Faculty of Health and Medical Sciences

Quantitative and Systems Genetics Analyses of Lipid profiles in a Pig Model for Obesity

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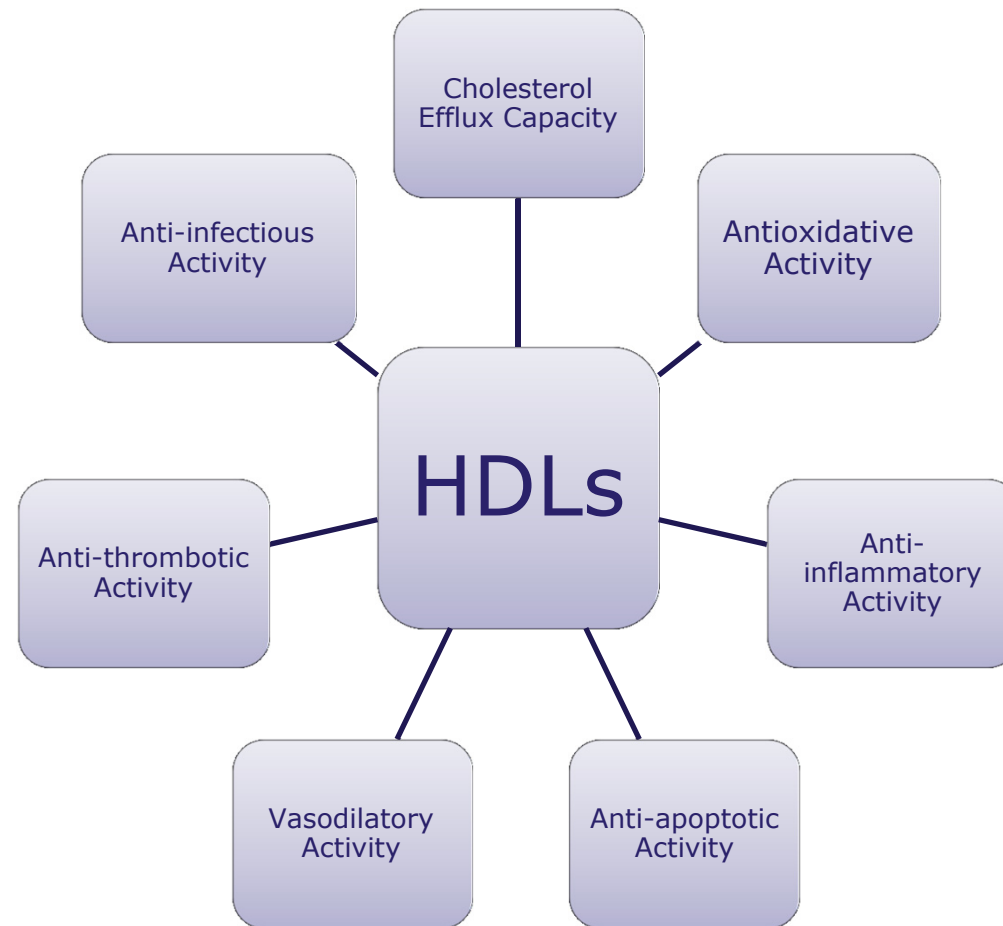
Outline

