Molecular Genetic Studies of Porcine Genes for Obesity

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Summary

The similarities between humans and pigs at the physiological and genomic levels can provide advantages for the use of the pig as a genetic model for human obesity. Several approaches have been used to identify chromosomal regions or genes affecting obesity-related phenotypes in pigs. Current approaches include the use of candidate genes, quantitative trait loci (QTL) scanning, and gene transcript profiling. Many pig populations have been generated from crosses between breeds with different genetic backgrounds, and QTL analyses in these populations have identified several major pig chromosomal regions that influence obesity-related phenotypes. Homologous human chromosomal regions might be potentially important for genetic causes of human obesity. A single nucleotide polymorphism (SNP) causing an amino acid substitution in the porcine *melanocortin-4 receptor* (*MC4R*) gene was significantly associated with increased levels of backfat and similar *MC4R* mutations resulted in several cases of human obesity. In addition, we have identified several polymorphisms (SNPs) in other candidate genes that are associated with obesity phenotypes. Further analyses of these SNPs will be useful for dissecting the genetics of human obesity. Other published research has included the use of human microarrays to study gene expression in various tissues at different growth stages between young pigs with extremes in fat content. Many of these genes may play a significant role in obesity. New research to integrate these QTL studies, candidate gene discovery, and transcript profiling in pigs can provide novel insights into the genetic components of human obesity and their molecular and physiological mechanisms.

Introduction

The physiological system governing energy storage in the form of fat might be the most fundamentally adaptive systems in humans and other animal species. These systems are now the target of extensive biomedical research to solve causes of human obesity. Experimental animals, mainly mice and rats, have been used for a number of obesity studies designed to identify genetic factors that regulate energy balance. Surgical, chemical, and dietary approaches have successfully revealed some physiological mechanisms leading to obesity. In addition, heritable forms of obesity in animals have been used as model organisms to identify genetic factors that may control human obesity.

We have used the pig as a model to identify obesity-related genes for two reasons. First, the genetic components of human obesity may play important roles in regulation of pig performance traits such as fatness, growth rate, and feed intake. Because pork is a principal source of protein and pork production is an important business in agriculture on a worldwide basis, this research can provide valuable information for economically efficient lean pig production. More precisely, mapping of obesity-related genes on porcine chromosomes can be useful to breeding programs for marker-assisted selection (MAS) of those performance traits. Second, numerous physiological similarities between pigs and humans suggest that the pig may be a more realistic model of human obesity (3, 7, 13, 15) than other animal models such as rodent species. Furthermore, evolutionarily the pig genome is more closely related to the human genome than small laboratory animal species. Thus, identified significant DNA polymorphisms of obesity-related genes in the pig genome might provide useful targets for the genetic study of human obesity.

Candidate Gene Studies in Pigs

The number of genes or gene products that are known to control appetite or body weight is up to 130 and still increasing. Fifty eight candidate genes were found to be significantly associated with obesity-related phenotypes in humans (14) and more than 10 of these have been studied in the pig in our laboratory.

One of the most significant discoveries was a polymorphism identified in the porcine *MC4R* gene (8). This polymorphism revealed a missense mutation that replaces aspartic acid with asparagine at the amino acid position 298 of the MC4R protein. Interestingly, Asp298 is a highly conserved amino acid within other MCR subtypes and in other species. This *MC4R* type was significantly associated with less backfat thickness, slower growth rate, and lower feed intake. In contrast, the Asn298 mutant was associated with increased backfat, higher feed intake, and faster growing pigs from several commercial populations. The strong association between the *MC4R* variants with fatness, growth rate, body weight, and feed intake probably result from the fact that the variant amino acid residues of the *MC4R* mutation cause a significant change of the MC4R function, and this hypothesis is under investigation.

Because similar MC4R mutations have been found in humans with morbid obesity (14), the pig *MC4R* mutation will be useful for studying the physiological relationship between melanocortin signaling and human obesity. New mutations from other porcine candidate genes are also under investigation and results from them may be useful to determine naturally occurring gene mutations that may be ultimately responsible for some of human obesity.

Quantitative Trait Loci (QTL) Scanning in Pigs

A significant number of QTL have been identified in the pig in recent years. Bidanel and Rothschild (2002) reviewed all significant QTL studies performed with pigs. The first major QTL (named as *FAT1*) for fatness and growth was identified on chromosome 4 by using a Wild Boar intercross (1). This *FAT1* region on chromosome 4 in the pig is homologous to parts of human chromosome 1 and 8. The latest comparative mapping results between humans and pigs indicate that the QTL is located in a region homologous to HSA1q (2).

Bidanel et al. (2001) also conducted a QTL experiment with a Meishan x Large White F2 population and found several loci affecting important economic traits, such as growth rate and backfat thickness on chromosome 4 and 7. Wang et al. (1998) directly searched for QTL on chromosomes 4 and 7 for performance traits in five Chinese x American breed cross families and identified QTL for average daily gain on chromosome 4 and QTL for backfat thickness on chromosome 7.

A recent QTL study conducted in our laboratory at Iowa State University also identified a significant QTL for growth and fat content traits on the same region of pig chromosome 7 (10). Further investigation using biological and positional candidate genes in that region revealed that polymorphisms in a candidate gene, *high mobility group A1*(*HMGA1*) were consistently associated with observed variation in the F2 pigs of the QTL population and other genetically diverse commercial populations (9). The results suggest that the *HMGA1* gene is a strong candidate for the QTL reported in pig chromosome 7. As the corresponding human and mouse chromosomal region is also known to be associated with obesity (14), the *HMGA1* gene might be potentially important for human obesity and other model organisms. This result demonstrates that targeted comparative chromosomal studies that include pig genome may provide valuable information on the genetic control of human obesity.

Transcriptional Profiling in Pigs

Monitoring gene expression will be useful in elucidating molecular mechanisms in cells or tissues, and cDNA microarray can be a valuable tool for monitoring global gene expression differences in normal and obese individuals and in response to various environmental stimuli. Mathialagan et al. (2002) investigated pig gene expression patterns using human microarrays. In pigs with high and low lean growth rates, phenotypic data and serum samples were collected at four different time points from weaning until slaughter, and seven tissues contributing to the regulation of metabolism and growth were collected for transcriptional profiling. Pooled RNA from each tissue from high lean and low lean groups were analyzed on human microarrays. These microarrays identified 394 genes that may be differentially expressed. The genomic location of these differentially expressed genes is being determined and the results will be useful for further identification of the candidate genes for studying the mechanism of growth and fat deposition in pigs as well as humans.

Conclusions

At present, relatively limited genomic information and resources are available in pigs as compared with that of mice for being a model organism for complex genetic traits such as obesity. However, several studies have demonstrated that the pig genome for genetic control of growth and fat deposition traits is valuable for its economic importance in the pork industry and potential application to human obesity (8; 6, 12). Comparative genome information between humans and pigs is well established; comparative map-based genetic study is possible for identifying responsible genes in the targeted QTL regions between humans and pigs
http://www.toulouse.inra.fr/lgc/pig/compare/compare.htm

The most difficult challenge remaining is the development of a dynamic system that can integrate the various research components such as genetic, genomic, and physiological experiments for human medicine. The pig can be a useful model to link these various research components for the development of an extensive information system.

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