Genetic Factors for Overweight and CAD

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Abstract
Obesity is a growing clinical problem reaching epidemic proportions in developed and developing countries. It is associated with several comorbidities including cardiovascular diseases. There is strong evidence for the association of excess weight and established metabolic risk factors for coronary artery disease (CAD) such as hyperlipidemia, high blood pressure and type 2 diabetes. In addition, obesity may promote cardiovascular disease independent of these factors, possibly via hormones secreted by adipocytes, promotion of pro-inflammatory processes or other as yet unrecognized mechanisms. In this article the authors will outline the heredity of body weight and CAD/myocardial infarction and describe genetic factors involved in the etiology of these diseases. The methods commonly applied for the detection of such factors are described (e.g., animal models, linkage studies, association studies, etc.). These methods are discussed either in the paragraphs on obesity or on CAD; the described principles apply to both phenotypes.

Genetische Faktoren für Übergewicht und KHK

Zusammenfassung

Genetic Factors Influencing Obesity
In the past decades a powerful rise in obesity prevalence has occurred in both children and adults. Currently, obesity is most commonly classified by a body mass index (BMI, weight in kilograms/height2) in meters. Overweight is defined as a BMI of 25.0–29.9 kg/m2. Obesity is defined as a BMI ≥ 30 kg/m2, sub-divided into three classes (BMI of class I 30.0–34.9, class II 35.0–39.9, class III or extreme obesity ≥ 40 kg/m2). For children and adolescents the 90th and 97th BMI percentile are used to define overweight and obesity.

Despite intensive efforts, biomedical research has not been able to exactly pinpoint the reasons underlying the obesity epidemic. An altered environment is commonly assumed to underlie the secular trend; both an increased energy intake and a reduced energy expenditure figure as the two prominent factors in this discussion [1]. The reasons inherent to the difficulties in pinpointing the exact factors are presumably of physiological nature. Thus, energy intake needs to only minimally exceed energy expenditure on a daily basis; such a slight degree of overeating cannot be detected using available technology. In ad-
dition, several factors work in concert, each factor in itself making only a minute contribution. Palatability, availability and low price of food, portion size, TV and media consumption, and decreased levels of manual work and physical activity are relevant in this context.

An attempt to explain a genetic predisposition for obesity was made in the “thrifty genotype hypothesis” originally postulated by Neel in 1962 for diabetes mellitus (see [2]). According to this hypothesis genetic variations favoring energy storage have been fixed during evolution, thus increasing the probability of survival during periods of famine. Accordingly, both in humans and animals alleles predisposing to an elevated body weight and thus to obesity should be more common than alleles that do not favor energy storage. Whereas this hypothesis intuitively makes sense, it has not been convincingly demonstrated to apply to obesity.

**Heritability Estimates**

Twin studies have produced the most consistent and highest heritability estimates with values in the range of 0.6–0.9 for BMI (kg/m²). Heritability estimates of this magnitude indicate that the genetic component for body weight is almost as high as that for height (0.8). These high estimates apply to twins reared both together and apart. Except for the newborn period age does not affect heritability estimates to a substantial degree. Heritability of BMI is maximal (up to 0.9) during late childhood and adolescence. In comparison to twin studies, adoption and family studies have mostly resulted in lower heritability estimates. However, large and more recent family studies have also come up with heritability estimates of approximately 0.7. The genes relevant for weight regulation in childhood presumably only partially overlap with those operative in adulthood [3].

**Animal Models**

Generally, known genetic pathways and feedback systems involved in human weight regulation have first been identified in animal models. Furthermore, most monogenic forms of human obesity have first been identified as spontaneous mutations in rodents or in gene knockout animals. The fundamental importance of animal models in genetic studies is shown in the following examples.

Historically, the domain of rodents in obesity research has been the field of monogenic obesity models. Different single gene mutations were discovered leading to severe obesity in certain mouse strains. While monogenic causes of obesity are rare both in mice and in the human population, these animals are nevertheless of outstanding value for unraveling genetic pathways and physiological mechanisms controlling energy homeostasis. The most noted mutant is the obese (ob) mouse lacking the product of the hormone/cytokine encoding gene leptin (Lep<sup>ob</sup>). This mutant was discovered at the Jackson Laboratories in 1949 [4]. Another spontaneous mutation discovered at Jackson Labs is the diabetes mutation (db) lacking the long form of the leptin receptor (Lep<sup>db</sup>) [5]. Parabiosis experiments with joined circulatory systems of Lep<sup>ob</sup> and Lep<sup>db</sup> mice suggested that ob mice lack a secreted factor, while in db mice the receptor is missing [6]. In 1994 and 1995 the corresponding genes were cloned, confirming this assumption [7–9]. Complete failure of leptin signaling results in severe obesity. In humans, rare recessive mutations in the LEP gene have been discovered, resulting in extreme early-onset obesity [10, 11] that can be cured by leptin treatment [12–14]. This approach marks the first pharmacological treatment of a monogenic form of obesity in humans based on knowledge of the underlying genetic mechanism.

Another obese mouse model is the agouti Yellow (A<sup>y</sup>) mouse [15]. Yellow mice have been known for 200 years; they show a yellow coat color and obese. Overexpression of the agouti peptide in the skin blocks α-melanocyte-stimulating hormone (α-MSH) signaling at melanocortin-1 receptors in the hair follicle, resulting in the production of yellow pigments (pheomelanin). In the A<sup>y</sup> mouse agouti protein is ectopically expressed in all somatic cells [16]. Therefore, overexpression of agouti in the brain also antagonizes the anorectic action of α-MSH signaling at the melanocortin-4 receptor (MC4R), causing hyperphagia and subsequently obesity. α-MSH is produced by proteolytic cleavage of a prohormone by carboxypeptidase E (CPE) [17]. Mutated CPE leads to the fat mouse, another obese mouse model discovered at Jackson Labs [18].

In addition to the aforementioned spontaneous mutations, knockout and transgenic rodent models have proven successful in revealing and resolving gene function. They are the most straightforward way of doing reverse genetics, i.e., going from gene to phenotype. Several thousand knockout and transgenic models have been generated and many of them show evidence that the targeted gene is involved in processes of body weight regulation. Currently (version 11), the Obesity Gene Map Database (www.obesity.chair.ulaval.ca/genes.html) lists a selection of 164 knockouts and transgenics with obesity-related phenotypes. An example that will be taken on later in this chapter is the MC4R knockout mouse [18]. Inactivation of this receptor results in mice that develop maturity-onset obesity. Heterozygous mice show an intermediate phenotype suggesting that MC4R gene