The Genetics of Obesity

Thorkild I.A. Sørensen

Genetic and environmental factors both affect the development of human obesity. The prevalence of obesity has increased over the past 30 years, and changes in the environment must have played a key role in this increase. Studies of monozygotic twins have found differences in body weight that must be due to environmental influences. However, there is also considerable evidence suggesting a genetic basis for obesity. The body mass index (BMI) of adult offspring is correlated with the BMI of parents, and this can be entirely ascribed to the transmitted genes. Thus, the similarity of BMI is about twice as great among monozygotic twins as among dizygotic twins. Moreover, adoption studies have shown a correlation between the BMIs of biological parents, siblings, and adult adoptees, while the BMI of the adult adoptees showed no correlation with the BMI of their adoptive parents. A few major genes may contribute to the development of obesity. Genetic linkage and candidate gene studies have attempted to identify the genes involved in determining BMI in humans, but have so far produced mixed results.
Copyright © 1995 by W.B. Saunders Company

GENETIC EPIDEMIOLOGY is the study of interaction between genes and the environment. It is used to study the origin of diseases without giving priority to either genes or the environment. A number of research strategies are available to help define the genetic basis of a multifactorial phenotype such as obesity.

There are two fundamentally different types of strategy: the so-called top-down and bottom-up strategies. The top-down strategies start by observing the phenotype, such as body mass index (BMI), which is a measure of obesity, and then look at the distribution of this phenotype within families. The bottom-up strategies start from the genotype and relate specific patterns of genotype to phenotypes.

The bottom-up strategies include associations with candidate genes and genetic linkage studies. Linkage studies link the occurrence of the phenotype in families to the transmission of specific gene alleles whose location on the genome may be known. The quantitative trait loci (QTL) linkage approach involves scanning the genome to determine if a series of specific genetic markers are frequently associated with a particular quantitative trait. This gives an estimate of where on the genome the gene or genes responsible for the phenotype are located. Other strategies used to characterize the genes responsible for a specific phenotype include cloning techniques, DNA sequencing techniques, and the use of genetically engineered animal models.

A recent comprehensive literature review[1] clearly showed that the development of obesity is influenced by both genetic and environmental factors. However, it is important to define the phenotype of obesity. Obesity may be divided into four types: type I, in which there is an excess body mass or percentage of fat; type II, in which subcutaneous truncal-abdominal fat (android) is in excess; type III, in which there is an excess abdominal visceral fat; and type IV, in which gluteofemoral fat (gynoid) is in excess. These four types of obesity may result from different genetic, as well as environmental, backgrounds. Most studies of the genetic epidemiology of obesity have dealt with type I obesity.

From the Danish Epidemiology Science Center at the Institute of Preventive Medicine, University of Copenhagen, Denmark.

Address reprint requests to Thorkild I.A. Sørensen, MD, Danish Epidemiology Science Center at the Institute of Preventive Medicine, University of Copenhagen, Copenhagen Hospital Corp, Kommunehopitalet, DK-1399 Copenhagen, Denmark.

Copyright © 1995 by W.B. Saunders Company

0026-0495/95/4409-0103$03.00/0

ENVIRONMENT

There is no doubt that environment plays an important role in the development of obesity. Studies have found changes in the occurrence of obesity over time both within populations and within individuals, providing evidence that the environment influences the development of obesity.

The prevalence of obesity in young Danish army conscripts born between 1925 and 1942 was about one per 1,000. After 1942, there was a sudden, steep increase in the prevalence of obesity.[2] By the time those born in 1955 were conscripted, the prevalence of obesity was almost 10 per 1,000. This increased prevalence must be due to a corresponding change in important environmental causes of obesity.

When monozygotic twins, who are genetically identical, were overfed for 100 days, the twins showed correlated changes in body weight, possibly indicating a genetic component in weight gain.[3] However, there were differences of weight gain between twins, which must represent environmental components. In the same study, the increase in visceral fat was compared between twins. Again, there were discrepancies between twins, which shows that the environment exerts an influence on this compartment.

