5% of subjects with severe, early-onset pediatric obesity, making this the most common genetic form of obesity in pediatric age group



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Farooqi IS, Yeo GSH, Keogh JM, Aminian S, Jebb SA, Butler G, Cheetham T, O'Rahilly S. Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency. J Clin Invest. 2000;106(2):271–279

POMC

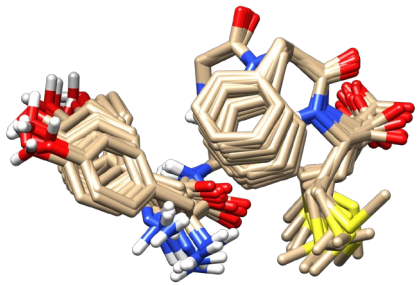
The secretion of pro-opiomelanocortin (POMC) from hypothalamic neurons is vital for energy balance regulation and neuroendocrine function, first identified in 1977

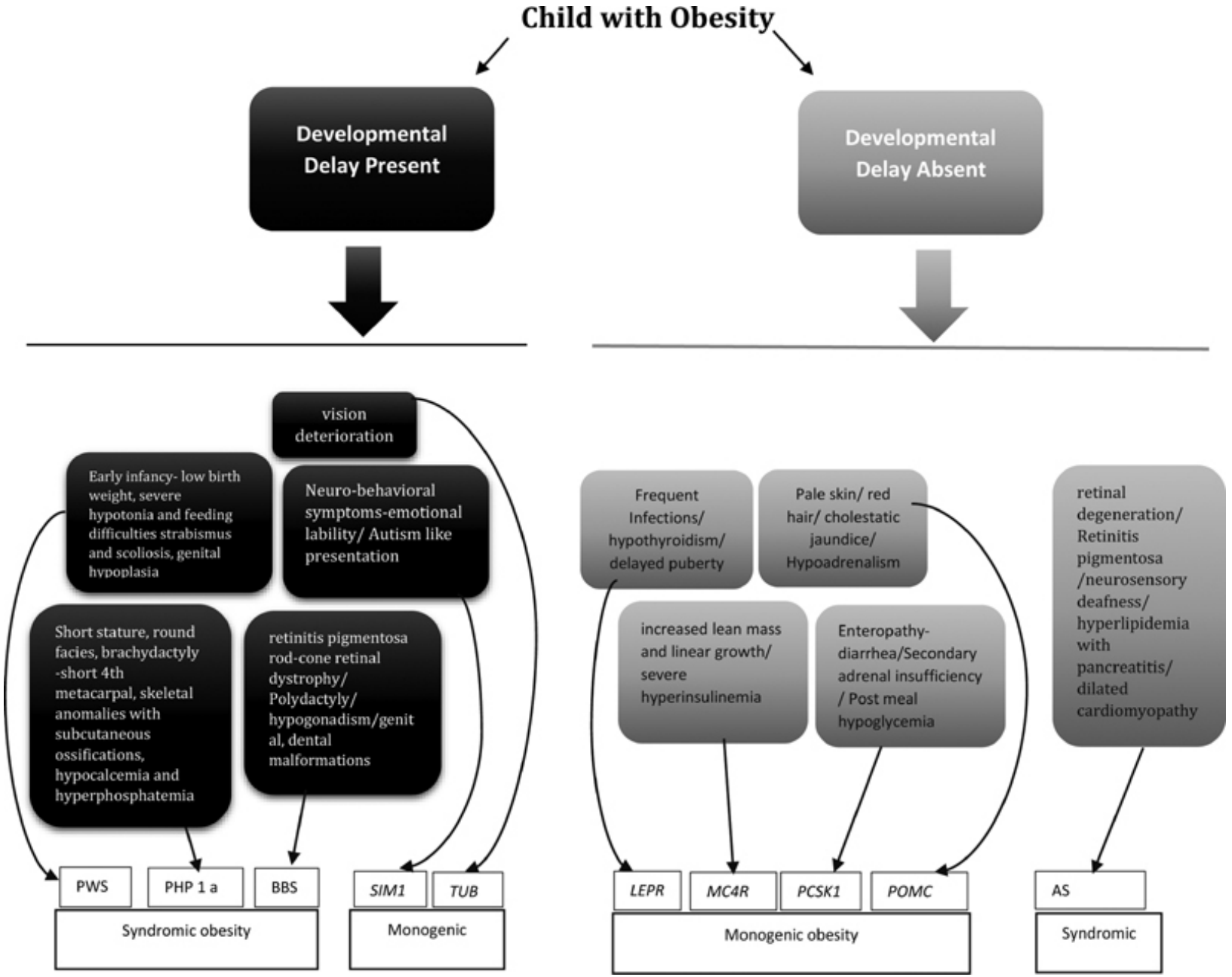
POMC is highly expressed in the pituitary, where its products are released into the bloodstream, and in the hypothalamus, where POMC-derived peptides function as neuropeptides

