



The WISH network method applied to obesity in an F2 pig population

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Genetics of obesity

Associated with several diseases:

- Type 2 diabetes
- Coronary artery disease
- Several types of cancer

Huge welfare and economical consequences!

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

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

Genome-wide association studies (GWAS):

- identified **32** loci
- those explain only **1.45%** of the genetic variation in BMI



A systems genetics approach

GWAS:

Each SNP is individually tested, which results in testing thousands or millions of SNPs:

→ multiple-testing problem

→ no interactions between SNPs are taken into account

Obesity is associated with multiple genes, environmental factors and their interaction

Gene	No. of nearby SNPs	No. of interactions	Associated genes
ATP10B	156	189	CHUK, CBARA1, SLIT3, WDR37, WWOX, NAV2, SLC10A7, NDUFB8, NDUFC2, NDUFS2, COX5A, etc.
FTO	19	52	NT5C2, AS3MT, CNNM2
<i>rs1281296</i>	42	42	<i>TMCO5, TFAP2D, RAPGEF1</i>
NAV2	17	18	JAKMIP2
SLC10A7	18	18	CDH13, ATP10B, R3HDM1
WDR37	9	15	RPGRIP1L, DNAJC15
PDZRN4	3	9	LOC301738
NRXN3	1	1	GRM8

Detecting their interaction patterns, could lead to the identification of functional pathways and gene networks.



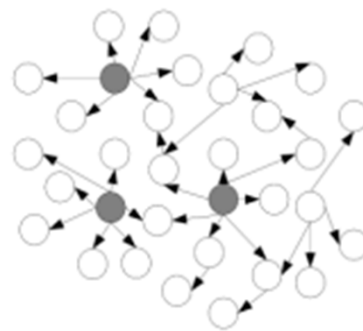
Networks in biology

Biological networks are scale-free:

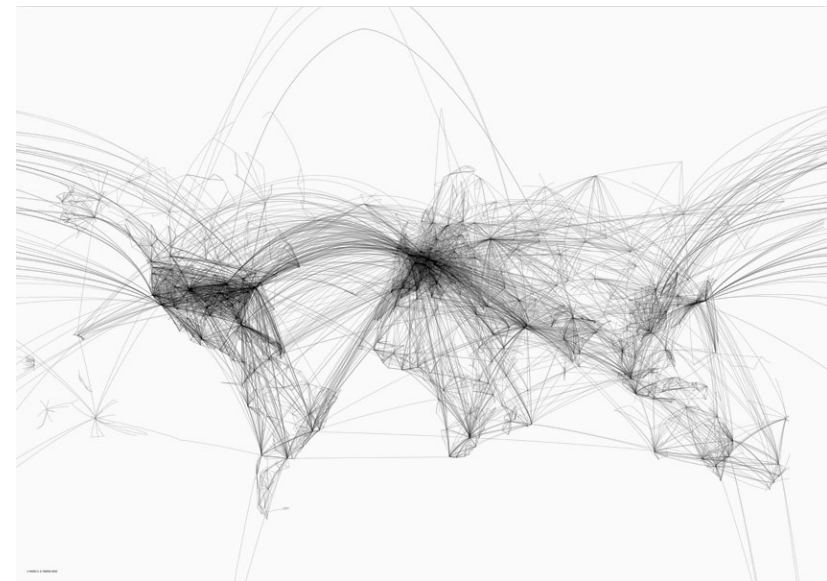
- hubs with many connections → important function!



(a) Random network



(b) Scale-free network



We like to detect those kind of clusters and hubs in high-throughput genotype data

The Weighted Interaction SNP Hub (WISH) Network method

WISH: SNPs are connected with each other, whereby the connection strength is defined by the correlations between the SNPs

- genotype correlations
- epistatic interactions

Connectivity of a gene:

The sum of correlations with all other genes

Highly connected genes (hub genes) are thought to be biological meaningful

Topological Overlap Measure (TOM):

A measure of the overlap between pairs of SNPs (interconnectedness)

Module detection:

Module: cluster of highly interconnected SNPs

Module selection: based on their correlation with the trait of interest.



