



Genome-wide association and pathway inference for Residual Feed Intake (RFI) in Duroc boars

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Background

Residual feed intake (RFI):

- $RFI = \text{observed daily feed intake (DFI)} - \text{expected DFI}$
- Expected DFI: predicted from production and maintenance requirements (daily gain, metabolic mid weight, backfat...)*
- Explains about 25-35% of variance of feed intake in growing pigs**



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Background

Selection of lower RFI:

- helps to reduce feed consumption (feed cost)
- does not (minimum) affect production traits (daily gain, weight...)
- gives better meat quality traits*
- has less impact on environment*



Background

Measurement of RFI in Danish pigs: two definitions

$$\text{RFI1} = \text{DFI} - (\beta_0 + \beta_1\text{BWd} + \beta_2\text{ADG})$$

$$\text{RFI2} = \text{DFI} - (\beta_0 + \beta_1\text{BWd} + \beta_2\text{ADG} + \beta_3\text{BF})$$

J Anim Sci. 2013 Jul 3. [Epub ahead of print]

Genetic parameters for different measures of feed efficiency and related traits in boars of three pig breeds

Do DN, Strathe AB, Jensen J, Mark T, Kadarmideen HN.

Heritabilities and genetic correlation

- Heritabilities: $\text{RFI1} = 0.34$ and $\text{RFI2} = 0.38$
- RFI1 and RFI2 have very high genetic correlation ($r = 0.96$)
- RFIs : high genetic correlation with DFI ($r = 0.90$) and FCR ($r = 0.84$), no genetic correlation with BF and ADG ($r \sim 0$)

Background and Objectives

Research gap

- Few QTL and candidate genes identified for RFI in pigs
- No GWAS for RFI in Danish pigs
- Little understanding the biological pathways for RFI

