

# AMGP "M.U.G."

## "Monthly Update in Genetics"

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AMGP MUG  
 June 2003  
 Vol 3: No 6

### Genetics and Obesity

NEJM 20 March 2003

During each decade of life, the average adult American eats 10 million calories -- an enormous amount of energy -- and gains only a few pounds (discoveryhealth.com). From this, we can calculate that the calories eaten are 99.83% of the calories burned. Someone who is "only" 99.5% efficient will gain weight at triple the usual rate. In today's society, easy access to high-caloric meals and an increasingly sedentary lifestyle, have combined to make obesity one of the major current public health problems (Figure 2 adjacent, source CDC).

During the course of human evolution, the ability to store calories for leaner times was adaptive and undoubtedly selected for. In brief periods of "plenty" our ancestors stockpiled calories for future use. Western society today provides us with continual "plenty" in terms of caloric options, in part contributing to the "epidemic of obesity". Unfortunately for our waistlines, our genetic history means that those same "calorie-storing" genes might put us at risk for unhealthy weight gain.

**The question therefore can be posed, is obesity an "environmental" or a "genetic" problem?**

The answer is probably a bit of both. In animal studies (rodents and livestock) there is substantial evidence that body mass index (**BMI**) is heritable. Human family studies have also demonstrated that relatives are more similar in terms of a variety of phenotypes, including body mass index. Combined with twin studies, the estimate is that between **40-70% of the variation in obesity-phenotypes is due to genetic factors** (Science 1998380;1374-77).

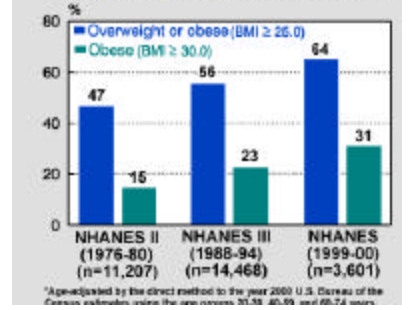
For the majority of obese persons the contributions of underlying genetic factors and dietary intake are highly complex and much remains to be understood. Recently the identification of several **rare single-gene obesity syndromes** has shed light on genes that regulate BMI and eating behavior (Table).

<b>Incomplete List of Human Single Gene Obesity Syndromes</b>		
Disorder	Gene Product	Inheritance
Leptin deficiency	Leptin	Autosomal Recessive
Leptin receptor deficiency	Leptin receptor	Autosomal Recessive
Bardet-Biedl Syndrome	BBS1 gene	Autosomal Dominant
Lipotropin deficiency	Proopiomelanocortin	Autosomal Recessive
MC4R Receptor obesity	<b>Melanocortin 4 Receptor</b>	Autosomal Dominant

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#### Update on Alzheimer's Disease Genetics

