Nutrigenetics and Nutrigenomics

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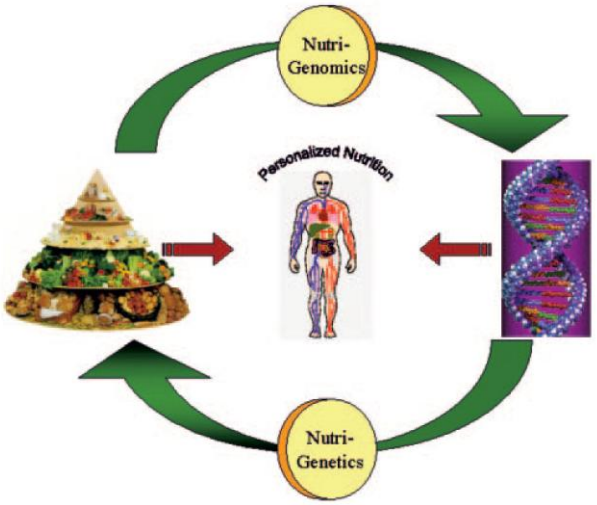
Nutrigenomics and Nutrigenetics



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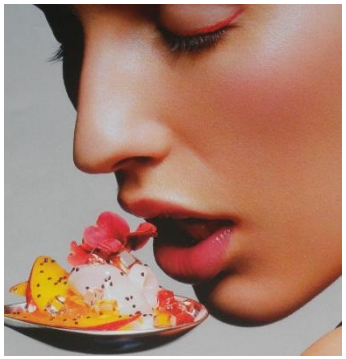
DIfE

- **Nutrigenetics:** the science of the effect of genetic variation on dietary response
- **Nutrigenomics:** the science of the effect of nutrients and bioactive components on gene expression
- **Aim** is to obtain a better understanding of nutrient-gene interactions depending on the genotype
- **Ultimate goal** is to develop **personalised nutrition strategies for optimal health and disease prevention**

Nutrigenomics and Nutrigenetics



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- **The biological effects of nutrients and food bioactives are elicited by interdependend physiological processes, including**
- absorption, transport,
- biotransformation,
- uptake, binding, storage
- excretion, and
- cellular mechanisms of action, such as energy metabolism, binding to nuclear receptors or regulating transcription factors.

May be affected by genetic variants exerting functional effects or affecting gene expression level