Pig as a model for human obesity

Similar metabolic features and disease progression

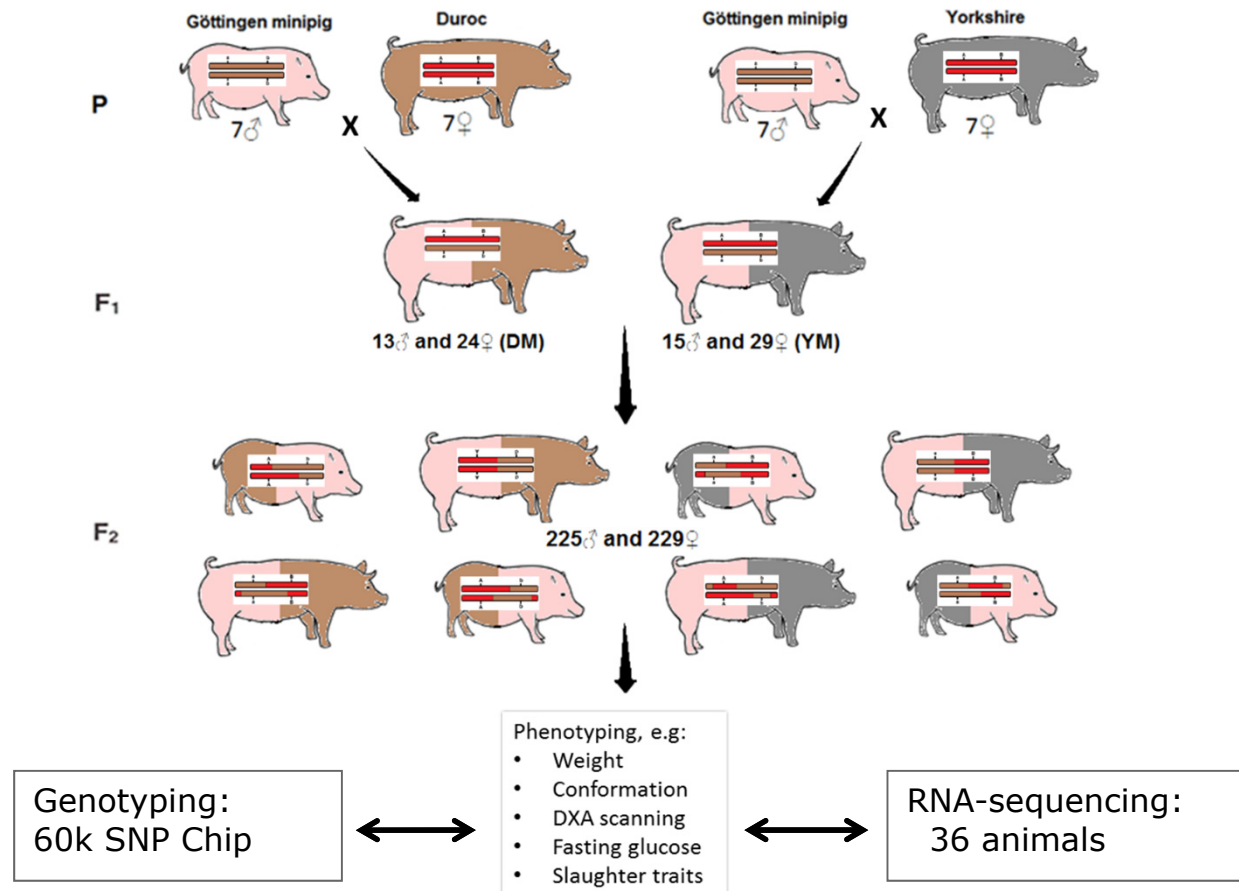
- Protein and lipid metabolism comparable with human
- Similar cardiovascular system
- Proportionally similar organ sizes

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



Materials: UNIK F2 pig population



Kogelman et al.: “An F2 pig resource population as a model for genetic studies of obesity and obesity-related diseases in humans: Design and genetic parameters”. *Frontiers in Genetics* 2013,4:29