- Background

- Objectives

- Materials and Methods

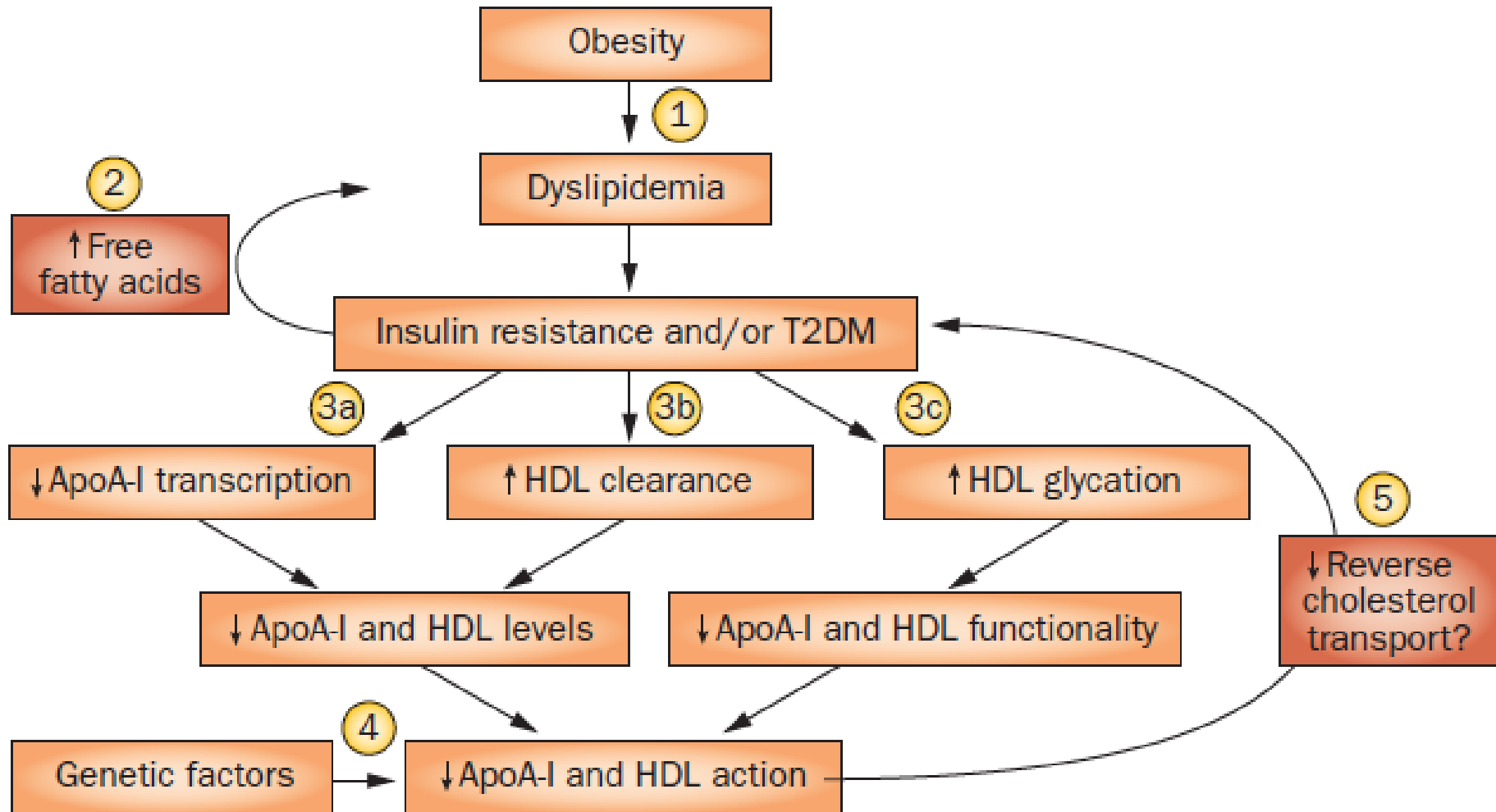- Results

- Discussion

- Conclusion

- Acknowledgement

Model: Pig Population

Focus: Obesity and High Density Lipoprotein (HDL) Traits
6 Traits: HDL-CE, HDL-CE/CT, pHDL-CL, pHDL-TG, pHDL-PL and pHDL-CE

Kontush & Chapman (2006): doi:10.1124/pr.58.3.1.

Connection between Obesity and HDLs

Obesity: $\uparrow$HDL-TG and $\downarrow$ HDL-C
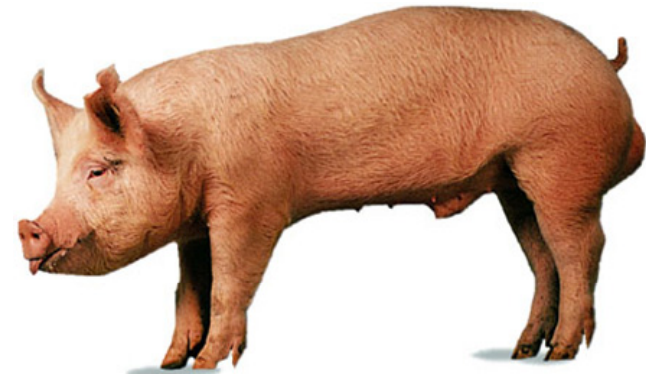
Aim:

