



Systems genetics analysis of obesity using RNA-Seq and genomic data in an F2 pig model for obesity

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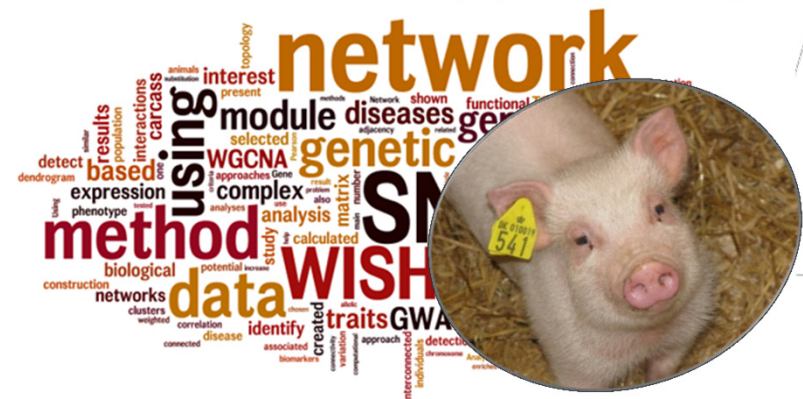
Presented by

Haja Kadarmideen

Animal Breeding, Quantitative Genetics and Systems Biology (AQS) group
HEALTH, University of Copenhagen, Denmark

<http://www.qsg.dk>

EAAP August 2014



Why obesity?

Obesity: excess of body fat

Associated with several diseases:

- Type 2 diabetes
- Heart diseases
- Several types of cancer

Huge welfare and economical consequences!

Interaction between **genetic** and **environmental** factors

Estimated genetic contribution to obesity (BMI): **40-70%**

To date, GWAS has been able to explain 1.45%
of the genetic variation



Last updated on October 7, 2013 at 6:13 EDT

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Pig Study Suggests Humans Are Predisposed To Overeating
October 3, 2013

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Pig as a model for human obesity

Similar metabolic features and disease progression

- Protein and lipid metabolism comparable with human
- Similar cardiovascular system
- Proportionally similar organ sizes

Genetically very close to humans:

- 2.8 billion basepairs vs 3.3 billion in human
- 21.640 protein coding genes vs 23.438 in human



Researchers find a gene for obesity

Long-term research involving pigs could mean people can find out if they are genetically susceptible to overeating

BY DAN NOSOWITZ

Rekommendationer: 8 28 1 0

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TOPICS: US, OBESITY, OVEREATING, HEALTHCARE, GENETICS, TECHNOLOGY NEWS, NEWS



Researchers at the University of Copenhagen set out on what seemed like a simple task: to find out if overeating is linked to any genetic difference. Four years and 1,200 (yeah, we'll get to that), they have an answer.



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Why some of us 'eat like pigs'

Ads by Google

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Vi tapper til dejlig æblemost. Til glæde for hele familien.

oestergaard-frugtplanlage.dk

Indian-born Australian researcher is studying pigs to find out why humans indulge in excessive eating

October 04, 2013

WASHINGTON

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The newly study - led by professor Haja Kadarmideen, a professor and research group leader from the Faculty of Health and Medical Sciences at University of Copenhagen - is the first in the world looking at pig to human comparative genetic mapping to reveal key genes on the human genome that are known to be involved in obesity.



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Pigging out on fast food can be all in the genes



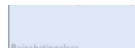
PLOS ONE

ed dramatically Facundo Arrizabalaga / EPA

THE AUSTRALIAN

Genome-Wide Association Study Reveals Genetic Architecture of Eating Behavior in Pigs and Its Implications for Humans Obesity by Comparative Mapping

Duy Ngoc Do¹, Anders Bjerring Strathe^{1,2}, Tage Ostersen², Just Jensen³, Thomas Mark¹, Haja N. Kadarmideen^{1*}



Researchers Find A Gene For Obesity

Just what we always wanted: a empirical reason why we binge-eat that isn't our fault.

By Dan Nosowitz Posted 10.03.2013 at 12:54 pm



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Pig Study Suggests Humans Are Predisposed To

October 3, 2013

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Pigging out can be all in the genes, study finds

HANNAH DEVLIN THE TIMES OCTOBER 04, 2013 10:10AM

A STUDY of more than 1000 pigs has revealed gene variants likely to be linked to overeating and obesity in human.