**Figure 2. Age-adjusted\* prevalence of overweight obesity among U.S. adults, age 20-74 years**

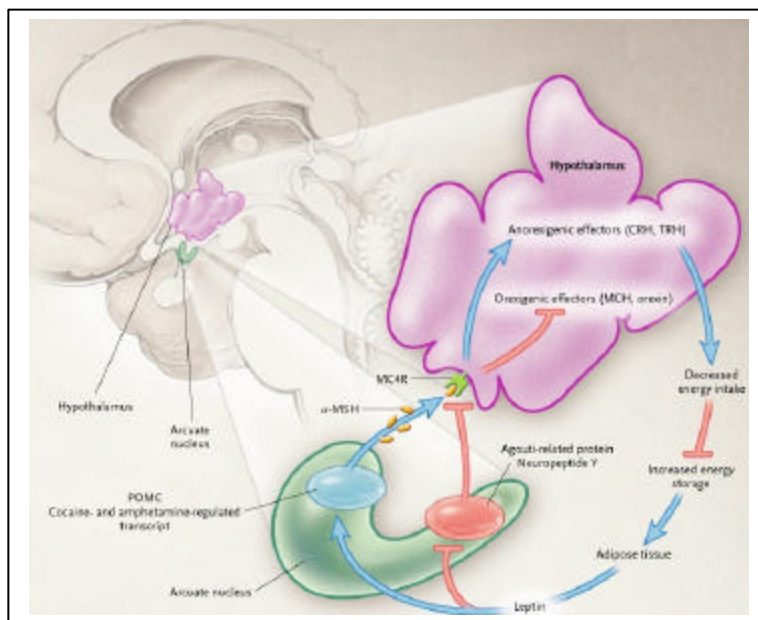


*Obesity, is it in the genes?* Slide from CDC

**PRACTICE SAFE GENETICS:**  
 The intent of this newsletter is to increase your familiarity with clinical genetics. Genetic evaluations and testing raise many issues and are often most appropriately addressed in a genetics clinic setting. Please feel free to contact me with any clinical questions that arise as you care for your patients.  
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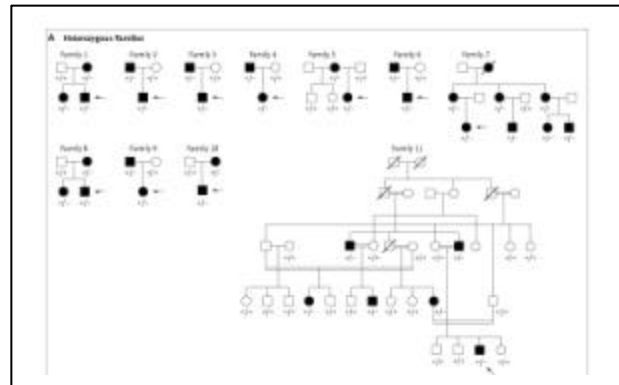
In the 20 March edition of the *NEJM* there are two articles reporting phenotypes caused by mutations in the **Melanocortin 4 Receptor** gene (**MC4R**). The authors of the accompanying editorial provide a figure highlighting how **MC4R** is proposed to function in the regulation of body mass homeostasis (figure below from *NEJM* 2003; 348; 1160-62).

In this model the action is in the hypothalamus; weight gain stimulates the production of **leptin** from fat tissue. **Leptin** stimulates the release of **alpha-melanocyte stimulating hormone** (**α-MSH**) which is anorexigenic (turns off drive to keep eating). The **α-MSH** functions through binding to **MC4R**, which in turn leads to the release of other anorexigenic proteins. The



message: **you need normally function MC4R to stay slim.**

Mutations in **MC4R** are known to cause obesity in rare cases, but the frequency of mutations in obesity and the various phenotypes were not clearly defined. Farooqi et al (*NEJM* 2003; 348; 1085-95) studied 500 children with severe obesity (weight >98% of normal population) that had onset before 10 years of age. 5.8% were found to have pathogenic mutations in **MC4R**. Mutation carriers had hyperinsulinemia and hyperphagia. 20% of the mutation carriers were **homozygous** (had 2 copies of **MC4R** mutations) and they had the most severe phenotype. **Thus, although the above table lists MC4R inheritance as autosomal dominant it may be more correct to describe the inheritances as codominant** (e.g. that the final phenotype is determined by the *combined* effect of *both* alleles).



By identifying mutation in the 500 probands, the investigators were then able to look at the *relatives* of the mutation carriers and identify other relatives with obesity (and families at *risk for future affected children*). **This is another illustration of how genetic mutation testing can be used to characterize who else (other than your patient) in a family is at risk for future disease and/or having other affected children** (pedigree figure; Farooqi article). When clinical genetic testing becomes available for mutations in these genes it will become necessary to decide *if and when* to integrate such testing into clinical care.

The second article by Branson et al (p: 1096-103) studied 469 severely obese Caucasians (mean **BMI** 47.7) and compared this group with 25 normal weight (**BMI** 21.6) controls. In agreement with the above study, 5.1% of the obese had **MC4R** mutations. In studying the mutation carriers it became apparent that **MC4R** mutations led to a **binge-eating** phenotype in *all* mutation carriers. This was highly significant when compared to obese persons without **MC4R** mutations (only 14% reporting binge eating).

This finding was suggested by the first study (where “hyperphagia” was reported), and is important as it documents a **behavioral phenotype in obesity**.

Collectively, mutations in **MC4R** appear to be “uncommon” monogenic causes of obesity and clinical genetic testing is not yet available. However, consider this in the context of **BRCA1/2** mutations in breast cancer (mutations of which cause ~4-5% of breast cancer) where genetic testing is becoming standard of care for familial breast cancers. The identification of **MC4R** mutations has also provided therapeutic pathway targets for future anti-obesity drugs and behavioral interventions.