Identification of Genes Predisposing to Clinically Severe Obesity: An Approach

Michael North, PhD; J. Robert Jacobs, MD; Leo Murphy, MD; Eugene Rumsey Jr, MD; Laurence Tanaka, MD; George Zorn, MD; Geoff Joslyn PhD; Mary Lou Walen

Background: Familial correlations, twin studies and adoption studies have all indicated that human obesity has a substantial genetic component. To date, obesity genes have only been identified using mouse models.

Methods: In an attempt to identify human obesity genes large numbers of multigenerational families, in whom extreme obesity segregates, are currently being collected.

Results and Conclusions: Relative risk estimates and models of genetic heterogeneity indicate that at least 500 affected sibling pairs will need to be collected to identify major genes.

Key words: Genes, morbid obesity, relative risk.

Introduction

Obesity is a growing public health problem, particularly in the USA. Current estimates indicate that over 30 million individuals in the USA are classified as obese (greater than 20% above ideal weight based on age, height and sex), and an estimated 100 million individuals are affected worldwide. Nearly $30 billion a year is now spent in the USA on efforts to combat obesity through weight loss or weight control programs.1

Typically, obesity is measured by body mass index (BMI), which is defined as the weight (kg) divided by the height (m) squared. In the USA mean BMI is 26.3, an increase of nearly 8% over the past decade. Estimates indicate that about 2 million individuals in the USA have clinically severe obesity (BMIs which exceed 40). These patients have a 6–10-fold increased risk of mortality when compared to normal counterparts of the same age group.2 Approximately 4 million individuals in the USA have a BMI between 35 and 40. It has been estimated that healthcare costs for disorders related to obesity are $59 billion a year.

Some of the most important advances in understanding the metabolic causes of obesity have come from studying mouse models. One of the most important findings from these models is that extreme obesity can be transmitted as a simple genetic trait under controlled environmental conditions.3 Such inheritance is not restricted to mice; for example, a recent study of genetic differences between the wild boar and the domestic pig revealed that a small region of pig chromosome 4 had a major effect on abdominal fat deposition.4 Crossbred animals inheriting wild boar alleles on chromosome 4 developed extra fat under controlled dietary conditions.

Human genetic studies have been complicated by the fact that the environment can clearly play a role in promoting obesity; hence, the widespread observation of strong familial clustering of regional fat distribution does not prove that genes are directly involved. For example, there is a strong inverse relationship between social class and obesity in developed countries. The first unambiguous evidence of a genetic component to obesity came from an adoption study in Denmark which demonstrated a high correlation of the BMI of adoptees with that of their biological parents and little correlation with that of their adoptive parents (for the mothers, p < 0.0001; for the fathers, p < 0.02). The study examined a sample (n) of 800 individuals aged 33–56 years, who were selected from a registry of 3651 adoptees.5

Reprint requests to: Mary Lou Walen, Pacific Bariatric Surgery Medical Group, 4060 4th Avenue, Suite 330, San Diego, CA 92103, USA. Tel: 619-224-2781; fax: 619-224-0206.

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Methodology

Strategy

Human obesity is not inherited in a strictly mendelian fashion. It is multifactorial and determined by the interaction of genes with the environment, especially the diet. The importance of the environment in expression of the obese phenotype is classically demonstrated by the Pima Indians. Large increases in BMI among Pima Indian men and women in post-World War II birth cohorts can be correlated to exposure to Western culture and diet (including reduced exercise and high-fat foods).

To reduce the potential influence of environmental components, genetic studies will first focus on identifying genes predisposing to morbid obesity. Families showing inheritance of morbid obesity are currently being collected (as described below). The families are identified by a proband of BMI > 40 and are pre-screened (by family history) to select for multiple affected and unaffected siblings and only one affected parent. A minimal family for collection consists of a proband with one affected sibling, one unaffected sibling and one unaffected parent. Large multigenerational sibships are most efficient in identifying genes and allow greatest flexibility in the methods of analysis used (parametric and non-parametric, quantitative and qualitative). Each family member will be typed for about 300 dinucleotide and tetranucleotide markers spaced at an average of 10 cm. This is referred to as a genome scan and allows inheritance patterns to be inferred (from, for example, affected parent to affected sibling).

Sample Size Estimates

One of the most efficient methods for identifying genes in traits where simple mendelian inheritance does not apply is the affected sibling pair (ASP) test. The test determines if alleles at any given chromosomal locus are more frequently shared by pairs of affected siblings than would be expected by chance. The measure of significance for linkage by the ASP test is the X² statistic (p value).

The number of affected sibpairs which need to be tested to identify predisposing genes to morbid obesity is a function of several variables including the polymorphism content of the markers used in the genome scan and the relative sibling risk for the trait (discussed below). One of the most important concepts is that of major and minor predisposing genes. As shown in Figure 1, modelling studies indicate that a major gene which accounts for 90% of the genetic predisposition to a trait with relative risk 3.5 can be detected (p < 0.01) with less than 100 ASPs. However, a gene which accounts for only 20% of the genetic predisposition may require over 3000 ASPs for detection at p < 0.01.

The strategy currently employed is to collect and genome scan a minimum of 500 morbidly obese ASPs in order to identify genes contributing to 50% or more of the genetic predisposition.

Results

Phenotype Measurements

BMI in the general population follows an approximately normal distribution with a positive tail. Figure 2 shows the BMI distribution (mean 25.5; SD 5.25) of 251 individuals from one extended family. Larger populations follow a similar bell-shaped distribution. By selecting probands with BMI > 40 at the extreme end of the distribution (< 1%), well removed from the normal range, the potentially confounding effects of environment can be reduced. Additionally, the pseudonormal distribution of BMI allows quantitative analyses to be performed as well as ASP analysis. For ASP analysis, affected status within morbidly obese families is defined as BMI > 30 after correction for age, sex and ethnicity. Shown in Figure 3 are two examples of families under collection which are suitable for genetic analysis by the criteria outlined above (the proband indicated by an arrow in each case).

A variety of additional clinical parameters are measured from family members including weight and height, skinfold measurements, waist-to-hip ratios, attempts at medically managed weight loss, nutritional history and a review of co-morbid conditions such as sleep apnea, diabetes, hypertension, pulmonary disease, etc.

Relative Risk Measurements

An important parameter in studying any genetic disease is the relative sibling risk (λs) defined as the disease risk given an affected sibling divided by the population prevalence. λs quantifies the added disease risk for individuals with a family history; the genetic risk. Quoted λs values for type II diabetes and schizophrenia are 3.5 and 10 respectively. A study of the Pacific Bariatric Surgery Medical Group population (n = 78) indicates that λs = 6 for BMI > 35. Estimates