Obesity: Common Symptom of Diverse Gene-Based Metabolic Dysregulations

Genetics of Human Obesity: Recent Results from Linkage Studies[1]

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ABSTRACT Excess body fat or body mass relative to height aggregates in families. It is commonly recognized that this familial aggregation of human obesity is accounted for in part by a significant genetic component. Thus the genetic heritability of the obesity phenotypes accounts for ~25–40% of the age- and gender-adjusted phenotypic variances. There is also growing evidence that single-gene effects can be detected under appropriate conditions. The focus of research has now shifted to candidate genes and DNA markers of various obesity phenotypes. To date, linkage results have been published from the Pima Indian Study, the San Antonio Family Heart or Diabetes Studies, the Paris Cohort of Obese Siblings, the University of Pennsylvania Family Obesity Study and the Quebec Family Study. The only genomic scan (with ~600 markers) reported to date is that from the Pima Indian sibling study. In that study, the strongest evidence for linkage with body fat was with markers on chromosome 11q, 6p and 3p. Evidence for linkage with markers on 7q was obtained in all family studies with the only apparent exception being the Pima Indians. Our own results from the Quebec Family Study suggest that there are linkages between body fat, as assessed from hydrodensitometry, and markers on 1p32–p22. Other linkages have been reported in the past but they are generally based on smaller sample size and weaker evidence. J. Nutr. 127: 1887S–1890S, 1997.

KEY WORDS: • *rodent models* • *quantitative trait locus* • *linkage* • *gene map*

Scientists involved in the study of the causes of human obesity have become optimistic about the possibility of identifying the genes associated with the predisposition to this disease. A growing understanding of the human genome, the high degree of homology between humans and common laboratory mammals for a large number of genes and chromosomal regions, and the availability of a whole variety of technologies and tools to study and manipulate DNA in the laboratory are among the most important reasons for the present level of hope in the obesity research community.

It is quite common to observe in population data that the prevalence of obesity reaches its maximum at ~50–60 y of age. After these ages, it often begins to decline. If we assume that 60 is the age at which we have the maximum prevalence of obesity, it is not surprising that a major imbalance between energy intake and energy expenditure has occurred so frequently by that age. Indeed, people of these ages have had a lifetime ingestion of ~55 million calories. Presumably, they have expended about the same amount of calories, but as the population data indicate, positive energy balance is extremely frequent in our environment.

Why is the chronic imbalance so frequent? One of the hypotheses is that the genes are involved. I will briefly review the status of the research regarding the genetic and molecular basis of obesity. But let me make one point clear at the onset: I believe that the current epidemic of obesity in the developed countries is not caused primarily by our genes. It is caused by a lifestyle that favors positive energy balance as a result of the easy access to a plentiful food supply and technological advances that are making us more and more sedentary. The preceding does not eliminate the possibility that there are people who are more susceptible than others, in the circumstances that we live in, to being in positive energy balance. Indeed, there were obese people early in this century and in past centuries. However, there were fewer of them.

HERITABILITY LEVEL

The level of heritability has been considered in a large number of twin, adoption and family studies. The level of heritability is simply the fraction of the population variation in a trait [e.g., body mass index (BMI)] that can be explained by genetic transmission. Results obtained by a good number of investigators indicate that the heritability level estimates depend on how the study was conducted and on the kinds of relatives upon which they were based. Two comprehensive studies incorporating twins, adoptees and nuclear family data have yielded heritability estimates of ~25–40% of the individual differences in BMI or body fat (Bouchard 1994). They were based on samples from Norway (Tambs et al. 1991) and Quebec (Bouchard et al. 1988).

These results have been confirmed by a recent reanalysis

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of the data from the Danish Adoption Study (Vogler et al. 1995), whose findings had been published earlier by Stunkard and his Danish colleagues (Stunkard et al. 1986). The new assessment, based on a path analysis approach, concluded that the heritability of BMI reached 34% (Vogler et al. 1995), a value quite compatible with the estimates reported from the Nord-Trøndelag Norwegian Study (Tambs et al. 1991) and the Quebec Family Study (Bouchard et al. 1988).

The risk of becoming obese. A number of studies have reported that obese children frequently had obese parents. Thus, in ~30% of the cases, both parents of obese children are obese, with a range in frequency of ~5–45%. It has also been estimated that ~25–35% of the obese cases occur in families with normal weight parents, despite the fact that the risk of becoming obese is higher if the person had obese parents. The risk of becoming obese when one or two of the parents are overweight or obese had not been quantified until recently. This risk can be estimated using the lambda coefficient (λ_R), which can be defined as the ratio of the risk of being obese when a biological relative is obese compared with the risk in the population at large, i.e., the prevalence of obesity (Risch 1990). Such estimates of λ_R were recently reported based on BMI data from twin and family studies (Allison et al. 1996). The risk of obesity is about two to three times higher for an individual with a family history of obesity and it increases with the severity of obesity.