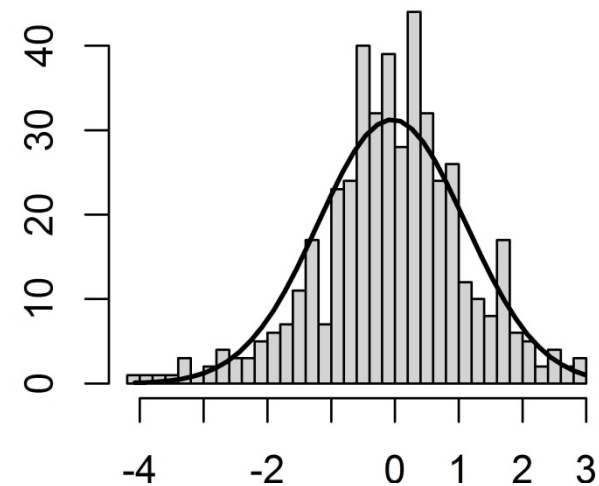


Obesity Index

Obesity Index: based on selection index theory

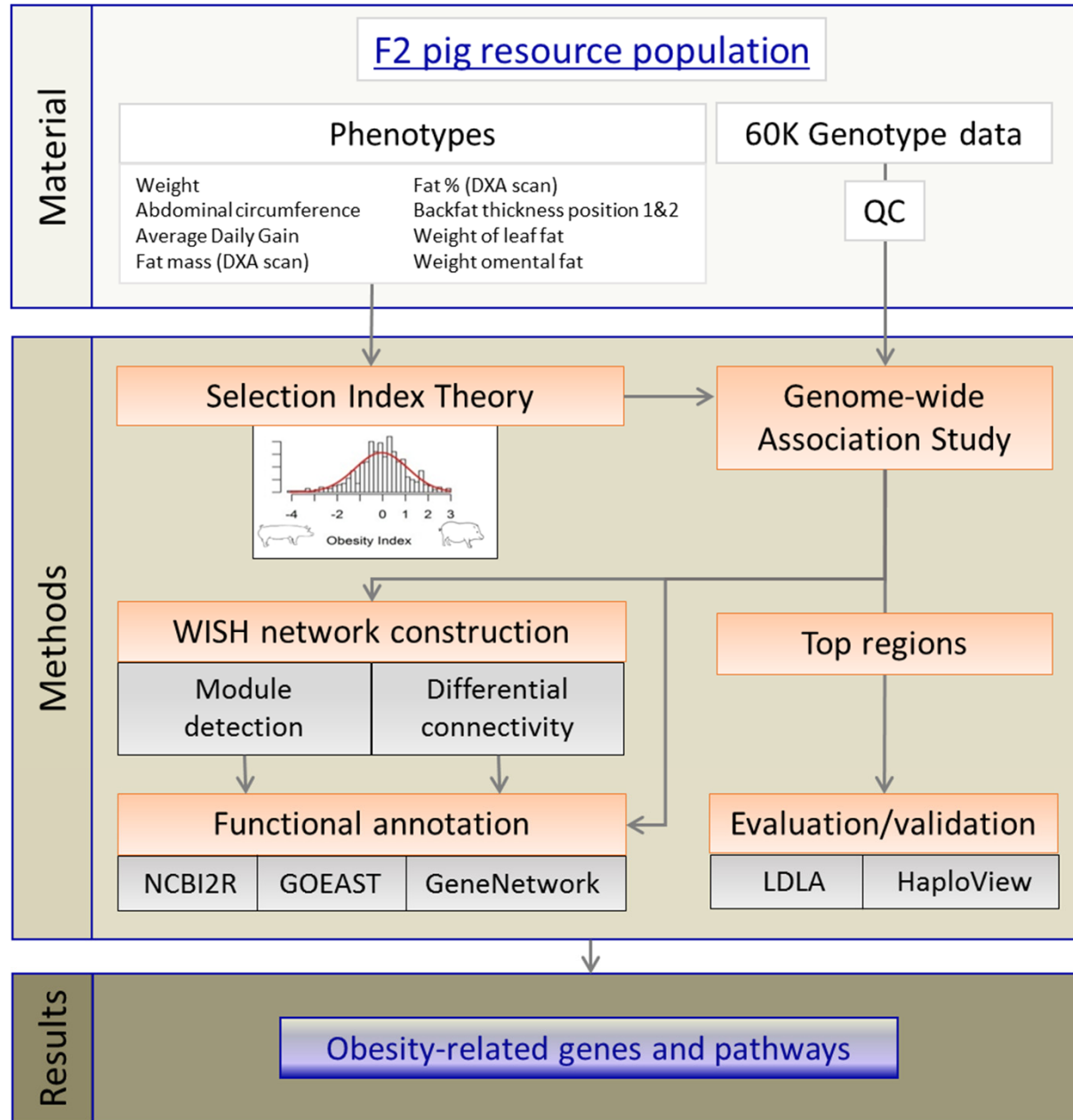
Phenotypes	
Weight	Fat % (DXA scan)
Abdominal circumference	Backfat thickness position 1&2
Average Daily Gain	Weight of leaf fat
Fat mass (DXA scan)	Weight omental fat

