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Review Article

Mitochondrial genetics and obesity: evolutionary adaptation and contemporary disease susceptibility

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ABSTRACT

Obesity is a leading risk factor for a variety of metabolic diseases including cardiovascular disease, diabetes, and cancer. Although in its simplest terms, obesity may be thought of as a consequence of excessive caloric intake and sedentary lifestyle, it is also evident that individual propensity for weight gain can vary. The etiology of individual susceptibility to obesity seems to be complex—involving a combination of environmental–genetic interactions. Herein, we suggest that the mitochondrion plays a major role in influencing individual susceptibility to this disease via mitochondrial–nuclear interaction processes and that environmentally influenced selection events for mitochondrial function that conveyed increased reproductive and survival success during the global establishment of human populations during prehistoric times can influence individual susceptibility to weight gain and obesity.

Contents

Obesity is currently the fifth leading risk for global death [1] as well as a major risk factor for cardiovascular disease, diabetes, and cancer, which, combined, accounted for over 1.2 million deaths in the United States in 2010 [2]. In general, weight gain and ultimately obesity are considered a consequence of excessive caloric intake and sedentary lifestyles commonplace in Western society. However, it is clear that some individuals seem to be more prone to weight gain than others and that certain racial groups are at greater risk for obesity. Studies endeavoring to find a clear genetic basis of this susceptibility have largely been unsuccessful, suggesting that the etiology of individual susceptibility to obesity is a combination of complex environmental–genetic interactions. We suggest that the mitochondrion plays a major role in influencing individual susceptibility to this disease via mitochondrial–nuclear interaction processes, and that environmentally influenced selection events for mitochondrial function that conveyed increased reproductive and survival

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success during the global establishment of human populations during prehistoric times, today, can influence individual susceptibility to weight gain and obesity.

Obesity is endemic in the developed world

Obesity is defined as increased deposition of adipose tissue, particularly in the abdomen, leading to increased waist circumference and a body mass index (BMI) of 30 or more [3]. Obesity rates have been steadily rising over the past 25 years, with current reports classifying more than one-third of U.S. adults as obese [4]. This is of particular concern in the southern states, with Alabama, Mississippi, and Louisiana all reporting obesity prevalence greater than 31%, compared to northern states reporting in the mid- to upper 20 s. Obesity is also a major risk factor for metabolic syndrome, or syndrome X—a cluster of risk factors that, when occurring together, increase a patient's risk for cardiovascular disease and type 2 diabetes (T2DM) [5]. Although there is no relationship between obesity and education level among men, there is a surprising link between obesity and income. It is reported that African-American and Mexican-American men with higher income are more likely to be obese than those with low income [6,7], which is contrary to classic dogma [7]. However, it should be noted that most documented relationships between obesity and socioeconomic status occur in children, adolescents, and women [8,9]. Obesity does have a documented racial disparity, with non-Hispanic African-Americans having the highest age-adjusted obesity rate of 49.5%, compared to non-Hispanic Caucasians with a rate of 34.3% [10]. Although obesity can occur at any age, metabolic and lifestyle changes associated with aging increase obesity risk [11]. Poor diet and lack of exercise are implicated as the major contributors to the rising incidence of obesity [12–15], but there is also an increasing volume of research exploring possible genetic factors causing, or at least contributing to, obesity susceptibility in adult and juvenile populations.

Single-gene mutations that cause obesity are rare

Numerous studies have attempted to identify causal mutations that could explain the rising obesity rates. Multiple monogenic syndromes have been identified—in which afflicted patients are morbidly obese, and some exhibit multiple factors of the metabolic syndrome as a result of a single mutation in one nuclear gene. A number of these monogenic obesity syndromes were reviewed by Farooqi and O'Rahilly [16], including congenital leptin deficiency, leptin receptor mutations, and melanocortin-4 receptor (MC4R) mutations.

