Metabolomics

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Investigators Meeting
Genetics of Rheumatoid Arthritis in some Arab States
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“I have no competing interests to declare”
Transcriptomics
Proteomics

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Metabolomics …

… measuring the true end points of biological processes!
• Diagnostic ‘urine charts’ were widely used from the Middle Ages onwards

• These charts linked the colors, smells and tastes of urine to various medical conditions.

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Evolution of laboratory diagnostics
[Inborn errors of metabolism]

... are merely extreme examples of variations of chemical behavior

which are probably everywhere present in minor degrees

A.E. Garrod, Lancet, 1902
More than 100 years ago, Archibald Garrod already suggested a link between chemical individuality and predisposition to disease.
What makes us different?
What makes us different?
Phenotypes Association Studies

Genotype (SNPs)

Disease related phenotypes

Cardiovascular diseases
Obesity
Allergy
Other ...

Lifestyle & environment
Phenotypes

Metabotype

Genotype (SNPs)

Lifestyle & environment

Disease related phenotypes

cardio vascular diseases

obesity

allergy

other ...
KORA
Collaborative health research in the Region of Augsburg

General structure
- KORA: model of co-financing by partners, in addition to the basis funding of HMGU
- KORA: Custodian for data and biosamples
- KORA-gen: biobank for genetic studies

Resource
- Cohort study (**18,000 participants**, recruitment age 25 – 74 y)
  Recruitment 1985, 90, 95, 2000 (**S1-S4**); follow-up 1995, 2000, 05 (F3), 08 (F4)
- Interview, questionnaire, physical measurements, blood, urine, DNA
- Myocardial infarction registry (recruitment age < 75 y, since 1985)
KORA F3 pilot study: 40 diabetes / 60 controls measured on 3 different platforms

Total: 482 metabolites (423 unique)

Suhre et al., PLoS One, 2010
Metabolic Footprint of Diabetes: A Multiplatform Metabolomics Study in an Epidemiological Setting

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Suhre et al., PLoS One, 2010
GWAS with non-targeted metabolomics

DZD-funded fee-for-service measurements of 2800 samples from KORA & TwinsUK; 300 named & 220 unnamed compounds
GWAS with non-targeted metabolomics

Human metabolic individuality in biomedical and pharmaceutical research

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Suhre et al., Nature, September 2011
The “genetically determined metabotype” … aka “metabolic individuality”

- **Strong-responder**
  - MAF = 20%
  - major = 64%
  - hetero = 32%
  - minor = 4%

- **Poor-responder**

- **Non-responder**

GDMs provide access to:
- Personalized medication / pharmacogenomics
- Identification of gene-environment interactions
- Functional basis of complex disease associations
- Targets for therapeutic intervention
Hexagons: 37 genetically determined metabolotypes, displaying exceptionally large effect sizes of 10-60% per allele copy in 25 of these loci.

Suhre et al., Nature, 2011
NAT8 is a CKD risk locus

What is the role of N-acetylornithine in chronic kidney disease?
Diabetes risk locus GCKR associates with glucose / mannose ratio

- Mannose / glucose
  +10.1% per C-allele
  p=5.5x10^-53
  p-gain = 1.5x10^21

- Mannose
  -9.3% per C-allele
  p=8.4x10^-34

- Lactate
  +3.3% per C-allele
  p=1.2x10^-6

Mannose as a differential biomarker for diagnosis?

Point of intervention in diabetes care?
loci associated with traits of biomedical and pharmaceutical interest

Suhre et al., Nature, 2011
Conclusion

• Metabolic individuality is a major factor in gene-environment interaction
• Key to personalized therapy
• We run a virtual metabolomics core at WCMC-Q
• Using different metabolomics providers and the Helmholtz metabolomics core GAC
• A number of studies with metabolomics support are currently implemented in Qatar (diabetes, obesity, ovarian cancer, Ramadan, …)
Serum branched-chain amino acid to histidine ratio: a novel metabolomic biomarker of knee osteoarthritis

Guangju Zhai,1 Rui Wang-Sattler,2 Deborah J Hart,1 Nigel K Arden,3 Alan J Hakim,4 Thomas Illig,2 Tim D Spector1

Diagnostic properties of metabolic perturbations in rheumatoid arthritis

Rasmus K Madsen¹, Torbjörn Lundstedt²,³, Jon Gabrielsson³, Carl-Johan Sennbro⁴, Gerd-Marie Alenius⁵, Thomas Moritz⁶, Solbritt Rantapää-Dahlqvist⁵, Johan Trygg¹*

Results: RA patients were diagnosed with a sensitivity of 93% and a specific detection of 52 metabolites. Patients with RA or PsA could be distinguished with a specificity of 94%. Glyceric acid, D-ribofuranose and hypoxanthine were increased. Threonine and threonine acid, methionine, cholesterol, asparagine and threonine were all decreased in RA patients compared to controls.
Proposal:

• Collect blood, urine, and saliva
  – Larger quantity than original proposal (30ml vs. 10ml)
  – EDTA, Citrate, Serum, PAXtube (mRNA expression)

• Compatible to other WCMC-Q studies
  – with full Clinical Research Support

• Urine & Saliva collected in all other studies
  – Metabolomics studies in combination is a “First”
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