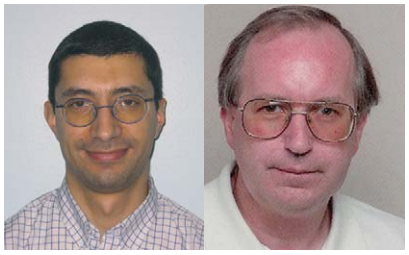
editorial



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Commercial pigs: an untapped resource for human obesity research?

According to the World Health Organization, ~8% of the adult world population (~300 million people) are clinically obese [as defined by a body mass index (BMI) of ≥30 kg/m^2] and two to three times as many could be considered overweight. Because its prevalence is rising worldwide, obesity is seen as a global pandemic, and is reaching epidemic proportions in the industrialized world and in some developing countries [1]. In the USA alone, 65% of adults are considered overweight (BMI 25.0–29.9) and almost 1 in 3 adults can currently be defined as clinically obese [2]. The same problem is also affecting children.

The factors causing excessive weight gain are largely unknown. Although it is clear that environmental, behavioural and sociocultural factors have a significant role in the development of obesity, epidemiological studies over the past two decades have clearly demonstrated a genetic component, and it is estimated that 30–70% of the variation in body weight and adiposity might be attributable to genetic factors. Recent efforts in obesity research have thus focused on identifying of genes involved in the regulation of levels of body fat [3]. There are two possible approaches for identifying genes for susceptibility to obesity-related phenotypes. The first, linkage analysis, consists of genome-wide scans of large collections of samples (from populations exhibiting obesity) aimed at detecting chromosomal regions showing linkage with obesity. The second approach is the candidate gene approach, which involves testing the association between obesity and a specific allele of a gene that appears to be a good candidate (e.g. a gene involved in the regulation of food intake), either in a family study or in large cohorts of unrelated controls and patients. To date, >600 genes, markers and chromosomal regions have been associated with human obesity [4]. However, only a relatively small number of genes, such as leptin, causing Mendelian (monogenic) forms of human obesity have been identified. Although these genes have provided insights into pathways involved in obesity, they are loss-of-function polymorphisms that are relatively rare and have little relationship with common obesity. Consequently, the genes affecting common (polygenic) human obesity remain unknown.

In addition to genetic studies in humans, experimental animals, mainly mice and rats, have been used to identify the genetic factors of polygenic obesity. In this editorial, we would like to argue the case for the use of use of commercial pigs specifically bred and raised for meat production, as a model organism to help dissect the genetics of obesity.

The similarities between humans and pigs at the physiological and genomic level are an advantage for the use of pigs as genetic models for human obesity. Pigs are similar to humans in size, digestive physiology, dietary habits and fat deposition. Furthermore, the pig genome is more closely related to the human genome than rodent species. Taken together, these similarities make the pig a good model for human obesity. In addition, pigs bred for meat production are available, together with data on obesity-related traits, in sufficiently large numbers

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2006.04.009

to provide the statistical power required for genetic studies of obesity.

During its domestication, the pig has undergone strong selection for meat and/or fat production, which has led to marked phenotypic changes and genetic adaptation to various environmental conditions. These can still be observed between breeds of pigs, as exemplified by the differences between European and Chinese breeds in terms of body size and adiposity. Pig populations used in present-day breeding programmes consists of different closed lines that are selected for characteristics of economic importance to the pig industry (e.g. costs associated with feeding) or the consumer (e.g. preference for lean meat) and which are also relevant for obesity [5]. To make improvement through selection, pig breeders must measure these traits accurately on large numbers of animals. Despite selection, current pig populations have many naturally occurring alleles that effect obesity-related traits like adiposity. Therefore, current developments in the farming of fast-growing lean pig lines have created new resources for the study of human obesity [6].

Numerous linkage and candidate-gene studies in humans have tried to identify obesity genes. Few studies have had a large enough sample size to yield sufficient statistical power to detect common genes with small effects. In addition, human studies are confounded by genetic heterogeneity. People can have the same phenotype (i.e. obesity) for different underlying reasons, so evidence for linkage of obesity to a specific chromosomal region or gene in some families is not supported in other families (where a different region or gene is involved). The power of a study can be improved by increasing the number of subjects, refining the phenotype or by increasing the number of phenotypes available, but this is very expensive and time-consuming. By contrast, pigs allow considerably more latitude in obesity-gene discovery and characterization. Studies with pig lines being bred for pork offer the advantages of less genetic heterogeneity (owing to the limited effective population size compared with large outbred human populations) and the absence of confounding factors typical of humans (e.g. smoking or alcohol consumption). Pigs can even be bred to produce models where the role of a specific gene can be tested, for example, leptin, leptin receptor and melanocortin receptor-4 (*MC4R*). Pigs have large litters and a short generation time, and their environment and feeding regime can be manipulated, which makes it possible to compare, for example, the response to different dietary stimuli (nutrients or drugs) in pigs with high and low lean-growth rates.

Furthermore, pigs offer potential for refining the phenotype being studied. For instance, BMI has been widely used for human obesity research but it cannot distinguish fat mass from lean mass and thus might not measure true adiposity. Body-fat mass and percentage fat mass are more appropriate as phenotypes for human obesity research but cannot be measured easily and inexpensively. By contrast, in commercial pig-breeding farms, growth-related traits and body-fat distribution are routinely measured, and some of these traits, such as percentage fat mass, could be used in obesity research as an exact phenotypic measurement of fat distribution and composition, rather than indirect measures such as BMI.

To date, the identification of pig genes involved in obesity and component traits, such as growth and body-fat distribution, has relied on information from human or rodent models rather than from the approach proposed here. For example, a single nucleotide polymorphism (SNP) causing an amino acid substitution in the seventh transmembrane domain of the porcine *MC4R* gene, a G-protein-coupled receptor gene involved in human and mouse obesity, is significantly associated with fatness, growth and feed intake [7]. This result shows that such obesity-related genes do explain variation in modern pig breeds and that they can be effectively identified. It was obtained after analyzing growth and performance records and *MC4R* genotypes of >1800 animals from five different lines of pigs. The more technically advanced pig breeders have accumulated millions of phenotypic records and tens of thousands of DNA samples. This vast amount of data are being used to discover genetic markers associated with variation in economically important traits, such as lean growth rate, that can be included in genetic improvement programmes (marker-assisted selection). We suggest that these resources can also be used to identify new genes that are involved in obesity.

Several large genomics projects have already been initiated in the pig and its genome will be sequenced in the coming months. Moreover, significant resources are available for genome analysis, for example, more than 5500 pig SNPs have been identified and deposited in the public domain [8]. The analysis of a subset of these SNPs in commercial pig populations showed a high percentage of polymorphic markers, which demonstrates their utility for the identification of loci responsible for economically important traits [9]. Some commercial pig breeding companies, such as PIC, also have private collections of SNPs. Because it is possible to assemble large numbers of animals with defined genetic and environmental backgrounds, and because of the relatively large extent of linkage disequilibrium [10], some whole-genome SNP association studies are already underway in the pig. This is the situation that underlies our proposal that the pig represents an untapped resource for human obesity research.

Since domestication, human and pig lives have been intertwined. In recent years, based on information from the human genome, scientists have identified genes involved in pig growth and fatness. With the current developments in pig genomics, we believe that now it is time to add commercial pigs and the plethora of associated data to the weaponry used to identify appropriate drug targets to fight human obesity.

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