1. Quantitative Genetics: Estimate heritabilities

2. GWAS: identify genetic variants

3. Systems genetics: WGCNA and pathways

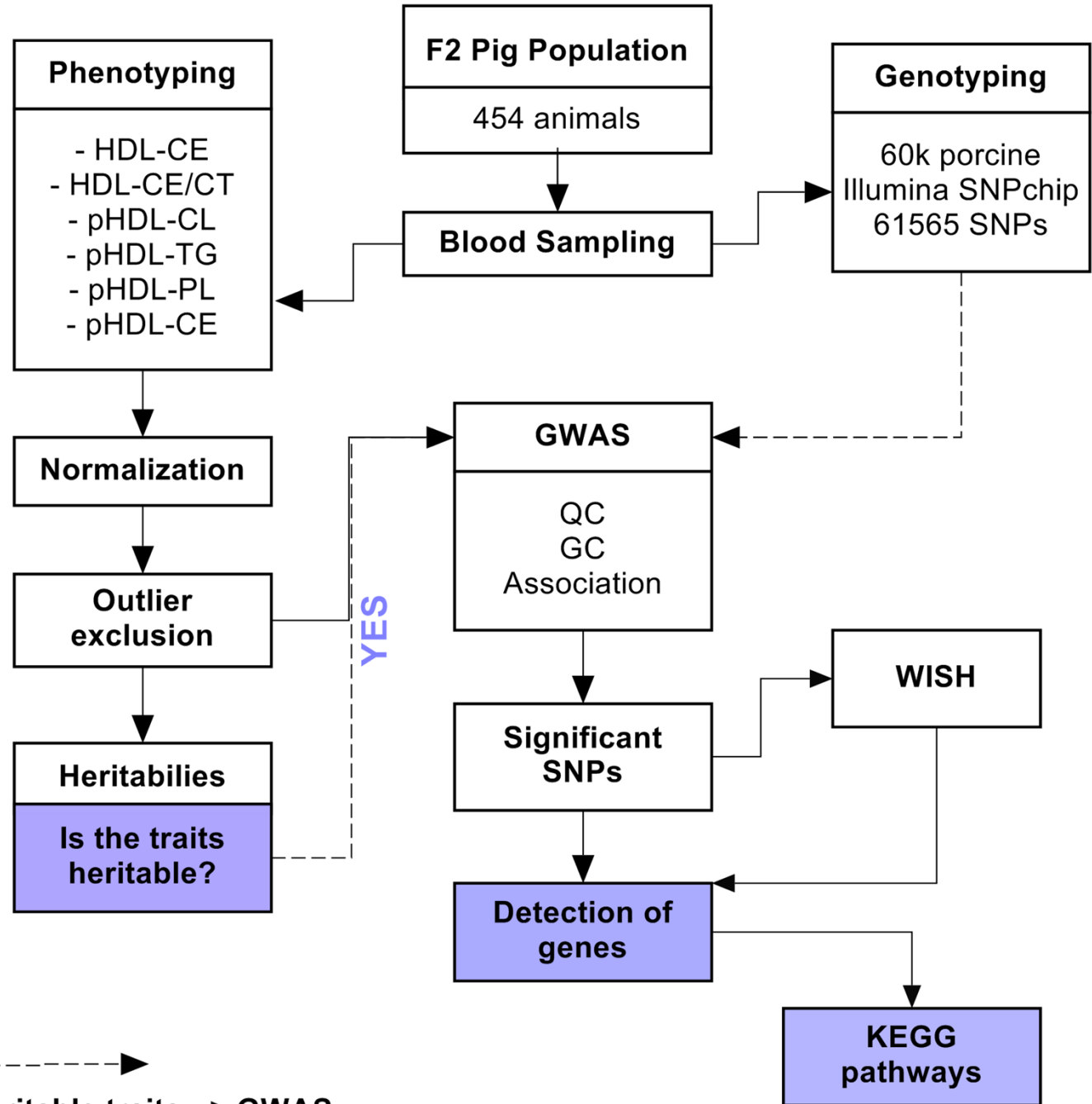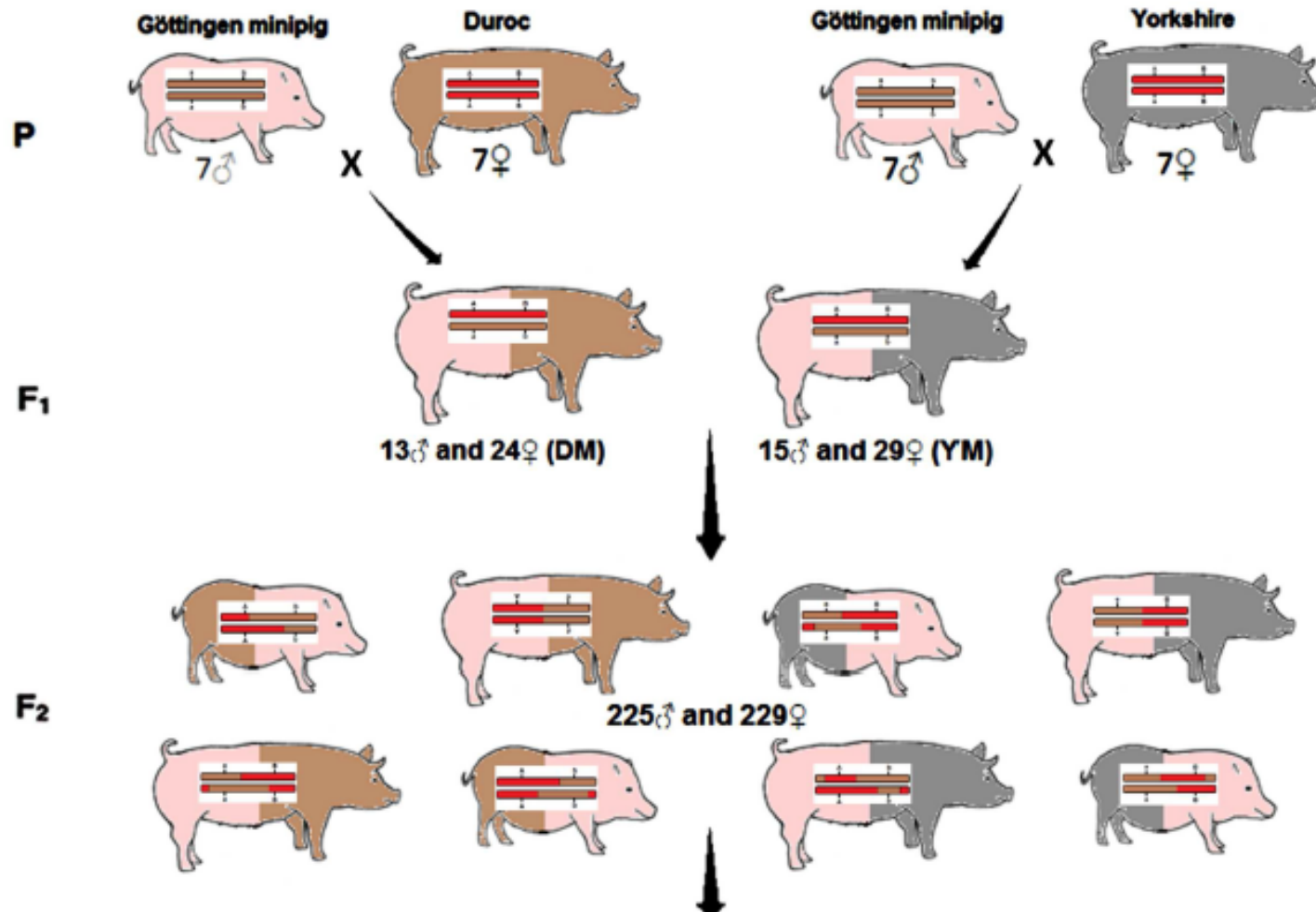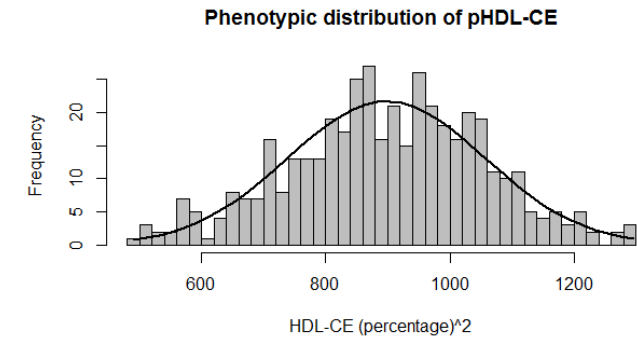# Materials and Methods