GENETICS

There is a tendency for family members to have similar BMIs.[1] Studies have shown a clear relationship between the BMI of parents and their offspring. Four large family studies, the Framingham study, the Canadian fitness study, the Quebec family study and the Norwegian family study, confirmed the familial correlation of BMI. In these studies, obese parents produced the highest proportion of obese children. This suggests that genes and/or the family environment contribute to BMI and obesity. However, twin and adoption studies show that in adults genes alone are responsible for the familial correlation.[1]

TWIN STUDIES

Twin studies found that monozygotic twins have a higher correlation in BMI than dizygotic twins, despite having

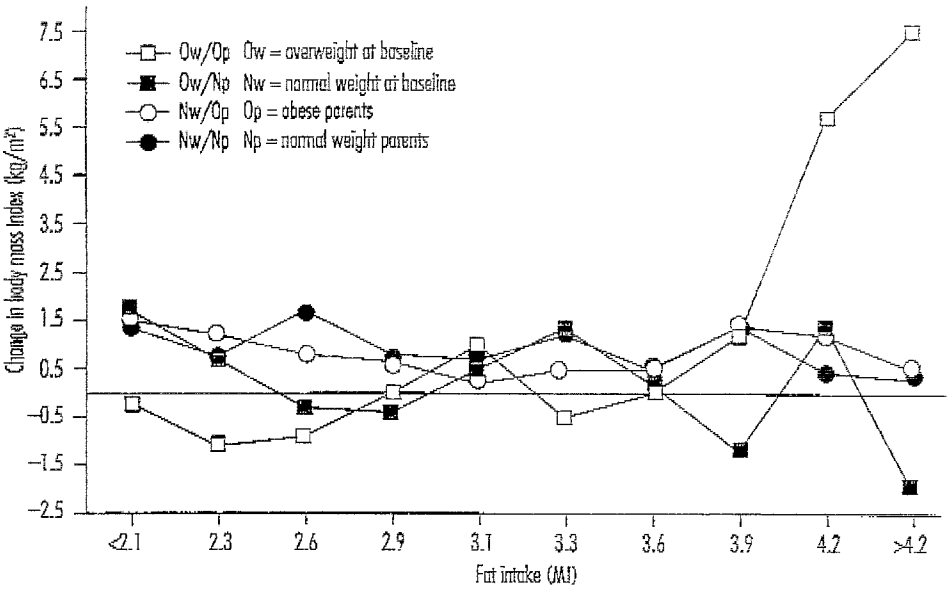

Fig 1. Correlation between dietary fat intake and change in BMI in a group of women: 6-year follow-up. (Adapted with permission.[11])

been raised in similar family environments.[4] This supports the idea that genes play a role in determining BMI.

More detailed twin studies measured other indicators of body fatness, such as subcutaneous skinfold thickness, fat mass, and fat-free mass.[5] In monozygotic twins, there is greater similarity in both fat mass and fat-free mass than among dizygotic twins. Similar results were found when subcutaneous skinfold thickness was measured at several sites.

However, twin studies can be confounded by environmental influences. Monozygotic twins are so like each other that they are more likely to be treated similarly than are dizygotic twins. Thus, monozygotic twins may share more similar environmental influences than dizygotic twins; this could falsely inflate the apparent role of genes in determining BMI.

ADOPTION STUDIES

To cope with this problem, adoption studies have been used to assess the roles of genes and the family environment in determining BMI.[6] A significant relationship between the BMI of biological parents and the BMI of adoptees was found in adults, as well as in children.[7,8] In contrast, there was no correlation between the BMI of the adoptive parents and the adult adoptee, and only a weak correlation for the adoptees in childhood. These findings suggest that there is a genetic influence on BMI, and that the family environment plays no role in establishing the familial resemblance of the BMI of the adult, and only a small role in determining childhood BMI.

Sibling studies have provided more evidence for a genetic basis to obesity.[8,9] Full siblings, born to the same parents, but who subsequently did not live together, were found to have similar BMIs, and this is particularly evident among obese siblings. A similar, although expectedly weaker, relationship has been found among half-siblings.