Mutual interactions of metabolites, hormones and phenotype / disease states

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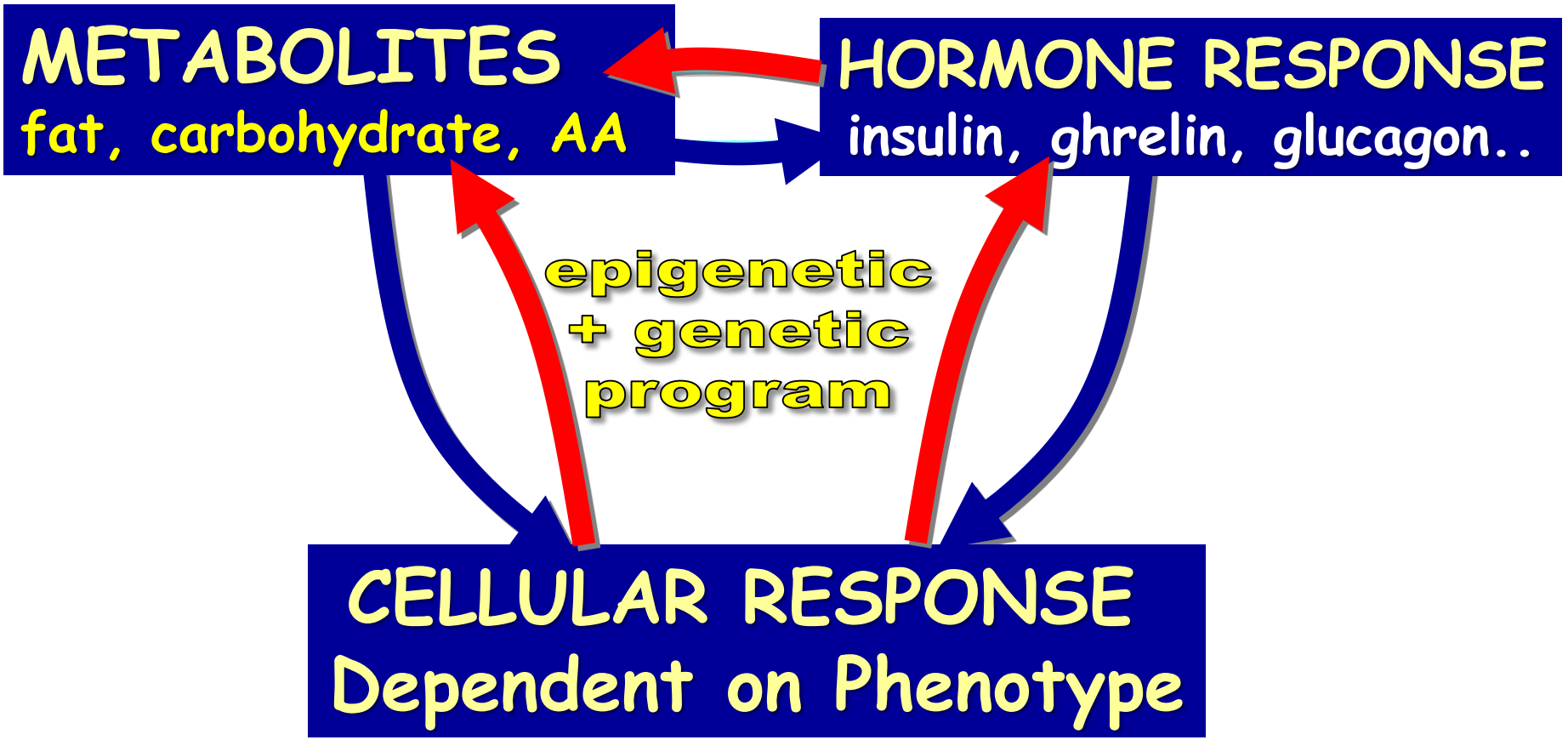
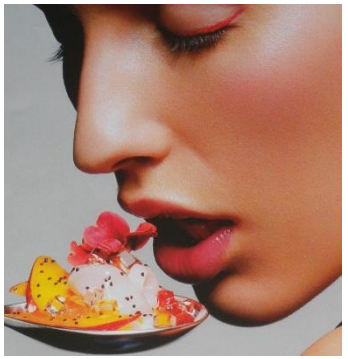
DIfE



Nutrigenomics and Nutrigenetics



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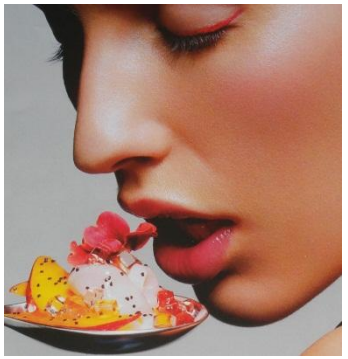
- The key challenge is to determine whether it is possible to utilise this information meaningfully to provide reliable and predictable personalised dietary recommendations for specific health outcomes

- Who will care? Will such predicitions be of sufficient magnitude and reliability to be provide a convincing argument to change one's life style (smoking as example) ?