Workflow

F2 Pig Population — 454 animals

Phenotyping
- HDL-CE
- HDL-CE/CT
- pHDL-CL
- pHDL-TG
- pHDL-PL
- pHDL-CE

Blood Sampling

Genotyping — 60k porcine Illumina SNPchip 61565 SNPs

Normalization

Outlier exclusion

Heritabilies — Is the traits heritable?

YES

GWAS — QC GC Association

Significant SNPs

WISH

Detection of genes

KEGG pathways

Heritable traits -> GWAS

Kogelman et al. (2013):
doi:10.3389/fgene.2013.00029

Animal Model

Fitting univariate mixed linear models:

Phenotypic distribution of pHDL-CE

$$y_{ijkl} = \mu + SEX_i + BATCH_j + \gamma(AGE_k) + ANIMAL_l + \varepsilon_{ijkl}$$

y_{ijkl}:   Phenotypic measurements of the HDL traits

SEX_i: Fixed effect (i = 0, 1)

$BATCH_j$:   Fixed effect (j = 1, 2, 3)

AGE_k: Covariate

γ: Regression coefficient for AGE_k

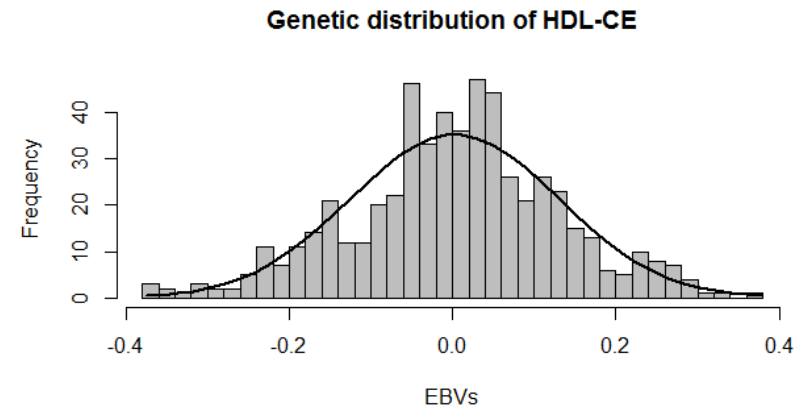$ANIMAL_l$:   Random genetic effect (l = 1, …, 454)

ε: Error term

Results

Heritabilies (h²)

Genetic distribution of HDL-CE

h²: Ranging from 0.17 to 0.99
- Variations in the phenotypic values influenced by genetic differences

EBVs: Normal distributed
- Genetically predisposed toward different lipid profiles

Table: Heritabilities estimated based on the univariate animal models.

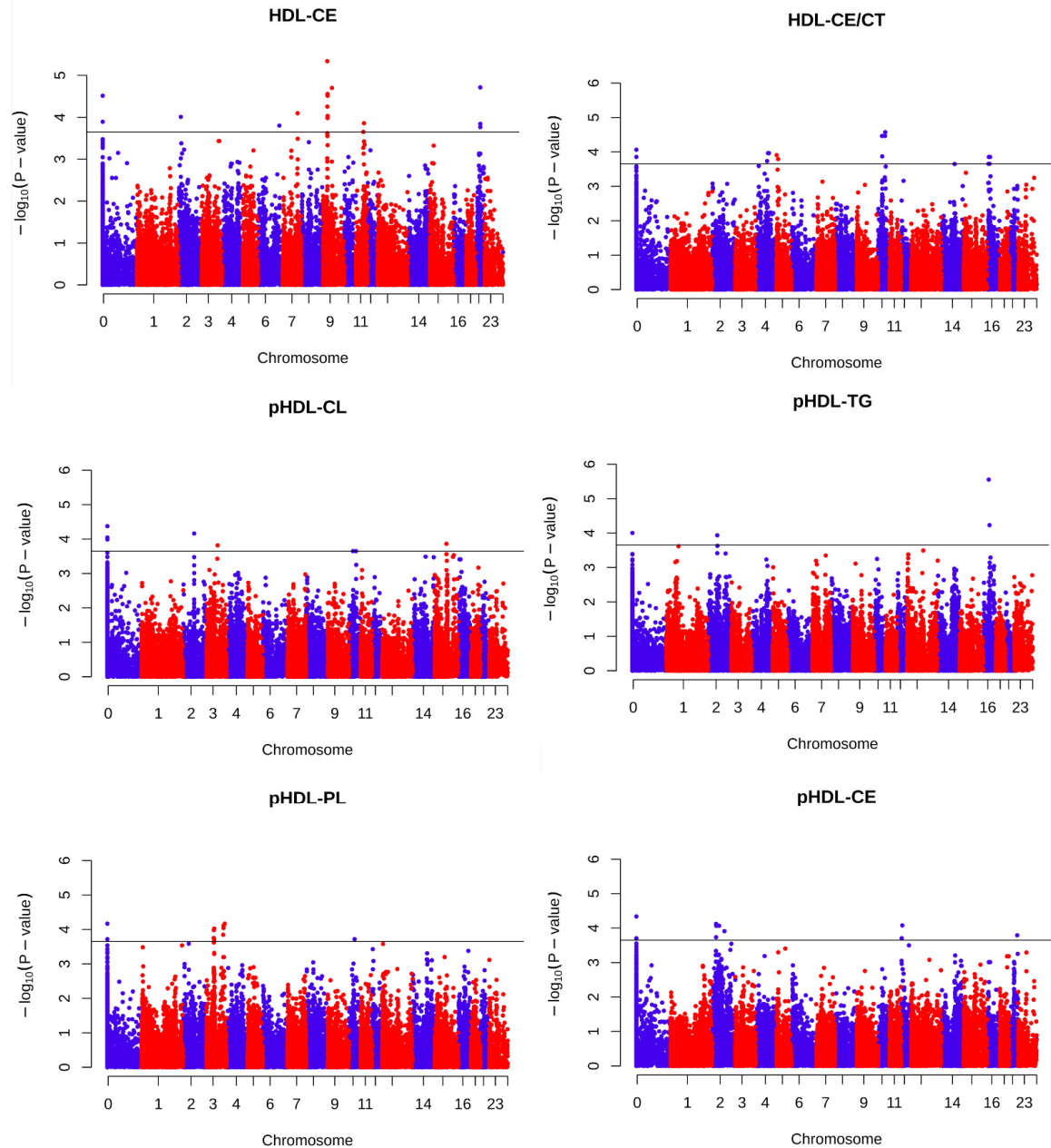|	HDL-CE	HDL-CE/CT	pHDL-CL	pHDL-TG	pHDL-PL	pHDL-CE
h²	0.98	0.37	0.17	0.77	0.99	0.41
SE	0.14	0.15	0.11	0.15	0.14	0.14