POMC deficiency is an autosomal recessive disease driven by loss-of-function mutations in *POMC*

POMC knockout mice exhibit adult-onset obesity, resulting from a combination of elevated feeding and changes to metabolism that reduce energy expenditure

Epigenetic marks such as DNA methylation may modulate *POMC* expression and provide a biological link from early life exposures; some human studies suggest *POMC* DNA methylation is influenced by maternal nutrition in pregnancy & associated with childhood/adult obesity





Diagnostic clues in a clinical setting. AS, Alström syndrome; BBS, Bardet–Biedl syndrome; *LEPR* , leptin deficiency/leptin receptor mutation; *MC4R* , melanocortin 4 receptor mutation; *PCSK1* , proprotein convertase deficiency; PHP 1a-pseudohypoparathyroidism 1 a; *POMC* , pro-opiomelanocortin deficiency; PWS, Prader-Willi syndrome; *SIM 1* , single-minded homolog 1 gene defect; *TUB* , Tubby bipartite transcription factor.

Malhotra S, Sivasubramanian R, Srivastava G. Evaluation and Management of Early Onset Genetic Obesity in Childhood. J Pediatr Genet. 2021 Sep;10(3):194-204.

Polygenic Obesity

Polygenic obesity (the most common type) is caused through the influence of susceptibility variants in multiple genes, with each having a relatively small effect

Genome-wide association studies (GWAS) represent a global method to identify associations between genetic loci and a trait

A limitation of GWAS is that they use single nucleotide polymorphisms (SNPs) to uncover alleles associated with traits of interest – but generally do not identify causal variants. They identify a region of linkage disequilibrium containing a potentially causal event. Follow up studies are needed to confirm GWAS signals

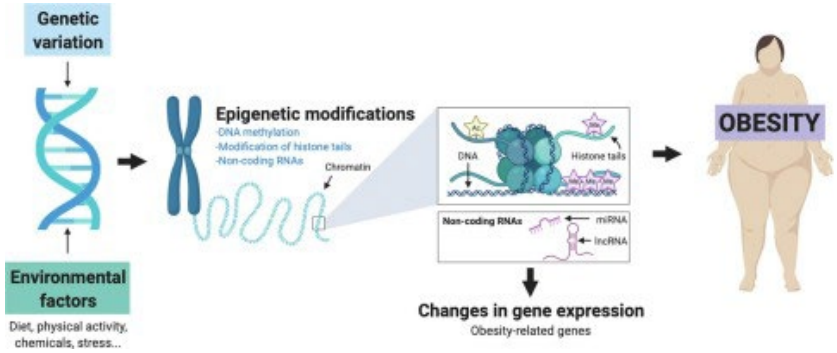
Hundreds of BMI loci have been uncovered through GWAS efforts, with an emphasis on adults

Polygenic Obesity and Future Directions

While GWAS has revealed a multitude of adult BMI and obesity loci, the genetic architecture of childhood obesity is far less characterized, despite there being what appears to be a large overlap

Polygenic risk scores, which incorporate the weights of respective risk alleles and address the overall risk burden within a given individual are actively being studied as potential predictors

Increasing evidence suggests that forms of syndromic and monogenic childhood obesity exist on a continuum and potential future therapeutic targets are actively being explored



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Genetic Testing

Genetic testing and identifying an underlying genetic cause of obesity, gives patients/families ability to acknowledge pathology, reducing self and societal blame

Identifying genetic etiology can help manage concerns early and treat associated endocrinopathies, hyperphagia, and other metabolic risks by early targeted, multidisciplinary treatment

Pediatric Endocrine society guideline recommends genetic testing in children with extreme, early-onset obesity before 5 years of age with hyperphagia, and/or family history of extreme obesity → should undergo next generation sequencing (NGS)

Gene panels are considered 1-tier tests: low costs, have a rapid turnaround time, low rate of nonspecific findings, but gene panels miss approximately 10% of mutations that can be detected by whole exome sequencing (WES) that provides superior coverage of targeted gene panels with greater number of genes included

Malhotra S, Sivasubramanian R, Srivastava G. Evaluation and Management of Early Onset Genetic Obesity in Childhood. J Pediatr Genet. 2021 Sep;10(3):194-204.

Treating Patients with MCR4 Variants

Previous studies published in 2011 and 2014 suggest that patients with heterozygosity of the *MC4R* gene can be treated effectively in the short term with MBS, with longer-term success rates being studied

Overall weight loss trends in response to MBS in patients with heterozygous *MC4R* mutations is similar to the response seen in general population with severe obesity

2022 study out the UAE study 70 patients that screen + for MCR4 deficiency and wild-type mutations who underwent surgical and pharmacological therapy (liraglutide)→ weight loss stable at 6 months, variable results long term (up to 10 yrs)

MBS was found superior to liraglutide on weight and glycemic control outcomes

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Thank you
Questions?