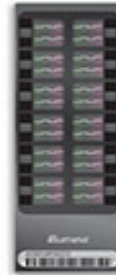
Aims: to find out

- Top SNPs
- Positional candidate genes
- Biological pathways for RFI

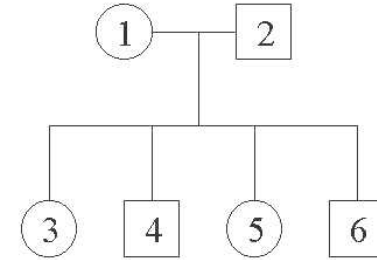
Materials and Methods



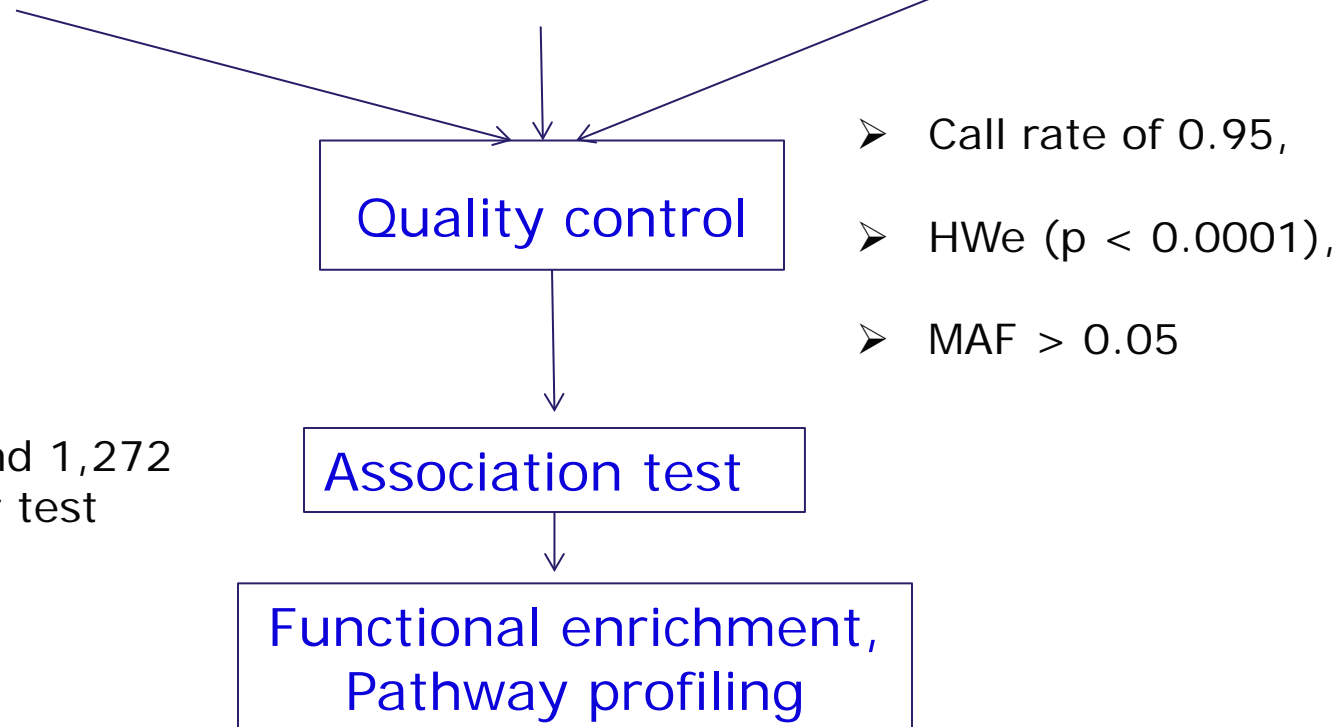
Phenotypic records
~ 9000 Duroc boars



Genotypic records
~ 1500 Duroc boars



Pedigree available
from 1970s



33,241 SNPs and 1,272
pigs used for test

Methods

Association test

Model: $y = 1\mu + \mathbf{Z}a + mg + e$

y: deregressed EBV (Garrick et al, 2009)

a: random polygenic effect

g: additive effect of the SNP

e: error term

Implemented: DMU package, and GW significance threshold using Bonferroni correction ($p = 1.5 \times 10^{-6}$)