GWAS

Manhattan plot

Different QTLs for
the 6 lipid traits.

P-value cutoff:

$p \leq 2.2 \cdot 10^{-4}$

HDL-CE: Possible KEGG pathways

Olfactory Transduction (Chr 2)
Olfactory receptors

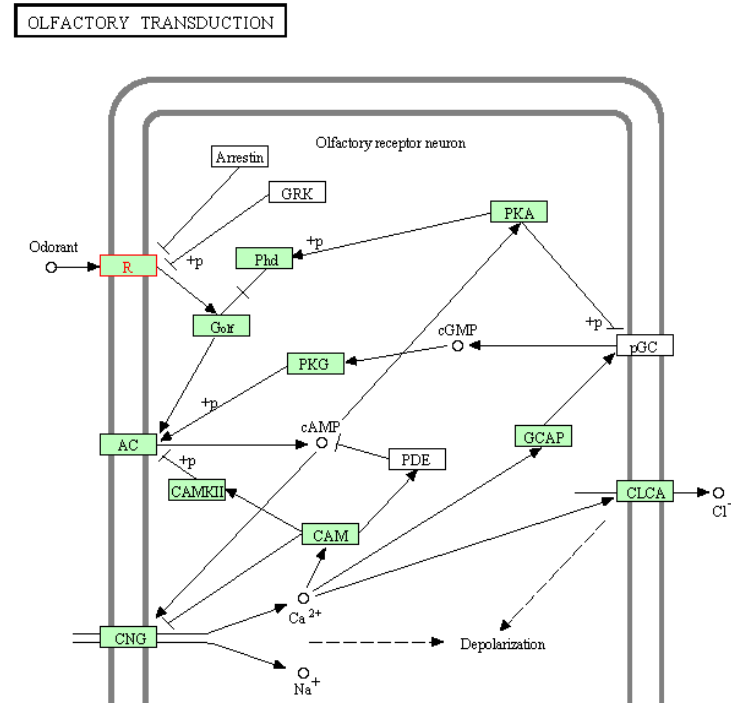**Metabolic pathways** (Chr 7 and 9)
Lipid and AA metabolism

OLFACTORY TRANSDUCTION

Table: KEGG pathways related to the gene sets (p < 0.05)

Trait	KEGG pathway id	KEGG pathway name	P-value
HDL-CE	04740	Olfactory Transduction	0.04
	01100	Metabolic Pathways	0.0004