THE SINGLE-GENE HYPOTHESIS

It is commonly observed that obese persons are, on the average, about 10–12 BMI units heavier than their parents, brothers or sisters. For instance, in a survey of members of the National Association for Fat Acceptance, Reed et al. (1993) observed that the mean BMI value of the respondents was 47. Several of these probands had parents whose BMI was <25. The mean BMI of the brothers and sisters of the proband was consistently 10–12 BMI units less than the proband's BMI. Even when both parents were obese, the proband was much heavier. These and other observations have led to the suggestion that there was potentially an autosomal recessive gene influencing body mass.

Several complex segregation analysis studies performed in various populations have reported that a single major gene for high body mass was segregating from the parents to their offspring. However, three studies did not find support for Mendelian transmission unless age and/or gender variations in the major gene were taken into account. From this small body of data, the trend seems to be for a major recessive gene accounting for ~20–25% of the variance, but with age-associated effects, with a gene frequency of ~0.2–0.3. These results must be viewed with great caution, however, because they are based only on the unmeasured genotype approach and the gene(s) has(have) not yet been identified (Bouchard 1994).

OVERVIEW OF METHODS TO IDENTIFY OBESITY-RELATED GENES

The approach to the identification of the obesity genes is multifaceted. No single strategy can provide all the answers. We have to rely on a variety of complementary approaches to zero in on the genes and, subsequently, on the mutations with functional implications. For this, animal studies can be very informative. Fortunately, in the field of obesity, we have single-gene models—five in the mouse plus one in the rat. These genes have been mapped and the mutations identified. All have been cloned. They are proving to be helpful for human studies as well because there are similar genes encoded in the human genome that bear a high degree of homology with the rodent genes. This has stimulated a whole series of studies aimed at establishing whether the rodent mutations were actually present in human subjects and whether these genes played any role in the susceptibility to obesity. This approach has not been as productive as anticipated thus far. However, much remains to be done before these candidate rodent genes can be entirely ruled out.

Human studies are currently dominated by two types of strategies. The first is the candidate gene approach and is based on the current understanding of the physiopathology of obesity, most commonly pathways related to the regulation of energy balance or to adipose tissue biology. Genes specifying molecules such as receptors, hormones, transporters and other proteins that are key elements of the pathways become candidate genes. These genes are studied for the presence of mutations or some kind of polymorphisms that are then used in association and linkage studies to test whether they provide useful information. A major limitation of the strategy is our fragmented understanding of the physiopathology of obesity at present.

Beside these candidate gene models, there is also available a strong and powerful method commonly used to identify a quantitative trait locus (QTL). The approach is based on the crosses of informative inbred strains and it allows identification of areas of the genome in which genes affecting the phenotype, in this case body fat, reside. It does not yield, by itself, the identity of the gene, but it implicates a chromosomal region. A QTL can signal the beginning of the search for a gene influencing a complex multifactorial trait such as obesity. After such a genomic region has been identified, the QTL rodent linkage group, including markers in the 5' and the 3' areas on both sides of the putative gene, is defined, and a search for a human equivalent can be undertaken in the human genomic data base.

Briefly, the 23 pairs of chromosomes are covered with a set of markers, mostly repetitive sequences that vary in length, used in about the same way as you would use kilometer posts to locate your position on a highway. It takes ~400 polymorphic markers to cover the whole human genome at ~10-cM intervals. Linkage analysis is then undertaken between these markers and the phenotype of interest. If strong evidence for linkage is found within a region of a given chromosome, then it becomes useful to screen that region with a much denser map of markers. If the signal remains strong, the relevant human chromosomal region can be scrutinized with a variety of techniques. More refined positional cloning could be undertaken and DNA sequencing would then follow. In many ways, animal and human research methods are interactive and complementary. Thus far, at least 24 QTL have been reported for body mass or body fat (Chagnon and Bouchard 1996, Pérusse et al. 1997).

