SYSTEMS GENETICS OF OBESITY AND RELATED METABOLIC TRAITS IN PIG MODEL TO IMPROVE HUMAN HEALTH ("SYSGEN OF OBESITY")

Human obesity, metabolic syndrome and diabetes (OMSD) is reaching epidemic proportions in developed countries. Unraveling the genetics and systems biology of this syndrome promises new interventions including drug therapies to treat obese individuals and those predisposed to overeating.

The SYSGEN OF OBESITY (Systems genetics of obesity and related metabolic traits in pig model to improve human health) project (http://www.qsg.dk/ and www.biochild.ku.dk) has worked on specially bred pigs to investigate the genomics and systems biology of obesity and related diseases. Three generations of crossing Göttingen minipigs genetically predisposed to obesity with production pigs that are bred to be lean produced around 600 animals for the study.

The researchers collected data on 50 different OMSD phenotypes or traits (such as body mass index, abdominal obesity, internal and external fatmass using DXA scan, glucose and cholesterol) on around 600 pigs at the University of Copenhagen's research farm in Denmark. Each one of these pigs was genetically characterized by using genome-wide DNA arrays that score each pig at over 60000 locations on their DNA (single nucleotide polymorphism or SNP genetic markers). A biobank has stored over 24 different types of tissue samples from pigs and blood for RNA and DNA extraction from all animals.

Researchers first applied advanced (systems) genetics and integrative biology methods to associate pigs 60000 DNA or genetic markers with OMSD phenotypes to map the genetic factors on the pig genome and catalog gene expression profiles of over 22000 genes in fat tissues of obese and lean pigs. Afterwards, they did translation of their findings from pigs to human using translational or comparative genomics. Results show substantial genetic variation in obesity. Heritability of OMSD syndrome is in the range of 0.22 to 0.81 which means that it runs in families and parents will pass on their genes causing this syndrome to their progeny (sons and daughters) who will then pass on their genes to their own descendants and so on. Therefore care must be taken to offset the actions of genes for instance by life style interventions (exercise and diets). Through family-based and population-based quantitative genetic analyses, researchers identified 229 QTLs (Quantitative Trait Loci or genomic regions) which associated with adiposity- and metabolic phenotypes at genome-wide significant levels. Some of these regions have been scrutinized. Several candidate genes in 18 of these regions influence body mass index and fatness traits. Researchers compared pig genes / QTLs for some traits with those of humans and indicated genes that potentially can cause this syndrome in humans. Furthermore, using next generation sequencing (NGS) methods, they sequenced pig's RNA and identified differentially expressed and co-expressed genes in fat tissues representing lean and obese individuals. This led to identification of genes and pathways of importance to the development of obesity and other syndrome. Researchers have identified many genes whose expression levels in fat tissue or blood could be used as biomarkers to predict obesity. Researchers also integrated these gene expression (transcriptomic) data of over 22000 genes with 60000 DNA marker or genomic data to find

real culprit or causal genes and investigated the mechanisms involved in obesity and related metabolic disorders using integrated systems genetics approach.

So far, 10 peer-reviewed international journals have featured research results on heritabilities and genetic correlations for all obesity related traits, genomic regions harboring potential genes causing obesity and related metabolic diseases in pigs and humans, genetic and gene-gene interaction networks, genome-wide gene expression differences or similarities of obese and lean individuals and transcriptional regulation of this syndrome or disease.

In a parallel study researchers also found out that there are real genetic differences in pigs that eat normal versus pigs that overeat; overeating pigs have implications for fatness and developing OMSD. Researchers found that eating behavior is heritable 0.17 to 0.25 (meaning this behavior also runs in families) and there are key genes that may cause this binge eating or over-eating condition in humans (shown via comparative genomics methods).

Extending these results could identify genes and highly predictive biomarkers for humans with OMSD by comparing pig-human systems biology and genomics. Combination with metabolic pathway profiling may reveal complex mechanisms that give rise to individual differences in development of OMSD.

A personalized approach to medicine and or nutrition could help combat this fast-growing global epidemic. This project's research on human overeating was published in PLoS One in 2013 and was then covered by major newspapers around the world. The original article is: http://news.ku.dk/all_news/2013/2013.10/why-humans-pig-out/ (Why Do Humans Pig Out). The projects key findings on genes causing obesity was published in 2014 (BMC Medical Genomics: http://www.biomedcentral.com/1755-8794/7/57) and in 2015 (PLoS One: http://journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0137356 and Genome Medicine: http://www.genomemedicine.com/content/7/1/105).

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