WISH – HDL-CE

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

BMC Systems Biology

RESEARCH   **Open Access**

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[*]

frontiers in GENETICS

ORIGINAL RESEARCH ARTICLE
published: 09 July 2014
doi: 10.3389/fgene.2014.00214

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

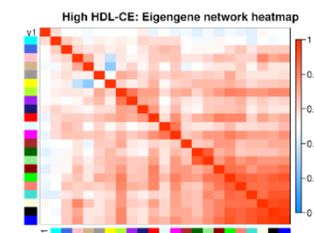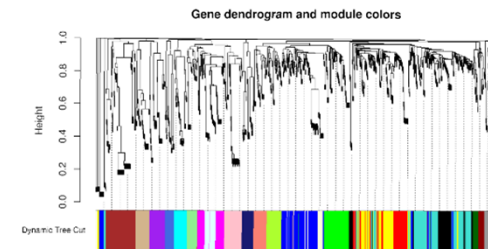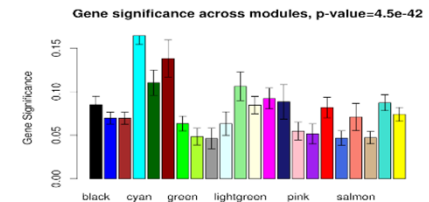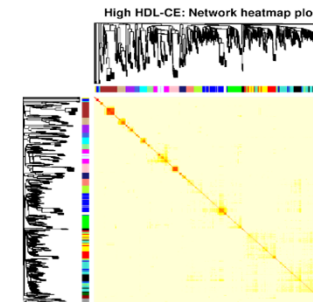Lisette J. A. Kogelman , Sameer D. Pant, Merete Fredholm and Haja N. Kadarmideen[*]

GMAT: Significant modules

High HDL-CE group
- Cyan: p < 0.05 and cor = 0.19
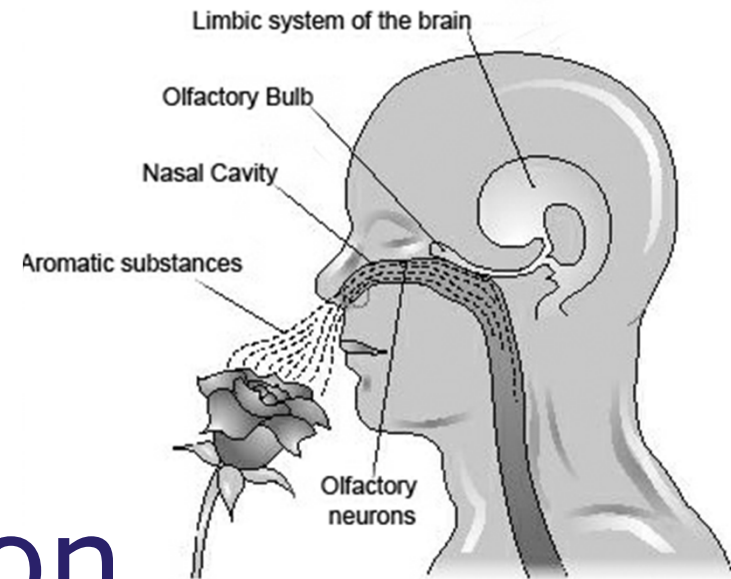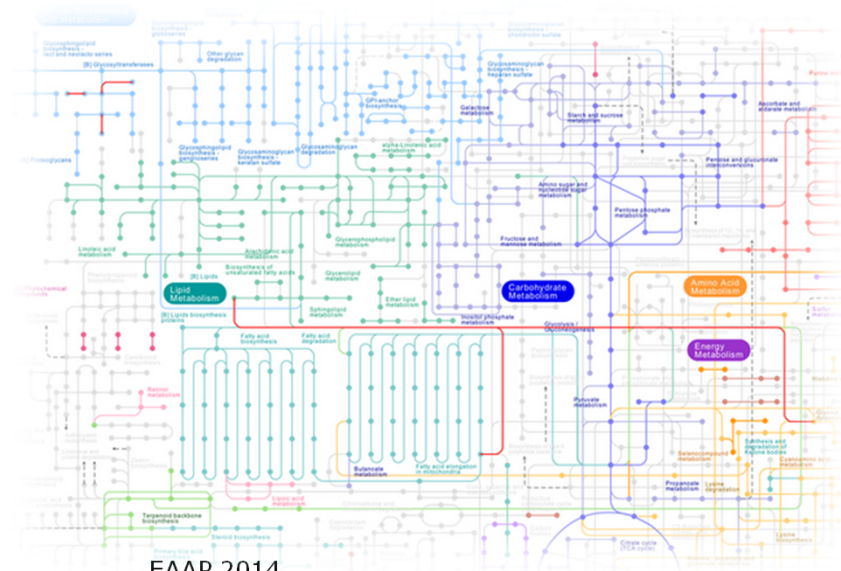
KEGG pathways: Metabolic pathways (p = 2.94E-05)

Slide 14
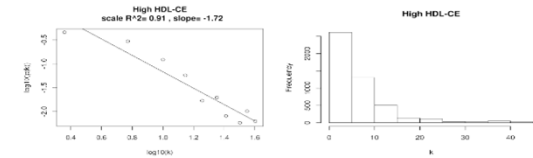
Discussion

Olfactory Transduction

Pig model: Largest repertoire of olfactory
receptor genes

Smell: Odorants bind to various receptors (one or more) →
different responses

Obesity: E.g. due to impaired olfactory detection

Obese vs. lean humans
Sensitivity or responsiveness of OR??