Nutrigenomics und Nutrigenetics:



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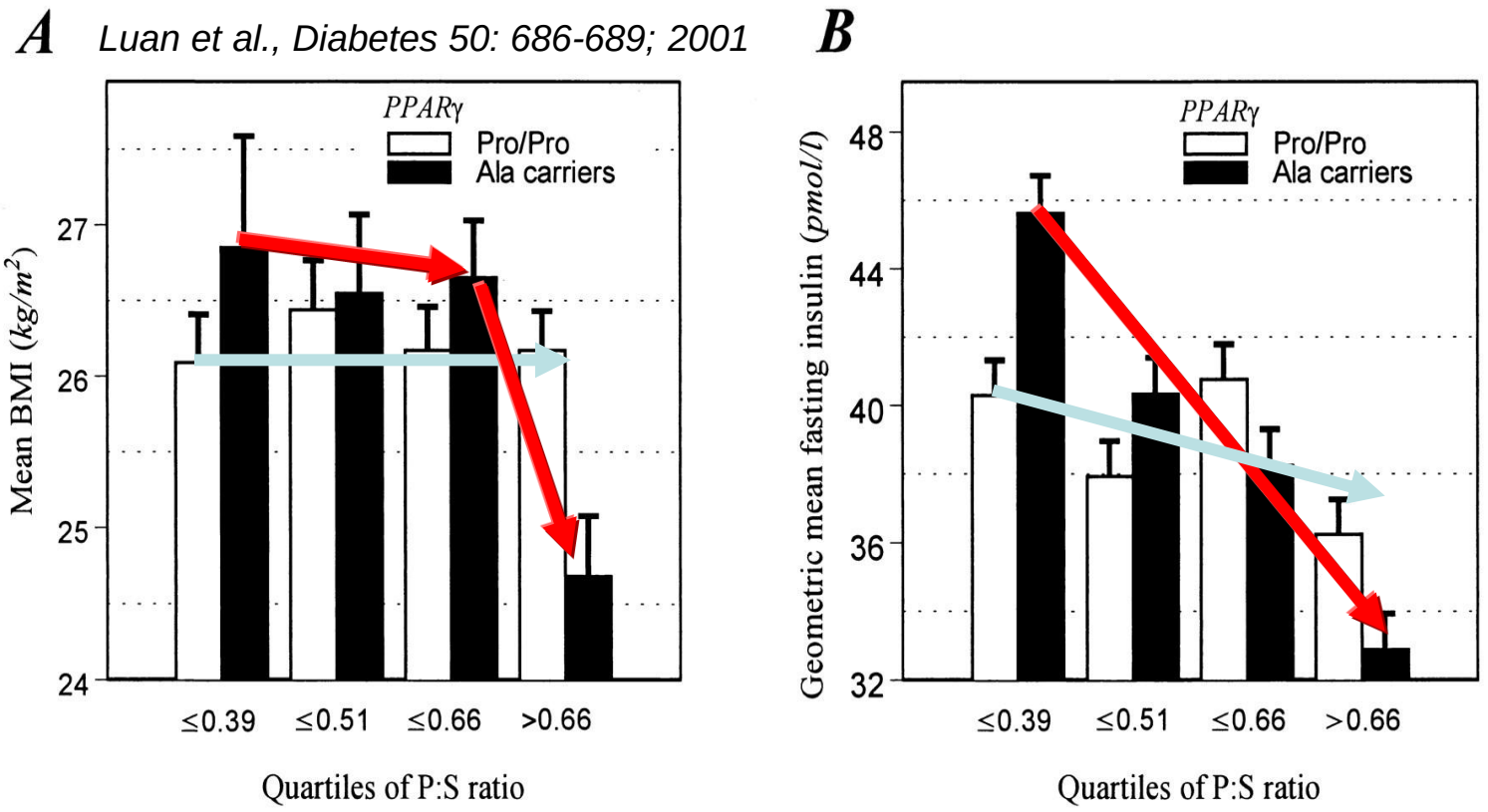
Candidate GENE effects

Candidate gene strategy

Technique: fasting insulin / BMI / pattern of fat ingestion

PPARγ2 - Pro12Ala Polymorphism: degree of fat saturation in food determines action on insulin sensitivity



L-FABP and hepatic glucose metabolism

Weickert et al., Am J Physiol 2007

L-FABP is highly expressed in hepatocytes

L-FABP affects lipid transport and lipid metabolism

L-FABP KO mouse is resistent to obesity under high fat diet (Newberry et al. Hepatology 2006)

Ala-Allele in position 94 in L-FABP associates with lower BMI (Brouillette et al. J Hum Genet 2004)