Leptin is a 16-kDa hormone that is synthesized in the adipocytes of white adipose tissue [17]. It has been shown to play a role in modulating energy expenditure and food intake by exerting effects on appetite and hunger as well as metabolism [18]. Leptin exerts its effects by binding its receptors in the brain to inhibit appetite [19]. Leptin is, along with insulin, considered an adiposity signal [20]; circulating leptin levels are proportional to body fat, though this can be altered with calorie restriction [21–23]. Given its function, leptin deficiency results in morbid obesity caused, in part, by an uncontrollable appetite. Documented cases of patients with congenital leptin deficiency are extremely rare, with less than 20 afflicted individuals identified since 1997 [24]. Some cases have been reported in consanguineous families [25]. Most of the patients in these studies were treated with exogenous leptin. Leptin therapy has been shown to promote weight loss as well as a decrease in hyperphagia associated with leptin deficiency [26]. The rodent model of leptin deficiency, the *ob/ob* mouse [27], is considered a classic obesity model for basic science research. Although a plethora of research has been conducted on this transgenic mouse model, as previously stated, leptin deficiency is an extremely rare cause of obesity in humans.

The leptin receptor, which binds the leptin hormone, is found in the brain stem as well as the hypothalamus [28]. A rodent model of leptin receptor (LEPR) deficiency, the *db/db* mouse, has also been widely studied. However, it is again clear that the LEPR deficiency seen in the *db/db* mouse is equally rare in humans, with fewer than 15 reported cases as of 2012 [24]. Leptin receptor mutations result in high levels of mutant receptor and subsequent elevated circulating leptin levels. The phenotype of LEPR deficiency is comparable to that of congenital leptin deficiency, characterized by morbid obesity, rapid weight gain and increased fat mass, severe hyperphagia, as well as some endocrine dysfunction [29]. As the gene defect is in the receptor, treatment with exogenous leptin is not therapeutic for these patients. Evidence points to uncoupling proteins as a potential therapeutic target in both rodents and humans [30,31], but significant pharmacological interventions have not yet been developed [28].

The MC4R is a G-protein-coupled protein receptor in the brain that binds α-melanocyte-stimulating hormone [32]. Studies of MC4R in rodents demonstrate its role in both feeding and metabolism. Mice with MC4R deficiency exhibit progressive obesity, hyperphagia, hyperglycemia, and hyperinsulinemia [32,33]. The frequency of MC4R mutations is higher than all other monogenic obesity syndromes; in U.K. and European populations, 1–2.5% of individuals with a BMI of 30 or greater were found to have MC4R mutations [34]. Individuals that are heterozygous for the gene mutation exhibit less severe symptoms than homozygotes [35]. Patients with MC4R deficiency do not currently have any widely available treatment options.

Although these monogenic syndromes do cause obesity, the frequencies of these mutations are low and therefore do not account for the rising rates of obesity currently observed in the developed world (Table 1). In addition, these rare monogenic syndromes have been reported in various ethnic groups and thus do not contribute to the racial disparity seen in obesity and metabolic disease. Finally, the rate at which obesity is rising in the population is too rapid to be explained by single-gene mutations in the nucleus and is probably due to environmental–genetic interaction processes as the primary cause [36]. Consistent with

Table 1
Some of the single-gene mutations that cause obesity.

Gene	Locus	Mutation	Inheritance	Prevalence	Mouse model
Leptin	7q31.3	Homozygous	Autosomal recessive	< 1/1,000,000	*ob/ob*
Leptin receptor (LEPR)	1p31.3	Homozygous	Autosomal recessive	< 1/1,000,000	*db/db*
Melanocortin-4 receptor (MC4R)	18q21.32	Heterozygous	Autosomal dominant	1–5/10,000	*Mc4r*^{tm1Lowl}

Listed are the genetic loci, mutation types, inheritance patterns, prevalence in the global population, and laboratory mouse model of the gene defect. Information presented was adapted from www.orpha.net.

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