Results from linkage studies. First, let us make a simple distinction. In the past 3–5 y, we have made important advances in defining the molecular mechanisms that are involved in regulating energy balance. Where progress has occurred is in the identification of some molecules that are involved in adipose tissue biology and regulation of energy balance. Very little progress has been made on the genetic front where we have not yet found a mutation responsible for the susceptibility to obesity in some people. Although we have made great strides in the molecular biology domain, we are literally stagnant on the genetics of obesity. We have not been able to take advantage of the advances in the understanding of the regulation of energy balance to translate them into molecules and mutations

that could be responsible for human variation in the susceptibility to obesity (Bouchard 1996).

Here, we are interested in the role of the specific DNA sequence variations that are co-segregating with obesity phenotypes. A summary of the linkage data indicates that there are now several positive findings. Unfortunately, the vast majority of these positive results have not been confirmed in independent studies. The only genome-wide search that has been completed to date for obesity-related genes was undertaken in pairs of siblings from the Pima Indian community. Persuasive evidence for linkage was observed only with markers on chromosome 11 (11q21–q22) and suggestive evidence on chromosome 3 (3p24.2–p22) (Norman et al. 1997). The scan was accomplished with ~600 markers. Markers on 6p21 were also found to be linked to obesity phenotypes in Pima Indians. Indeed, in 304 pairs of siblings, a fairly strong linkage with a marker ~10 cM away from tumor necrosis factor-α was reported (Norman et al. 1995). In the Quebec Family Study, significant linkages were found with DIS200, a marker on chromosome 1p32, and body fat (Chagnon et al. 1997).

There are now at least four linkage studies suggesting that the OB gene or a gene nearby on 7q31.3 might be involved in human obesity. Several hundred human *LEP* genes have been sequenced, and the OB mutation appears to be extremely infrequent in humans if it exists at all. However, linkage studies suggest that, in the vicinity of *LEP*, there are markers that are linked to obesity. The first of these studies is our Quebec Family Study in which ~400 pairs of siblings were typed for blood groups and red blood cell enzymes at entry into the study ~20 y ago. A strong linkage was found with the KELL blood group (Borecki et al. 1994). The KELL blood group is about 10–15 cM away from *LEP*. The strongest linkages were with BMI and the sum of six skinfolds. Over the last several months, three more studies have been reported on this topic.

A group in Paris typed eight microsatellites in pairs of siblings and found evidence of linkage, but only when the siblings had a BMI of at least 35. In these cases, three markers gave significant linkages. They also found linkage disequilibrium between some of the alleles when the BMI was $\geq$35. When the BMI was <35, the evidence was negative (Clément et al. 1996). Another study came from the Pennsylvania group, which used 78 families and 8 markers on 7q. They found evidence for linkage with some of the markers only when the BMI was $\geq$40. They also looked at linkage disequilibrium among alleles; the BMI became significant only when that of the siblings reached 40 or more (Reed et al. 1996). Both of these studies are based on small sample sizes, but they both provide suggestive evidence of linkage.

Finally, the last paper is based on data from the San Antonio Family Diabetes Study. They relied on 545 pairs of siblings. They used the LOD score approach with several body fat phenotypes. Their strongest evidence for linkage was with an area close to the *LEP* gene but it was with the sum of five limb skinfolds, and not with the percentage of body fat or the BMI. Their maximum LOD score of 3.1 was with a marker about 10^6 bp from *LEP*. In other words, the linkage is probably not with *LEP* but it could be with a gene that is co-expressed with *LEP*, or interacting with *LEP*, or influences the expression of *LEP* (Duggirala et al. 1996).

We therefore have evidence that becomes progressively more persuasive to the effect that several regions of the human genome might be involved in the susceptibility to obesity. At this time, the most important human chromosomal regions exhibiting linkage seem to be on 1p, 3p, 6p, 7q, and 11q. These results from human studies plus the evidence accumulated in the QTL studies strongly suggest that a good number of genes have the potential to influence energy balance and fat storage. There are probably other areas, but these genomic regions are among the most interesting to investigate at this time.

CONCLUSIONS

On the basis of these data, and others that cannot be reviewed here, we have recently revised the human obesity gene map as of October 1996 (Pérusse et al. 1997). The human obesity gene map incorporates the loci from single-gene mutation rodent models of obesity, all QTL from crossbreeding experiments, all relevant Mendelian disorders that have been mapped to a chromosomal region, and genes or markers that have been shown to be associated or linked with an obesity phenotype (Pérusse et al. 1997). Only 4 of the 24 chromosomes are not represented on the obesity map at this time: chromosomes 9, 18, 21 and Y.

Several chromosomal areas are characterized by the presence of several positive findings. The chromosome arms with at least three entries in the map are the following: 1p, 1q, 3p, 4q, 6p, 7q, 8p, 8q, 11p, 11q, 15q, 20q and Xq. We expect that the number of genes and other markers associated or linked with human obesity phenotypes will increase dramatically in the coming years. The main task will remain that of identifying the genes and mutations that are contributing in a major way and under what circumstances.