- **=> Invite subjects with the Ala/Ala or Thr/Thr phenotype for a detailed metabolic characterization. Select subjects from the „Metabolic Syndrome Berlin Potsdam“ cohort (n=2700)**

A Thr^{94}Ala mutation in human liver fatty acid-binding protein contributes to reduced hepatic glycogenolysis and blunted elevation of plasma glucose levels in lipid-exposed subjects

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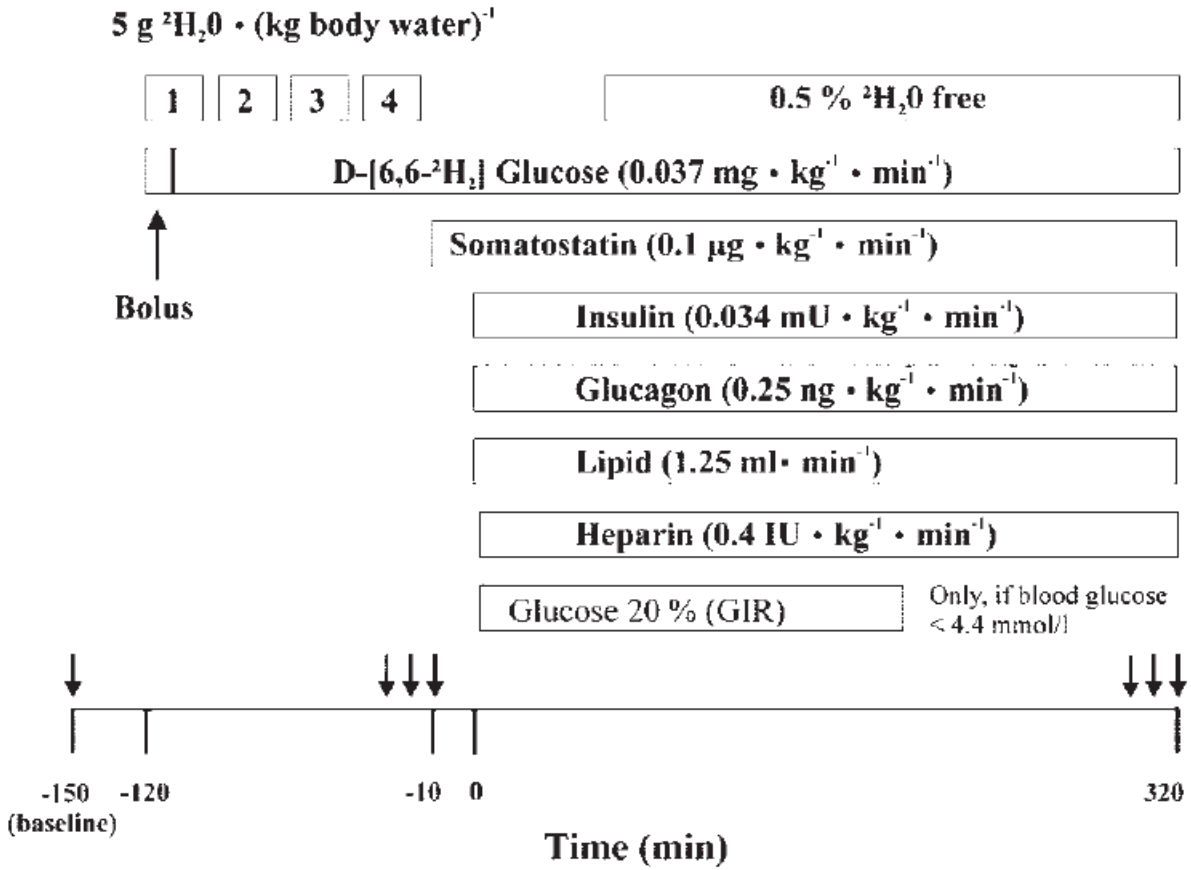
Weickert et al., Am J Physiol 2007