Palouzier-Paulignan et al. (2012): doi:10.1093/chemse/bjs059
Groenen et al. (2012): doi:10.1038/nature11622
Young & Trask (2002): doi: 10.1093/hmg/11.10.1153

Metabolic pathways

Impact of genes - Broad Overview

- Role against oxidative damage

    - Obesity → oxidative stress

- Influence on glucose tolerance and development

  of insulin resistance

- Level of free FFA and TG

- Role in atherosclerosis

- Role in weight gain/loss
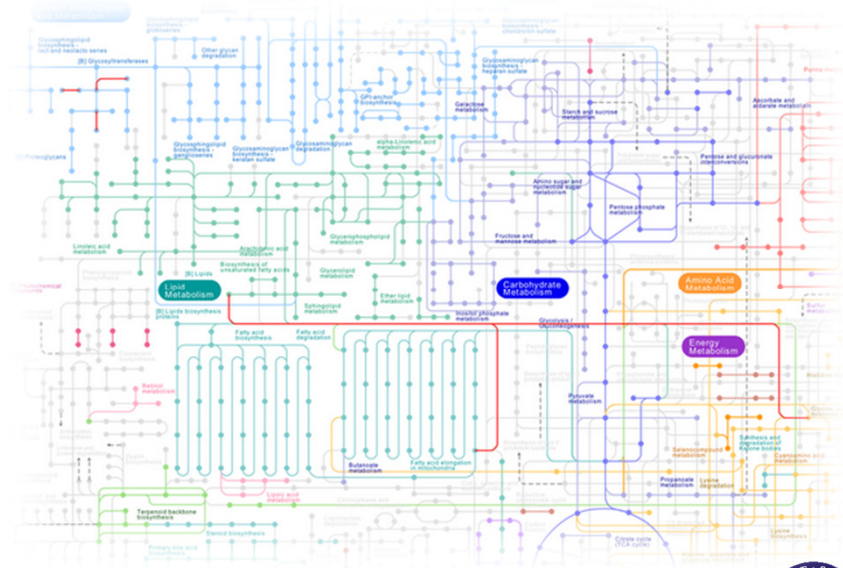
Bhandari (2014): htp:/www.scholarly-journals.com/SJSRE
Li et al. (2014): doi: 10.1128/MCB.05893-11.
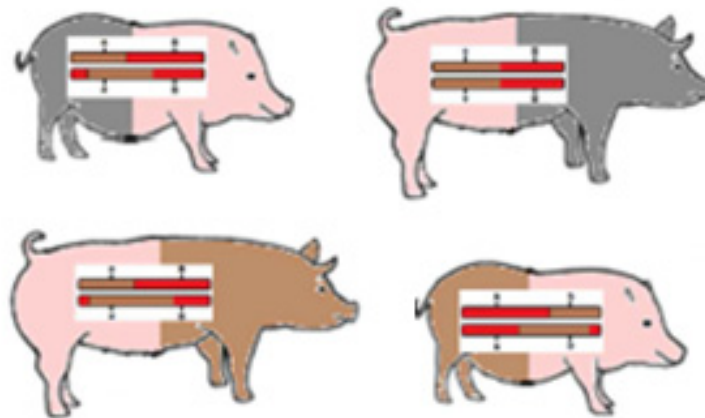Homeister et al. (2004): doi: 10.1161/01.ATV.0000141844.28073.df
Bikman & Summers (2011): doi:10.1172/JCI57144

Conclusion

Indication of significant genomic variation in lipid profiles in our porcine model.

Possible reasons:

Genomic variation → Phenotypic differences possibly due to differences in olfaction and metabolism pathways

Acknowledgement

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(http://biochild.ku.dk/)

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Supervisors and co-authors:
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- Sameer D. Pant   *Adjunkt*

Co-authors:
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THANKS FOR YOUR ATTENTION ☺

Questions?