Methods

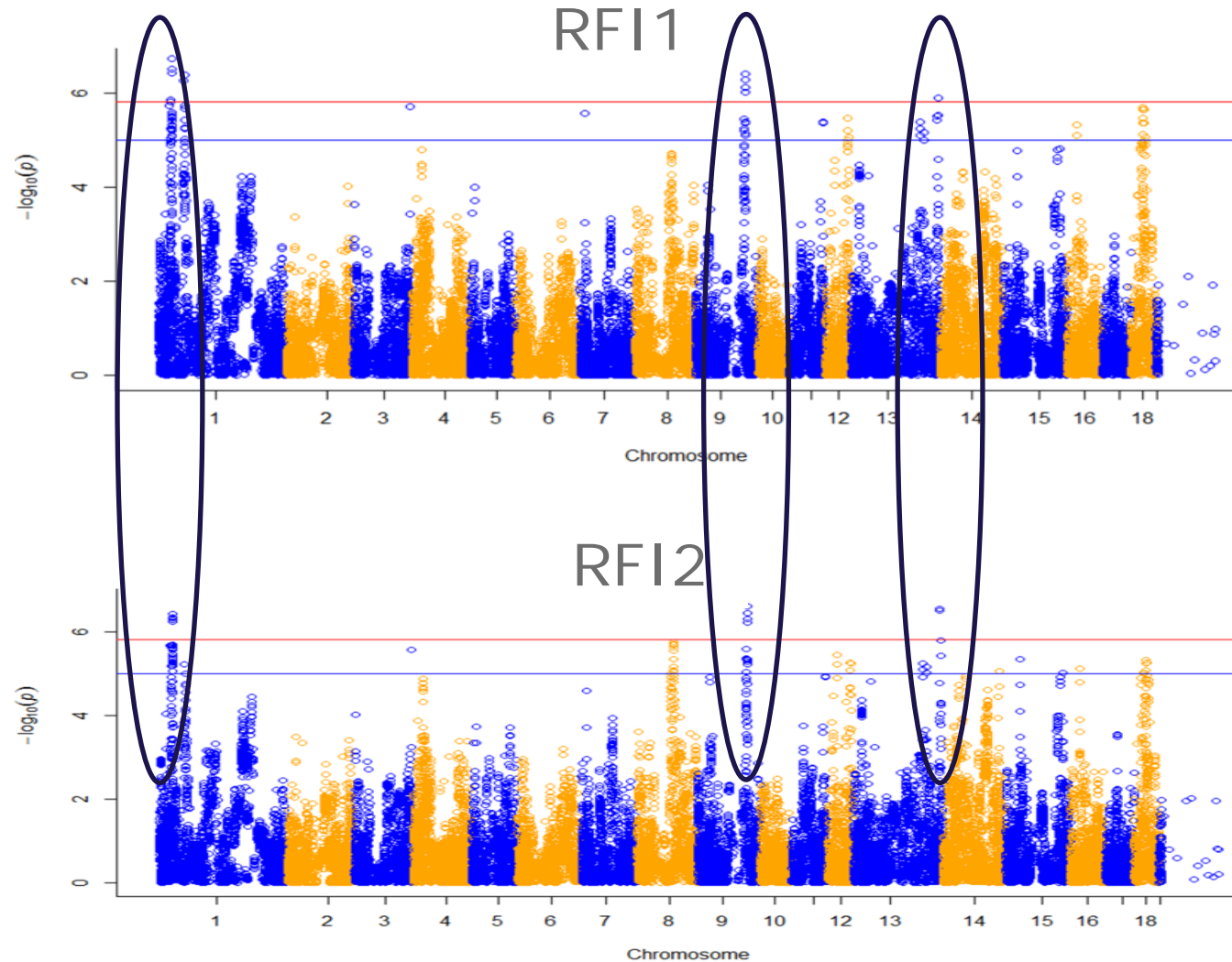
Scan for positional candidate genes

- The positional candidate genes within 0.5 Mb size flanking significant SNPs were scanned using the NCBI2R package

Pathway profiling

- The genes were assigned to Kegg pathways, the Gene Ontology
- Pathway enrichment test used modified Fisher exact test
(Wang, 2007)

Results: Manhattan plot of $\log(p\text{-values})$ for RFI1 and RFI2



➤ QTL for RFI1 and RFI2 are identical

➤ Significant QTL in SSC 1, 9 and 13

red line: significance GW threshold (1.5×10^{-6}), blue line = suggestive GW (5×10^{-5}) threshold

Results: Significant markers for RFIs

SSC	p-value	Variance.Explained (%)	Nearest gene
1	5.64×10^{-7}	0.19	<i>MAP3K5</i>
1	4.68×10^{-7}	0.19	<i>MAP3K5</i>
1	5.09×10^{-7}	0.19	<i>MAP3K5</i>
1	4.54×10^{-7}	0.19	<i>MAP3K5</i>
1	3.67×10^{-7}	0.20	<i>MAP3K5</i>
9	3.64×10^{-7}	0.20	<i>ENSSSCG00000022338</i>
9	2.49×10^{-7}	0.20	<i>ENSSSCG00000022338</i>
9	6.02×10^{-7}	0.20	<i>ENSSSCG00000022338</i>
9	5.02×10^{-7}	0.20	<i>ENSSSCG00000022338</i>
13	2.87×10^{-7}	0.13	<i>HLCS</i>
13	3.07×10^{-7}	0.13	<i>HLCS</i>

- No SNPs with major effect on phenotypic variance (max = 0.2%)
- Several SNPs/genes have biological relevance to RFI

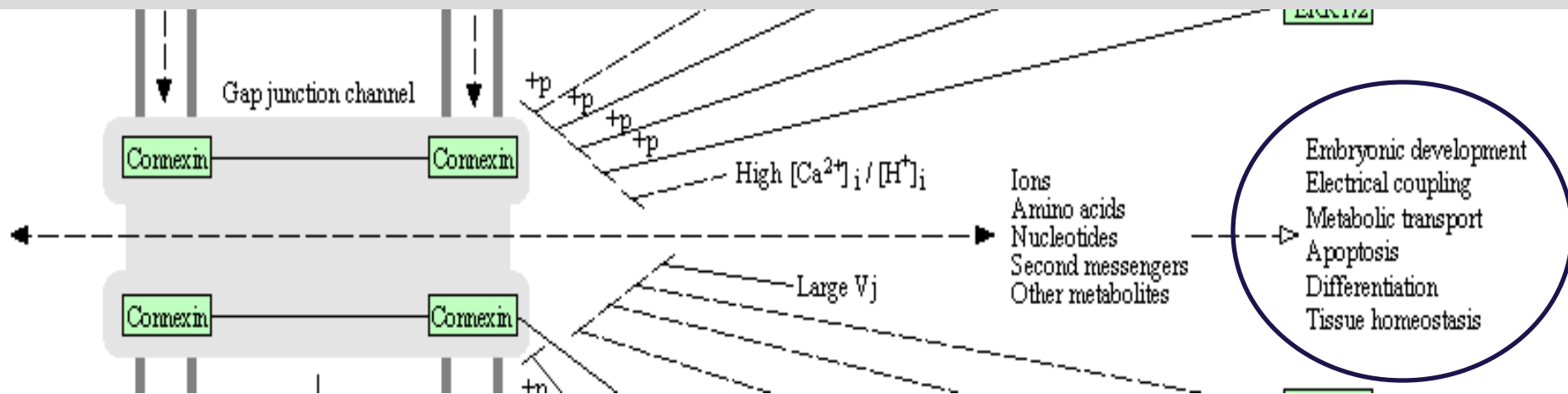
Results: KEGG-pathways associated with for RFIs