Frequency



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





GWAS and pathway analysis

Top Genes:

NPC2: role in regulation of cholesterol transport

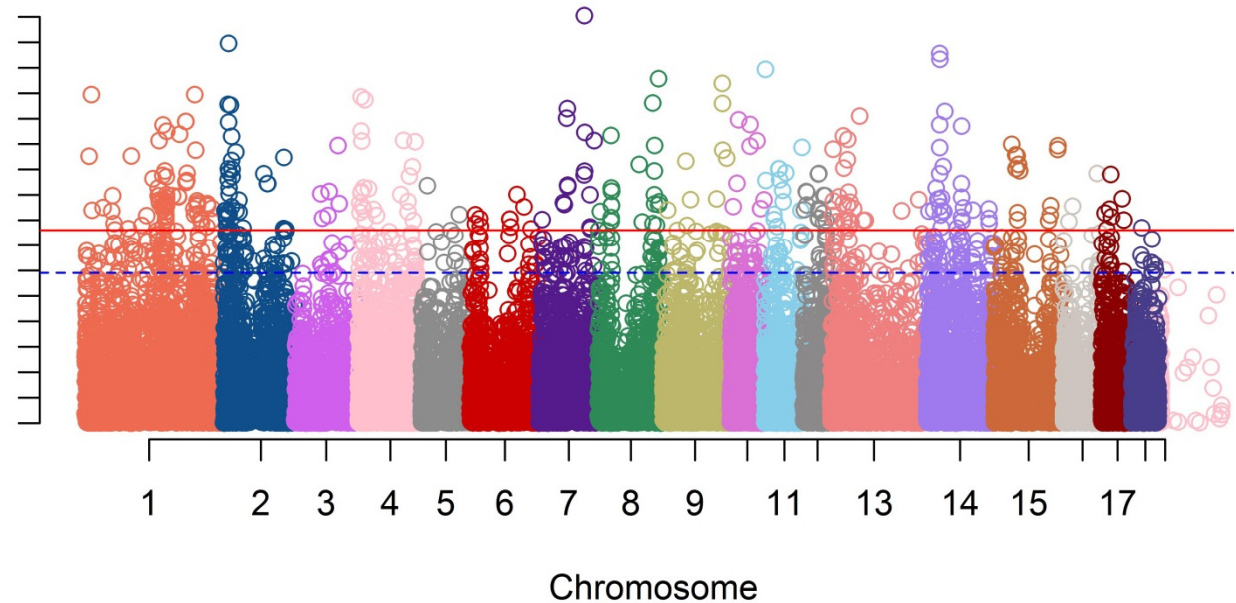
OR4D10: olfactory receptor gene

CACNA1E: previously associated with insulin resistance

Top Pathways:

Decreased inflammatory response

Negative regulation of insulin secretion



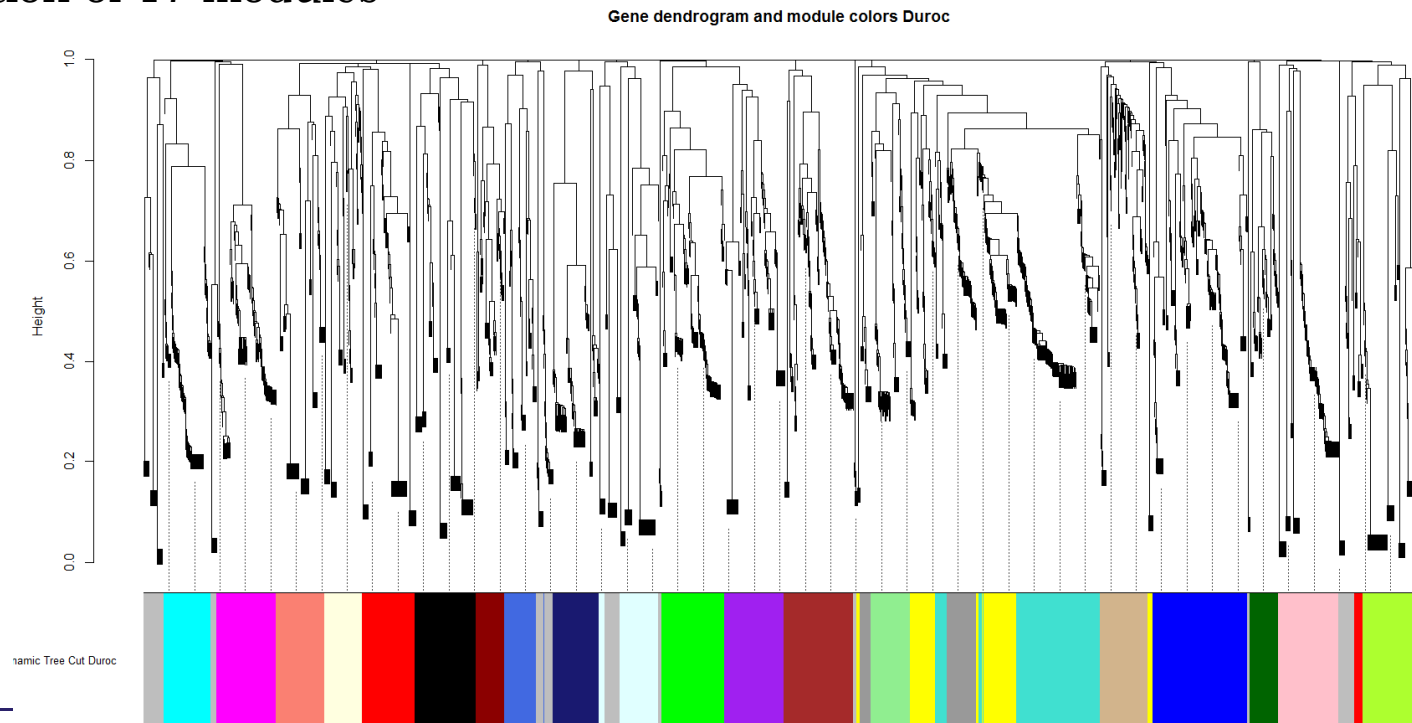
WISH network applied to obesity

Selection of top 2500 SNPs:

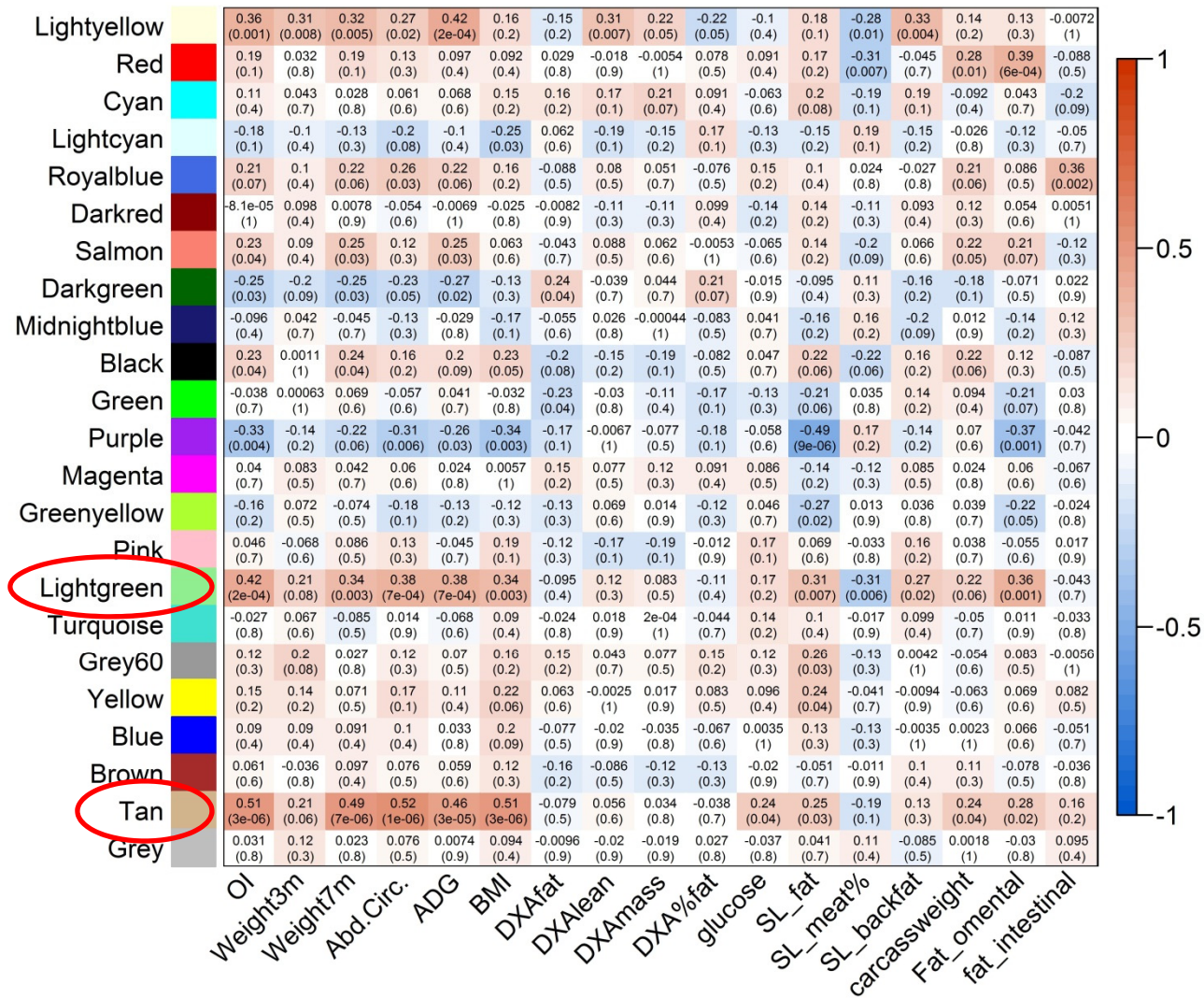
- GWAS p-value < 0.05
- Connectivity

Network construction:

- minimum 50 SNPs per module
- detection of 17 modules



WISH network construction



Pathway analysis WISH modules

Tan:

- actin filament pathway
- diabetes: abnormal pancreatic beta cell morphology
- branched chain family amino acid metabolic process

Lightgreen:

- purinergic receptor activity:
 - P2RX7: regulation of beta cells (diabetes)
 - ADORA2A: hypotension
- fructose 2,6-biphosphate metabolic process:
 - PFKFB4: glycolysis



Differentially wired network of SNPs

Differential network → differential connectivity:

Detecting SNPs which are highly connected in one sub-network but lowly connected in the other sub-network

Hub genes in lean sub-network:

UBR1: associated with fat metabolism in mice

CNTNAP2: suggested neuronal impact on obesity

Hub genes in obese sub-network:

NUCB2: regulating food intake and energy homeostasis

BCL11A: associated with type 2 diabetes and pancreatic beta cell function



Conclusions

We developed a network method to analyze high-throughput genotype data:
the WISH network method

The method successfully detected modules of highly interconnected SNPs
and we were able to biologically link them to obesity

The method can be used on all high-genotype data, in all species, also
human!

Will be published as R-package in autumn 2014

Contact us if interested!

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



RESEARCH

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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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