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Soon, blood test to help win 'battle of the bulge'

Submitted by Mohit Joshi on Sat, 10/05/2013 - 06:35 Health News London United Kingdom

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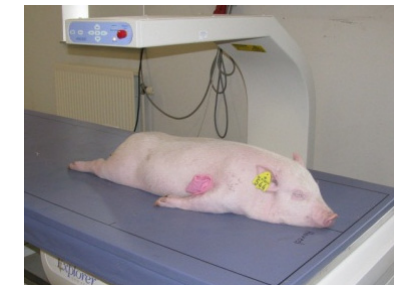
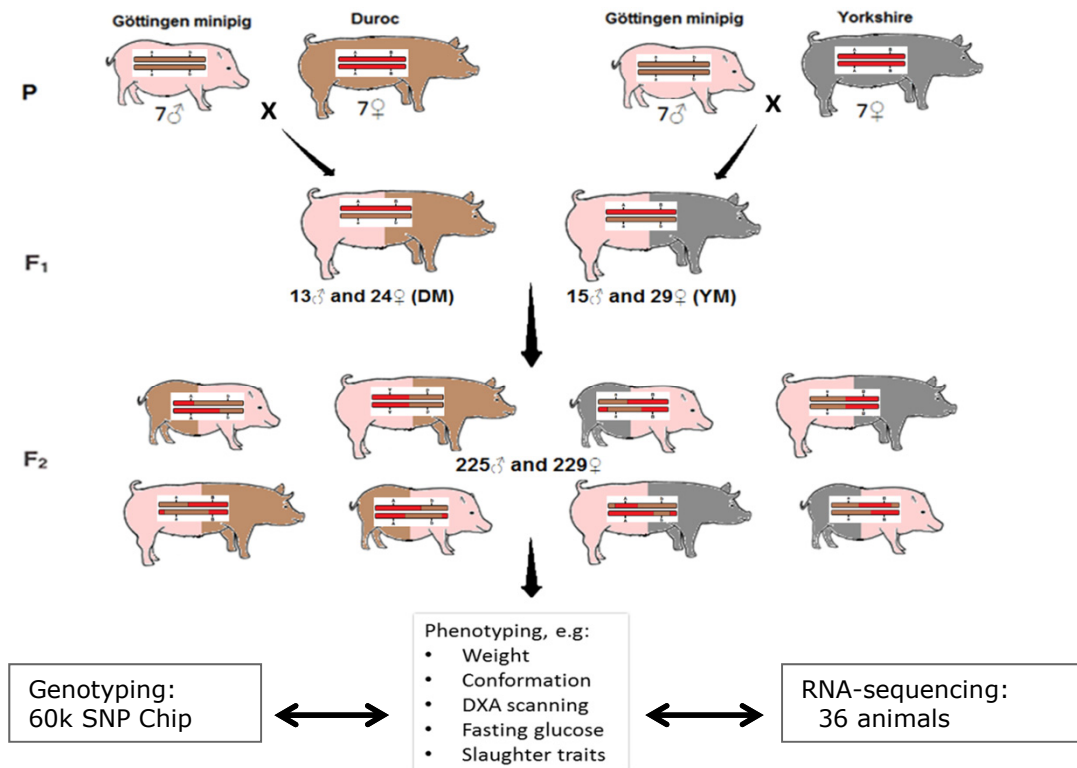
London, Oct 5 - A simple blood test could help beat obesity as researchers have found what makes us gorge on junk food.



An F2 pig resource population as a model for genetic studies of obesity and obesity-related diseases in humans: design and genetic parameters

Lisette J. A. Kogelman, Haja N. Kadarmideen, Thomas Mark, Peter Karlskov-Mortensen, Camilla S. Bruun, Susanna Cirera, Mette J. Jacobsen, Claus B. Jørgensen and Merete Fredholm*

Department of Veterinary Clinical and Animal Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark



Obesity Index

Obesity Index: based on selection index theory



$$\begin{aligned}
 \text{OI} = & b_{\text{WT7m}} * X_{\text{WT7m}} + b_{\text{ABD7m}} * X_{\text{ABD7m}} + b_{\text{ADG}} * X_{\text{ADG}} \\
 & + b_{\text{DXAfat}} * X_{\text{DXAfat}} + b_{\text{DXA\%fat}} * X_{\text{DXA\%fat}} + b_{\text{BF1}} * X_{\text{BF1}} \\
 & + b_{\text{BF2}} * X_{\text{BF2}} + b_{\text{SLfat}} * X_{\text{SLfat}} + b_{\text{SLfat_om}} * X_{\text{SLfat_om}}
 \end{aligned}$$



RNA Sequencing

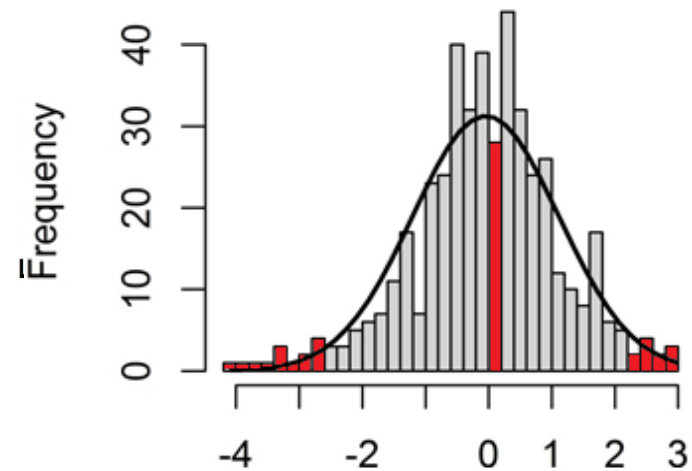
Animal selection:

Obesity Index (selection index theory)

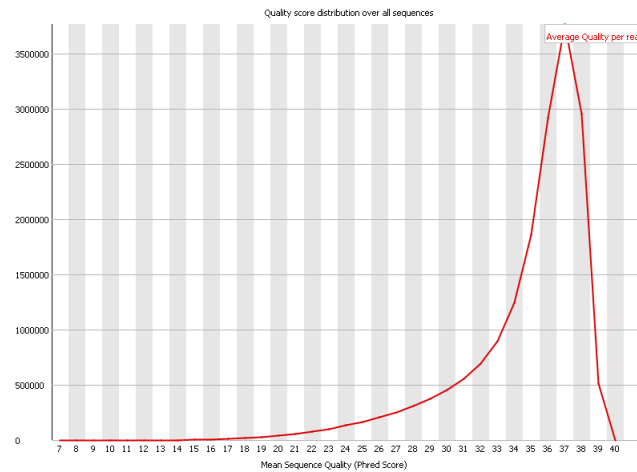
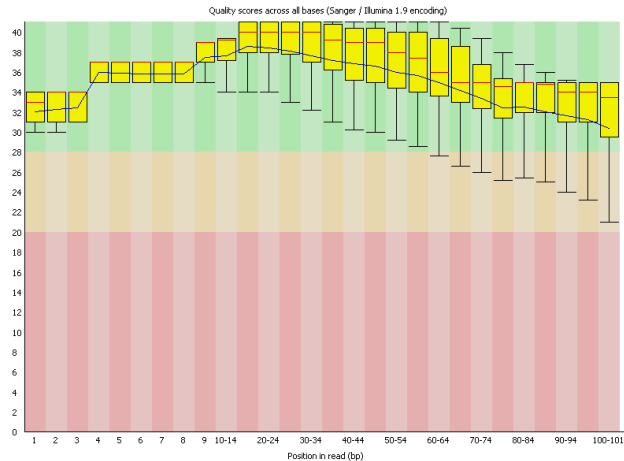
36 animals: 12 lean, 12 intermediate, 12 obese

RNA-Sequencing:

- Subcutaneous adipose tissue
- Illumina HiSeq2500
- ~30 million reads per sample
- Alignment: STAR
- Count reads: HTSeq
- Normalization and corrected for sex



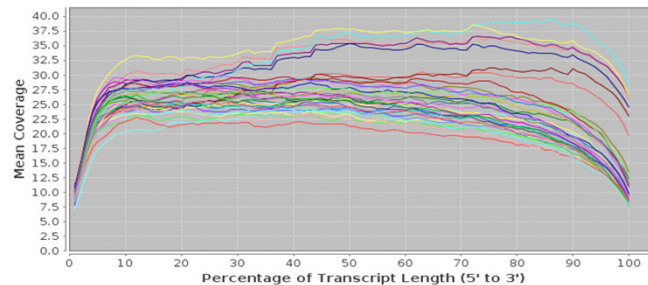
RNA-Seq Quality Control



a. Transcript-associated reads

| Sample | Note | Intragenic Rate | Exonic Rate | Intronic Rate | Intergenic Rate | Expression Profiling Efficiency | Transcripts Detected | Genes Detected |
|--------|------|-----------------|-------------|---------------|-----------------|---------------------------------|----------------------|----------------|
| A | | 0.822 | 0.677 | 0.145 | 0.177 | 0.677 | 20,011 | 11,632 |
| B | | 0.820 | 0.676 | 0.144 | 0.179 | 0.676 | 20,248 | 11,744 |
| C | | 0.828 | 0.702 | 0.126 | 0.171 | 0.702 | 20,760 | 12,101 |
| D | | 0.818 | 0.683 | 0.135 | 0.181 | 0.683 | 20,276 | 11,826 |
| E | | 0.812 | 0.651 | 0.161 | 0.187 | 0.651 | 19,833 | 11,523 |
| F | | 0.824 | 0.682 | 0.142 | 0.175 | 0.682 | 19,937 | 11,610 |
| G | | 0.824 | 0.687 | 0.137 | 0.174 | 0.687 | 20,466 | 11,916 |

b. Coverage for medium expressed transcripts



c. Transcript details for one sample

| Rank | Transcript ID | Length | Total Cov. | Mean Cov. | Std Dev |
|------|---------------|--------|------------|-----------|----------|
| 1 | ENSSSCT000 | 784 | 71408051 | 91081.70 | 60566.13 |
| 2 | ENSSSCT000 | 681 | 51272218 | 75289.59 | 39019.04 |
| 3 | ENSSSCT000 | 688 | 45588421 | 66262.24 | 35953.07 |
| 4 | ENSSSCT000 | 204 | 18809646 | 92204.15 | 31122.86 |
| 5 | ENSSSCT000 | 1140 | 48640816 | 42667.38 | 35537.76 |