All of the adoption studies support the role of genes in determining BMI in both children and adults.[6] These studies found that a shared family environment exerted little or no influence on BMI.

MAJOR GENES

A complex of genes may control BMI. Alternatively, only a few so-called major genes may be involved in the development of obesity. Segregation analyses have suggested that there are a few major genes that control obesity.[1] However, there is also evidence that a number of genes are involved in determining BMI. There is considerable ongoing activity seeking to identify specific genes.

Attempts to identify these genes by the candidate gene approach or by genetic linkage studies have produced mixed results.[1] A number of genes have been positively associated with BMI and obesity in both humans and animal models. Using positional cloning and DNA sequencing, the mouse *ob* gene and the human homolog have recently been identified and characterized.[10]

FAT INTAKE

There is some evidence to suggest that there is a gene/environment interaction that controls obesity. A prospective study in women assessed the change in BMI in relation to fat intake at baseline over 6 years (Fig 1).[11] Individuals were divided initially into one of four groups: overweight with obese parents, overweight with non-obese parents, normal weight with obese parents, and normal weight with non-obese parents. In three of the four groups, there was no relationship between fat intake and subsequent weight gain. High fat intake was only correlated with subsequent changes in weight in the group of women who were overweight at baseline and had obese parents. This

particular subgroup appears to be susceptible to weight gain when fat intake is high.

Another study measured dietary fat intake and the prevalence of obesity among male army conscripts over a 35-year period.[2,12] Increases in the percentage of fat in the diet over the years have been followed by an increased prevalence of obesity, but there has been no change in the median BMI. Thus, high fat consumption affected a small subgroup of the total population to create an overall greater prevalence of obesity. These findings suggest that there may be a gene that causes weight gain when fat intake is excessive.

CONCLUSIONS AND PERSPECTIVES

Genetic influences clearly play a major role in determining BMI and its extreme variant—obesity. Environmental factors modify these genetic influences to either enhance or limit weight gain in susceptible individuals. Research is ongoing that aims to identify specific genes that control different factors determining BMI and fat distribution. In the future, characterization of these genetic influences may enable at-risk individuals to be identified early and steps taken to prevent weight gain and its associated health risks.

REFERENCES

1. Bouchard C: The Genetics of Obesity. Boca Raton, FL, CRC, 1994

2. Sørensen TIA, Price RA: Secular trends in body mass index among Danish young men. Int J Obes 14:411-419, 1990

3. Bouchard C, Tremblay A, Despres JP, et al: The response to long-term overfeeding in identical twins. N Engl J Med 322:1477-1482, 1990

4. Meyer JM, Stunkard AJ: Twin studies of human obesity, in Bouchard C (ed): The Genetics of Obesity. Boca Raton, FL, CRC, 1994, pp 63-78

5. Bouchard C, Perusse L, Leblanc C, et al: Inheritance of the amount and distribution of human body fat. Int J Obes 12:205-215, 1988

6. Sørensen TIA, Stunkard AJ: Overview of the adoption studies, in Bouchard C (ed): The Genetics of Obesity. Boca Raton, FL, CRC, 1994, pp 49-61

7. Stunkard AJ, Sorensen TIA, Hanis C, et al: An adoption study of human obesity. N Engl J Med 314:193-198, 1986

8. Sørensen TIA, Holst C, Stunkard AJ: Childhood body mass index—Genetic and familial environmental influences assessed in a longitudinal adoption study. Int J Obes 16:705-714, 1992

9. Sørensen TIA, Price RA, Stunkard AJ, et al: Genetics of obesity in adult adoptees and their biological siblings. Br Med J 298:87-90, 1989

10. Shang Y, Proenca R, Maffei M, et al: Positional cloning of the mouse obese gene and its human homologue. Nature 372:425-432, 1994

11. Heitmann Bl, Lissner L, Sørensen TIA, et al: Dietary fat intake and weight gain in women with genetic predisposition. Am J Clin Nutr 61:1213-1217, 1995

12. Lissner L, Heitmann BL: Dietary fat and obesity: Evidence from epidemiology. Eur J Clin Nutr 49:79-90, 1995