**Genetic Disorders and Obesity: (course 2, section of biopsychological contributions)**

This material is supplemental to the textbook chapter and may be of interest to some instructors. As described in the textbook, diet-induced obesity is the predominant phenotype. While genes influence intake, single-gene causes of obesity are quite rare. However, these presentations of obesity provide important clues to the biological contributions to energy balance. Here we describe two lines of evidence, the *FTO* gene and Prader-Willi Syndrome.

* The strongest genetic variant associated with obesity risk in humans are alleles (variants) of the *FTO* gene (Frayling et al., 2007). The allele of the *FTO* gene causes increased weight beginning in childhood and increased body fat mass due to greater energy intake which augments risk for obesity. Subsequent GWAS identified a melanocortin receptor MC4R mutation, which led to increased growth and hyperinsulimia, but it is only present in about 5% of patients with early-onset obesity (Farooqi & O’Rahilly, 2008; Martinelli et al., 2011). In contrast with more common types of obesity, rare cases of congenital leptin deficiency are successfully treated with leptin administration (Farooqi & O’Rahilly, 2008).
* Prader-Willi syndrome is a neurodevelopmental disorder caused by deletion of genes on chromosome 15. This syndrome is characterized by hyperphagia, hypotonia (lack of muscle tone), short stature, and mental deficits in addition to the presentation of obesity (Ramachandrappa & Farooqi, 2011). Elevated circulating ghrelin levels help explain the hyperphagia and subsequent high body weight. In these patients, food stimuli are associated with increased wanting of food and thus consumption, and the elevated ghrelin is hypothesized to mediate this relationship (Johnson, 2013).
	+ Web resources for Prader-Willi syndrome:
		- <https://www.fpwr.org/about-prader-willi-syndrome#diagnosis>
		- <https://rarediseases.info.nih.gov/diseases/5575/prader-willi-syndrome>
		- <https://www.nature.com/articles/gim0b013e31822bead0>

**Ideas for class exercise and discussion:**

* The instructor can follow up on this material by directing a class (or small group) discussion on the public perception of familial patterns of obesity. How does the average person understand the hereditability of body composition? And how does public perception compare with your understanding at this point in the course?
* Alternately, encourage students to find a (scholarly) case study of Prader-Willi syndrome. Ask them to share the details of their case study with a peer, as well as any variability in symptom presentation.

**Related references:**

Farooqi, I.S. & S. O’Rahilly (2008), ‘Mutations in ligands and receptors of the leptin-melanocortin pathway that lead to obesity’, *Nature Endocrinology & Metabolism,* 4(10): 569-577.

Frayling, T.M. et al. (2007), ‘A common variant in the *FTO* gene is associated with body mass index and predisposes childhood and adult obesity’, *Science,* 316: 889-894.

Johnson, A.W. (2013), ‘Eating beyond homeostatic need: how environmental cues influence feeding behavior’, *Trends in Neurosciences,* 36(2): 101-109.

Martinelli, C.E. et al. (2011), ‘Obesity due to melanocortin 4 receptor (MC4R) deficiency is associated with increased linear growth and final height, fasting hyperinsulinemia, and incompletely suppressed growth hormone secretion’, *JCEM,* 96(1): E181-E188.

Ramachandrappa, S. & I.S. Farooqi (2011), ‘Genetic approaches to understanding human obesity’, *The Journal of Clinical Investigation,* 121(6): 2080-2086.