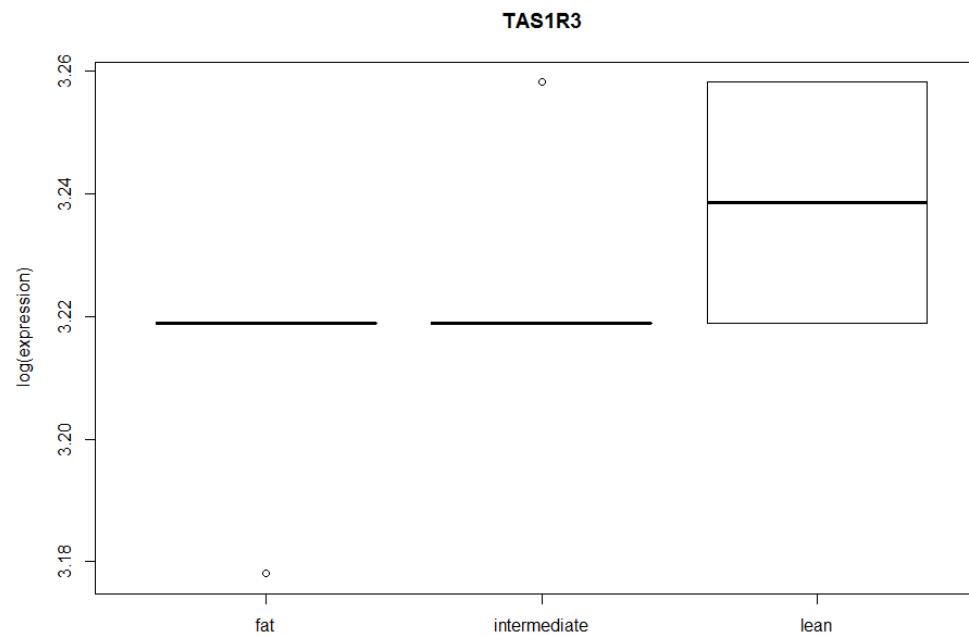
Differential expression Analysis on RNAseq data

Linear model in Limma:

$$OI = \text{sex} + \text{expression} + e$$

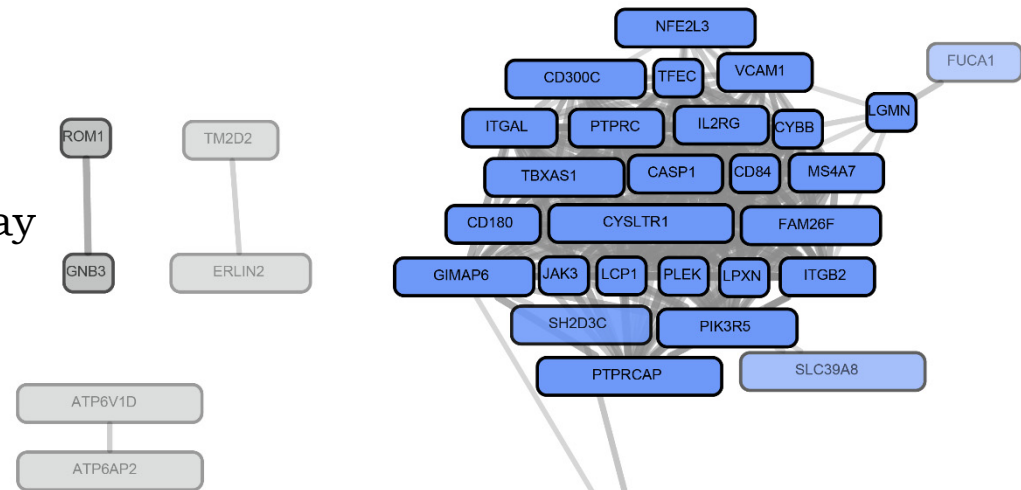
458 Differentially expressed genes

Top DE gene:

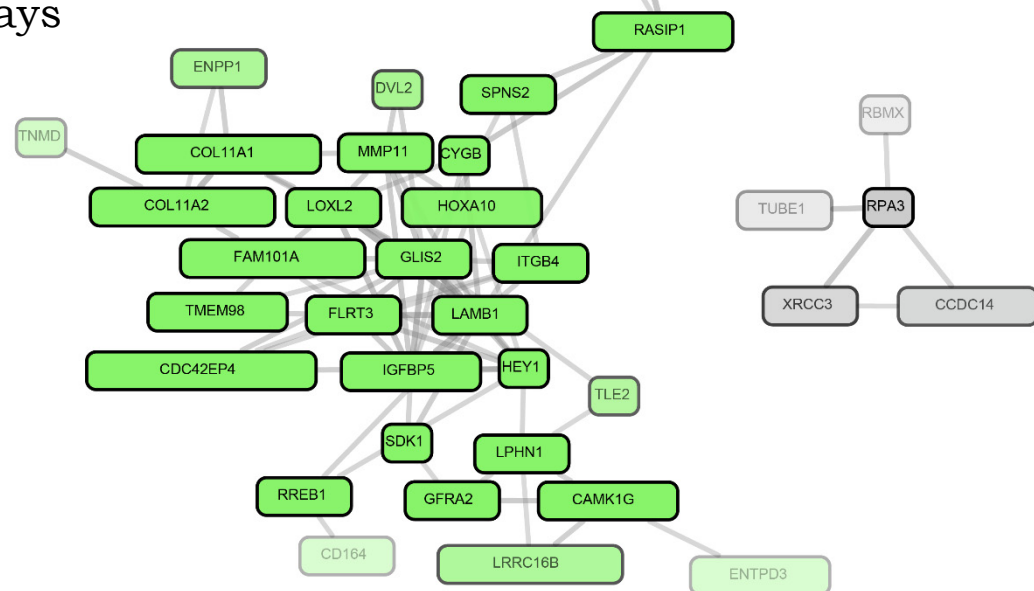


Functional annotation of DE

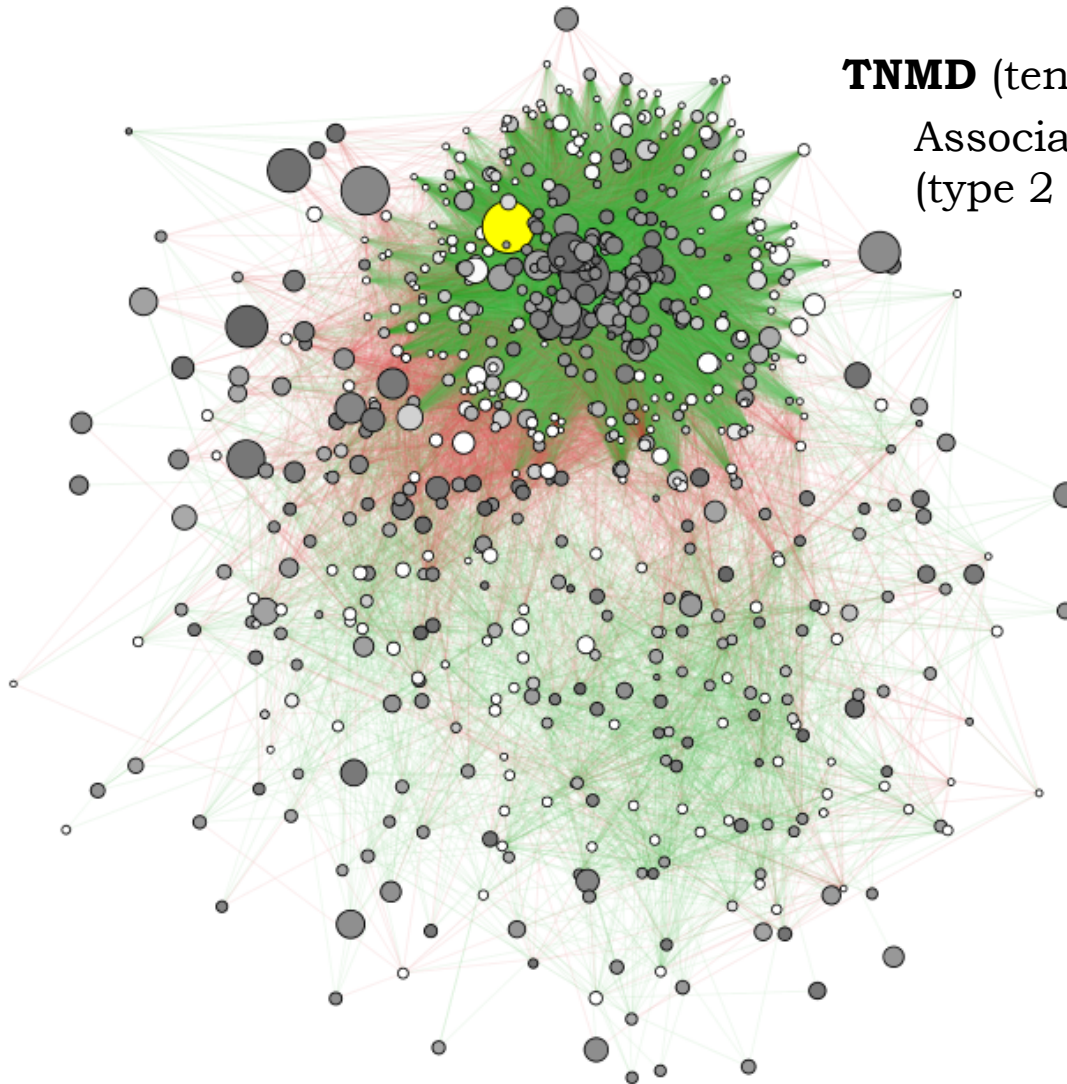
Blue: Immune related pathways
e.g. chemokine signaling pathway