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LITERATURE CITED

Allison, D. B., Faith, M. S. & Nathan, J. S. (1996) Risch's lambda values for human obesity. Int. J. Obes. 20: 990–999.

Borecki, I. B., Rice, T., Pérusse, L., Bouchard, C. & Rao, D. C. (1994) An exploratory investigation of genetic linkage with body composition and fatness phenotypes: the Québec Family Study. Obes. Res. 2: 213–219.

Bouchard, C. (1994) Genetics of obesity: overview and research directions. In: The Genetics of Obesity (Bouchard, C., ed.), pp. 223–233. CRC Press, Boca Raton, FL.

Bouchard, C. (1996) The causes of obesity: advances in molecular biology but stagnation on the genetic front. Diabetologia 39: 1532–1533.

Bouchard, C., Pérusse, L., Leblanc, C., Tremblay, A. & Thériault, G. (1988) Inheritance of the amount and distribution of human body fat. Int. J. Obes. 12: 205–215.

Chagnon, Y. C. & Bouchard, C. (1996) Genetics of obesity: advances from rodent studies. Trends Genet. 12: 441–444.

Chagnon, Y. C., Pérusse, L., Lamothe, M., Chagnon, M., Nadeau, A., Dionne, F. T., Gagnon, J., Chung, W. K., Leibel, R. L. & Bouchard, C. (1997) Suggestive linkages between markers on human 1p32–p22 and body fat and insulin levels in the Quebec Family Study. Obes. Res. 5: 115–121.

Clément, K., Garner, C., Hager, J., Philippi, A., LeDuc, C., Carey, A., Harris, T. J., Jury, C., Cardon, L. R., Basdevant, A., Demenais, F., Guy-Grand, B., North, M. & Froguel, P. (1996) Indication for linkage of the human OB gene region with extreme obesity. Diabetes 45: 687–690.

Duggirala, R., Stern, M. P., Mitchell, B. D., Reinhart, L. J., Shipman, P. A., Uresandi, O. C., Chung, W. K., Leibel, R. L., Hales, C. N., O'Connell, P. & Blangero, J. (1996) Quantitative variation in obesity-related traits and insulin precursors linked to the OB gene region on human chromosome 7. Am. J. Human Genet. 59: 694–703.

Norman, R. A., Bogardus, C. & Ravussin, E. (1995) Linkage between obesity and a marker near the tumor necrosis factor-α locus in Pima Indians. J. Clin. Invest. 96: 158–162.

Norman, R. A., Thompson, D. B., Foroud, T., Garvey, W. T., Bennett, P. H., Bogardus, C., Ravussin, E. and other members of the Pima Diabetes Gene group. (1997) Genomewide search for genes influencing percent body fat in Pima Indians: suggestive linkage at chromosome 11q21–q22. Am. J. Human Genet. 60: 166–173.

Pérusse, L., Chagnon, Y. C., Dionne, F. T. & Bouchard, C. (1997) The human obesity gene map: the 1996 update. Obes. Res. 5: 49–61.
Reed, D. R., Bradley, E. C. & Price, R. A. (1993) Obesity in families of extremely obese women. Obes. Res. 1: 167–172.
Reed, D., Ding, Y., Xu, W., Cather, C., Green, E. D. & Price, R. A. (1996) Extreme obesity may be linked to markers flanking the human OB gene. Diabetes 45: 691–694.
Risch, N. (1990) Linkage strategies for genetically complex traits. I. Multilocus models. Am. J. Human Genet. 46: 222–228.
Stunkard, A. J., Sorensen, T.I.A., Hannis, C., Teasdale, T. W., Chakraborty, R., Schull, W. J. & Schulsinger, F. (1986) An adoption study of human obesity. N. Engl. J. Med. 314: 193–198.
Tambs, K., Moum, T., Eaves, L., Neale, M., Midthjell, K., Lund-Larsen, P. G., Naess, S. & Holmen, J. (1991) Genetic and environmental contributions to the variance of the body mass index in a Norwegian sample of first- and second-degree relatives. Am. J. Human Biol. 3: 257–267.
Vogler, G. P., Sorensen, T. I., Stunkard, A. J., Srinivasan, M. R. & Rao, D. C. (1995) Influences of genes and shared family environment on adult body mass index assessed in an adoption study by a comprehensive path model. Int. J. Obes. 19: 40–45.