Pathway Name	Involved genes	p-value
Gap junction	<i>TUBA4A, ERK2, ADRB1, PRKG1, TUBA3D, TUBA1A</i>	0.002
Phosphatidylinositol signaling system	<i>PTEN, PIK3R5, PLCD4, PI4KA</i>	0.013
Insulin signaling pathway	<i>ERK2, SLC2A4, PIK3R5, PRKAR1A, PRKAG3</i>	0.031
...

How does gap junction pathway involve in RFIs?

GAP JUNCTION

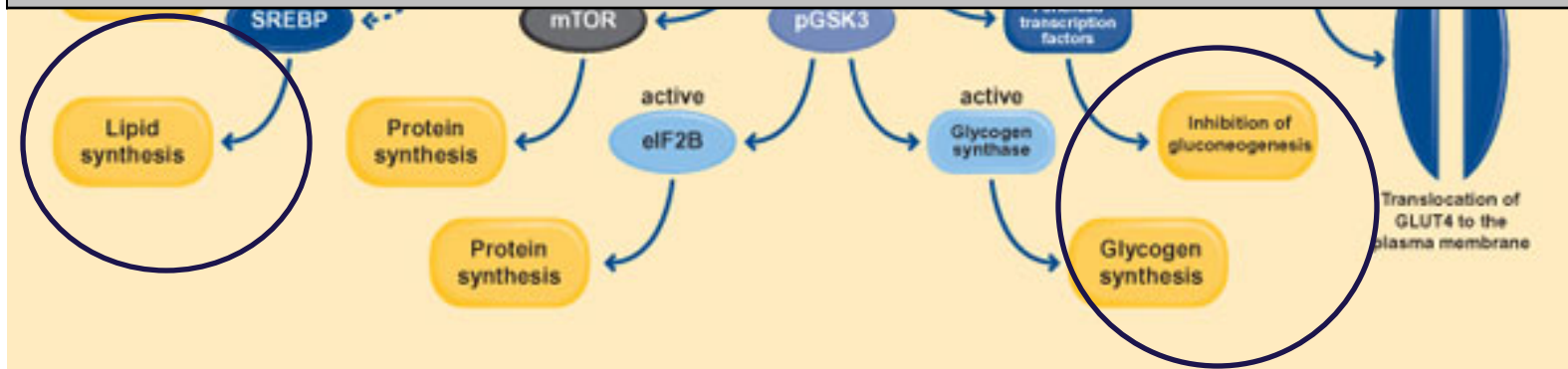
- Gap junction: communicating between the cytosolic compartments of adjacent cells
- Essential for metabolic transport, apoptosis and tissue homeostasis
- Candidate genes for RFI contribute to the background use of energy in the cell (as apoptosis, cell progression, ion channels and flux) (Barendse et al, 2007)



Insulin signalling pathway affecting RFI via glucose and lipid metabolism???



- Saltiel AR & Kahn CR. **Insulin signalling and the regulation of glucose and lipid metabolism.** Nature (2001)
- Glucose and lipid metabolism involved regulation of RFI (Lkhagvadorj et al (2009; 2010), Le Naou et al, (2012)...))



Conclusion

- Two important genomic regions on pig SSC 1 and 9 and some positional genes influencing RFI measures were detected
- The study indicates role of insulin signaling pathway and revealed some other possible pathways in regulation of RFI
- The results would be useful for further investigations of **key candidate genes** (?) for RFI and for development of biomarkers

Future perspectives:

OPEN ACCESS Freely available online

 PLOS ONE

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

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- Comparative mapping/fine mapping: Are QTL for RFI in pigs homologous with QTL for food intake/energy balance in human?
- GWAS for component traits of RFI, for RFI in other breeds
- Genomic prediction/selection for RFI in single/multiple traits

Acknowledgements

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Assoc. Prof. Thomas Mark

Dr. Anders Strathe

Thank you



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