Green: Developmental related pathways
e.g. Wnt signaling pathway



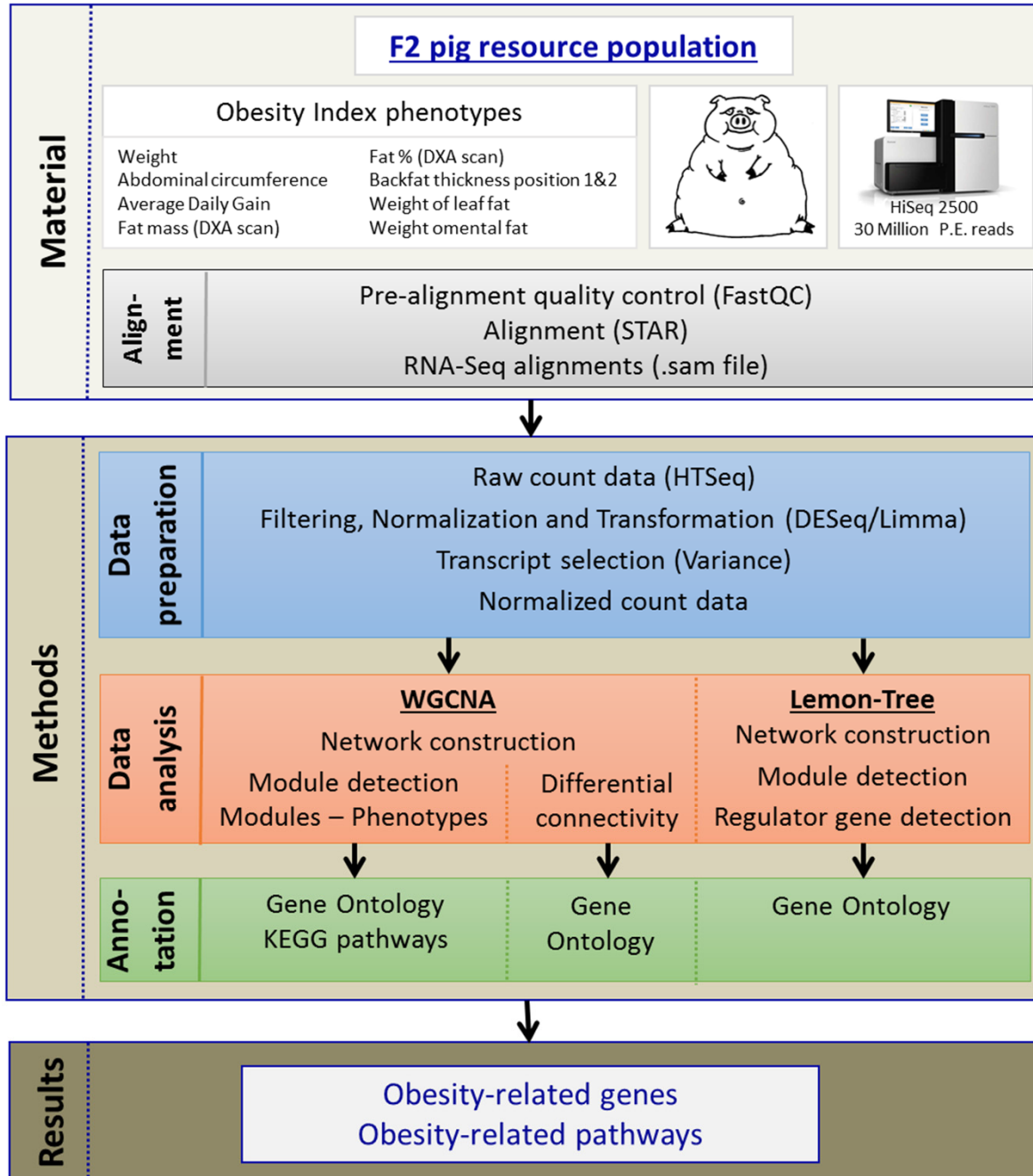
Co-expression of DE genes



TNMD (tenomodulin):

Associated with glucose metabolism
(type 2 diabetes) and central obesity

Overview



Expression QTL (eQTL) mapping study

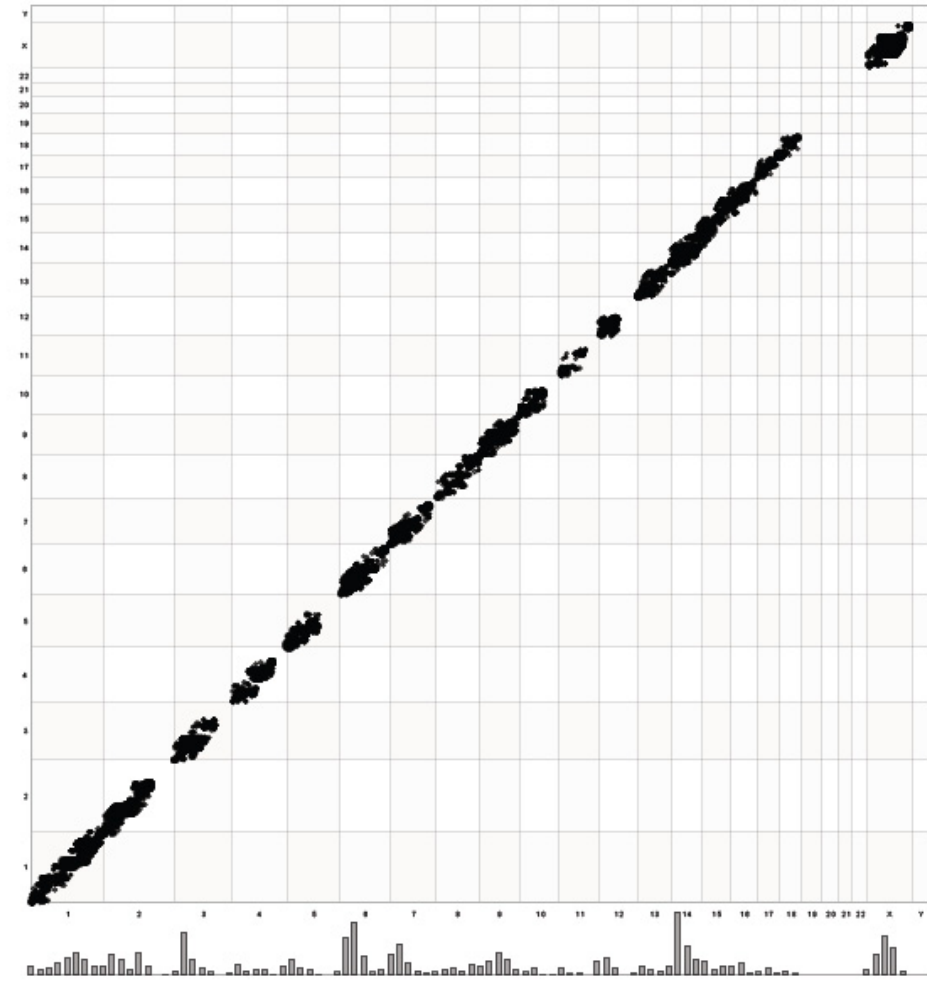
Integration of genotype (60K) and RNA-Seq data:

A full scale eQTL mapping means mapping some 21000 phenotypes using 60k chip

Adapted cis-eQTL mapping for DE transcripts

→ to detect causal variants¹

Detection of 987 cis-eQTLs (<1 Mb)



¹Kadarmideen, et al. (2006) Mammalian Genome 17: 548-64

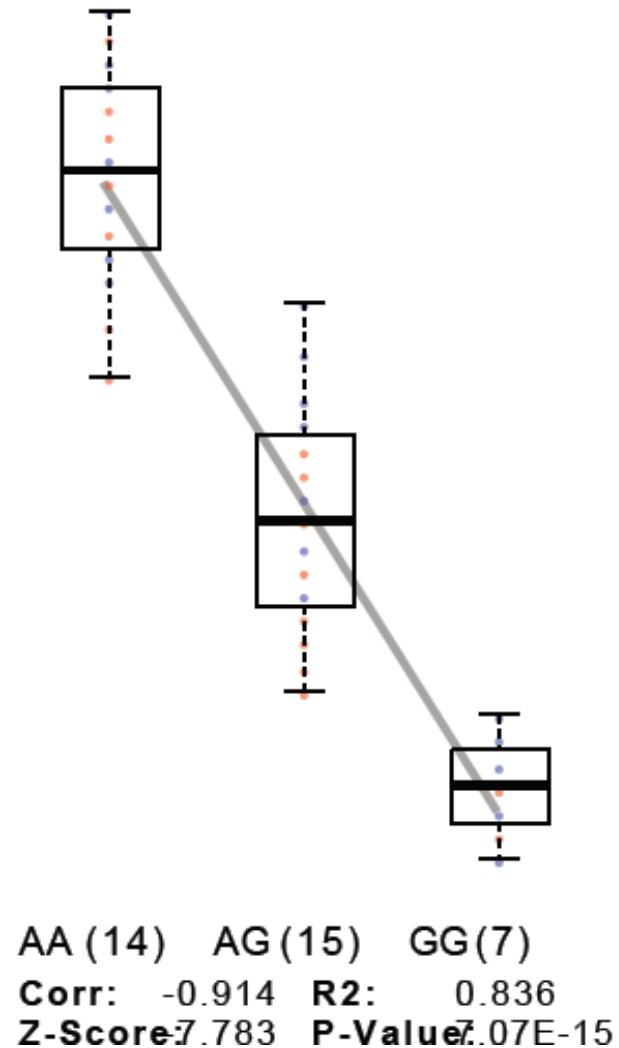
Kadarmideen (2008) IET Systems Biology 2: 423-441

Kadarmideen (2014) Livestock Science 166: 232-248

eQTL study: one example

PEX10:

- Important for the accumulation of very long chain fatty acids and branched chain fatty acids
- Has been detected as differentially expressed between obese and non-obese asthmatic individuals



eQTL study: pathway analysis

GO Biological Process:

- Co-factor metabolic process
- Coenzyme biosynthetic process
- Water-soluble vitamin process
- Peptide metabolic process

KEGG:

- Amino sugar and nucleotide sugar metabolism
- Pyrimidine metabolism
- Valine, leucine and isoleucine degradation
- Glutathione metabolism
- Purine metabolism



Kogelman and Kadarmideen *BMC Systems Biology* 2014, 8(Suppl 2):S5
<http://www.biomedcentral.com/1752-0509/8/S2/S5>



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ORIGINAL RESEARCH ARTICLE
 published: 18 March 2013
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RESEARCH

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Weighted Interaction SNP Hub (WISH) network method for building genetic networks for complex diseases and traits using whole genome genotype data

Lisette JA Kogelman, Haja N Kadarmideen*

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Systems genetics of obesity in an F2 pig model by genome-wide association, genetic network, and pathway analyses

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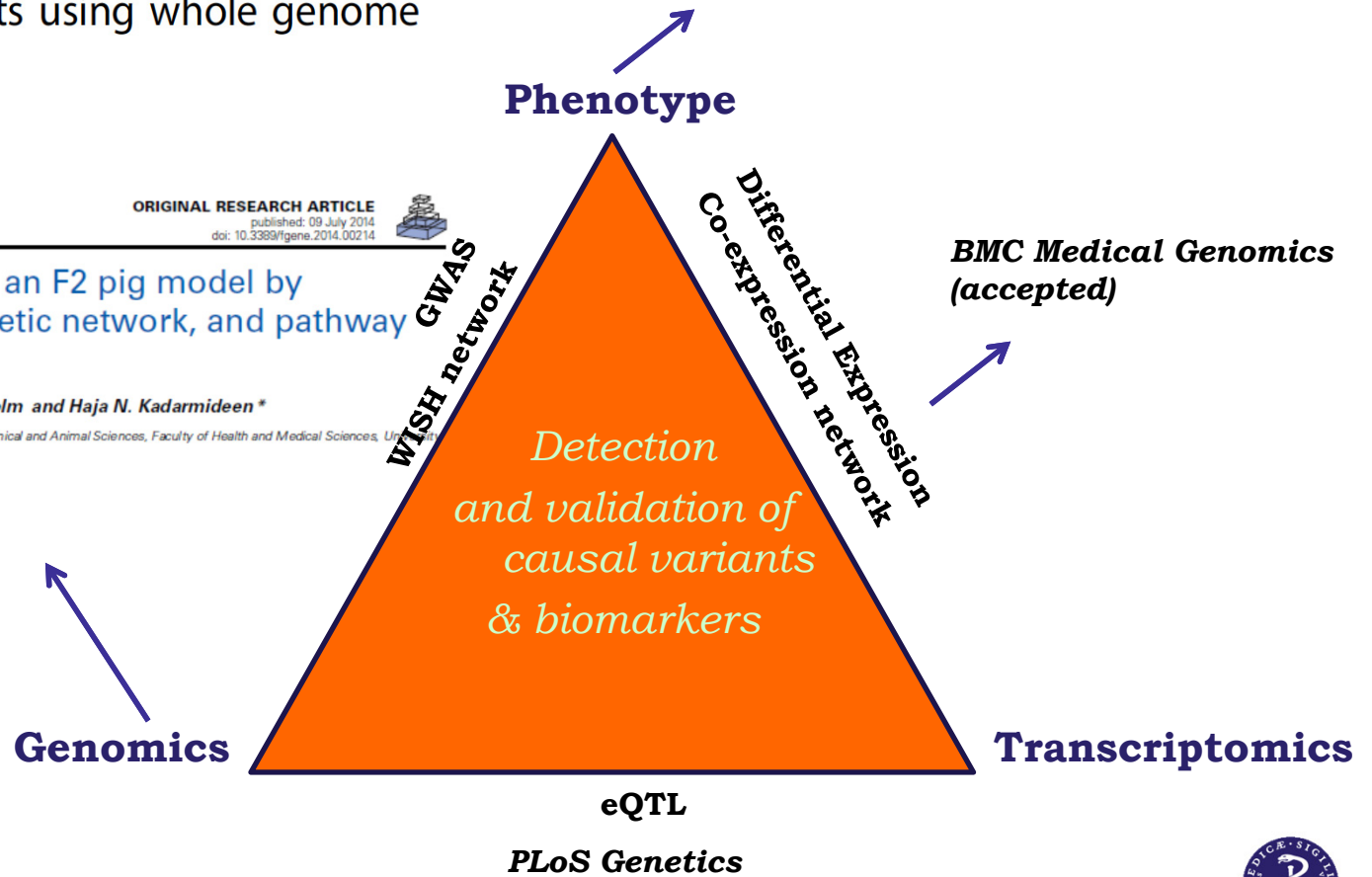


Figure adapted from Kadarmideen, HN. (2014). *Genomics to Systems Biology in Animal and Veterinary Sciences: Progress, Lessons and Opportunities*. **Livestock Science**, 166: 232-248 <http://dx.doi.org/10.1016/j.livsci.2014.04.028>



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