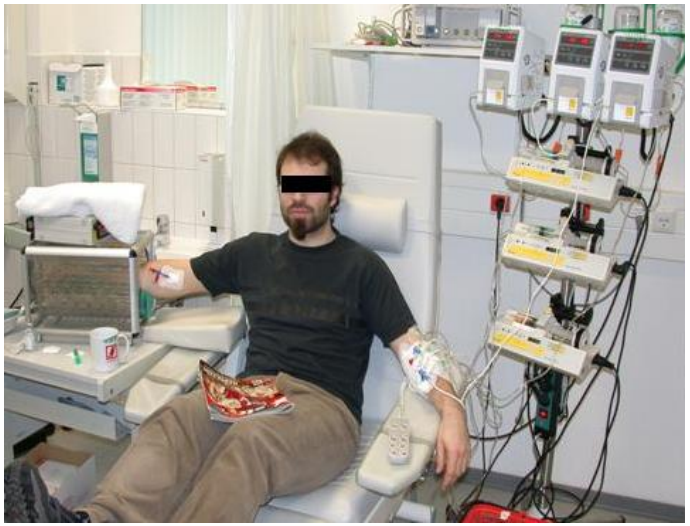
DIfE

Does the Ala94-mutation of FABP affect lipid induced hepatic glucose production?
Study design: n=2 x 9 homozygous subjects Thr/Thr or Ala/Ala



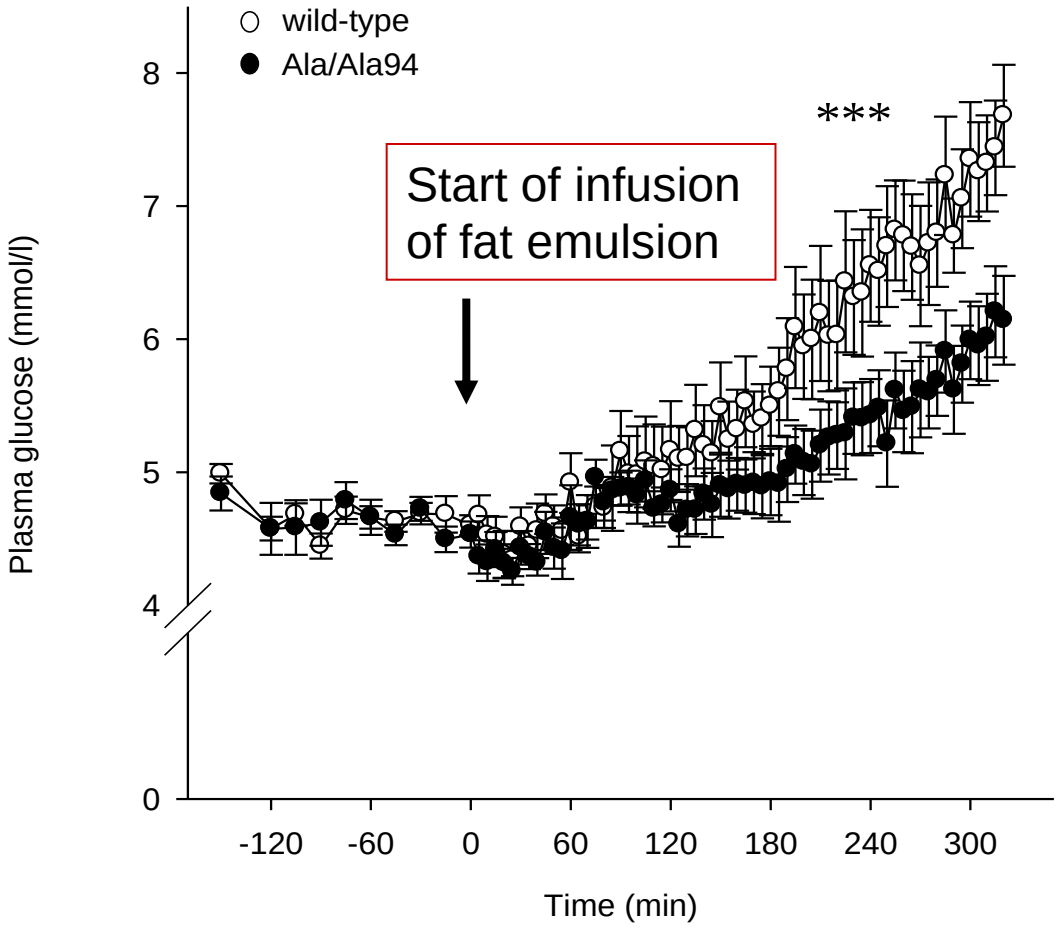
Effect on BMI:

Thr/Thr: 29.5 BMI wt
Thr/Ala: 28.6 BMI
Ala/Ala: 28.2 BMI
p < 0.003; n= 1453



L-FABP and hepatic glucose production: infusion of lipids induces increased glucose production the carriers of the wild type allele Thr^{94}/Thr^{94}

Weickert et al., Am J Physiol 2007



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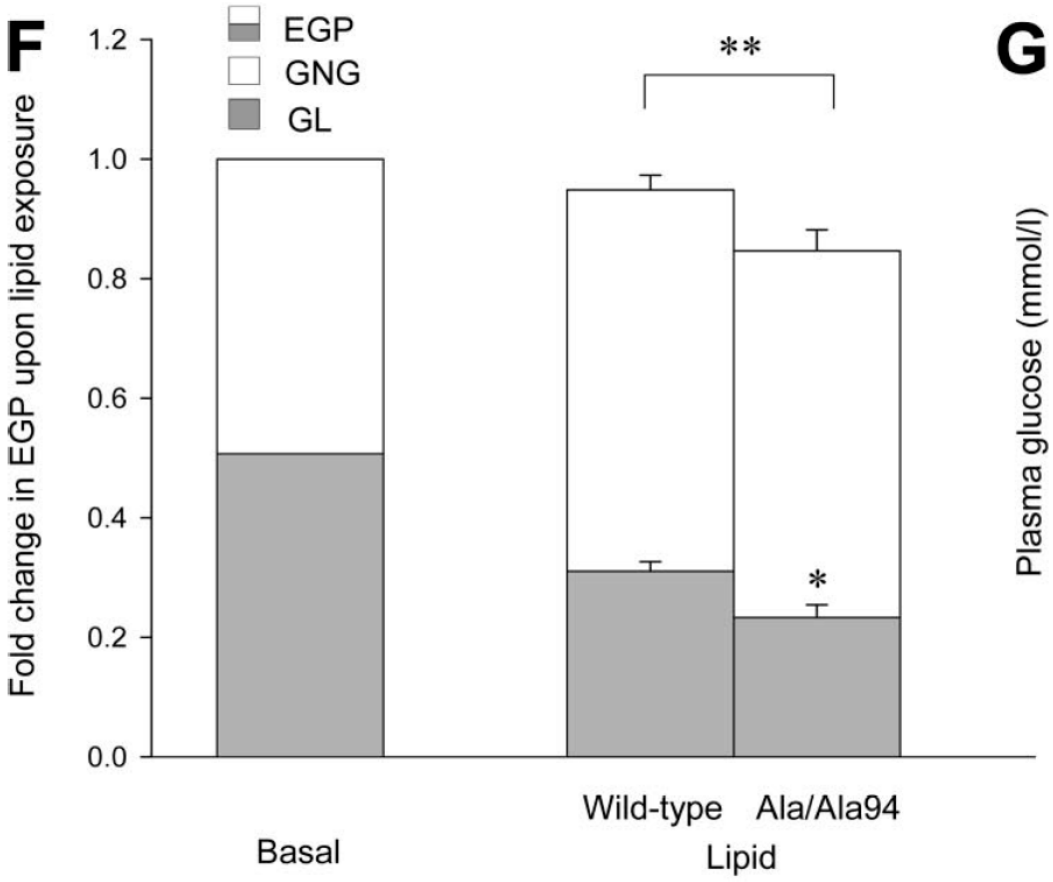
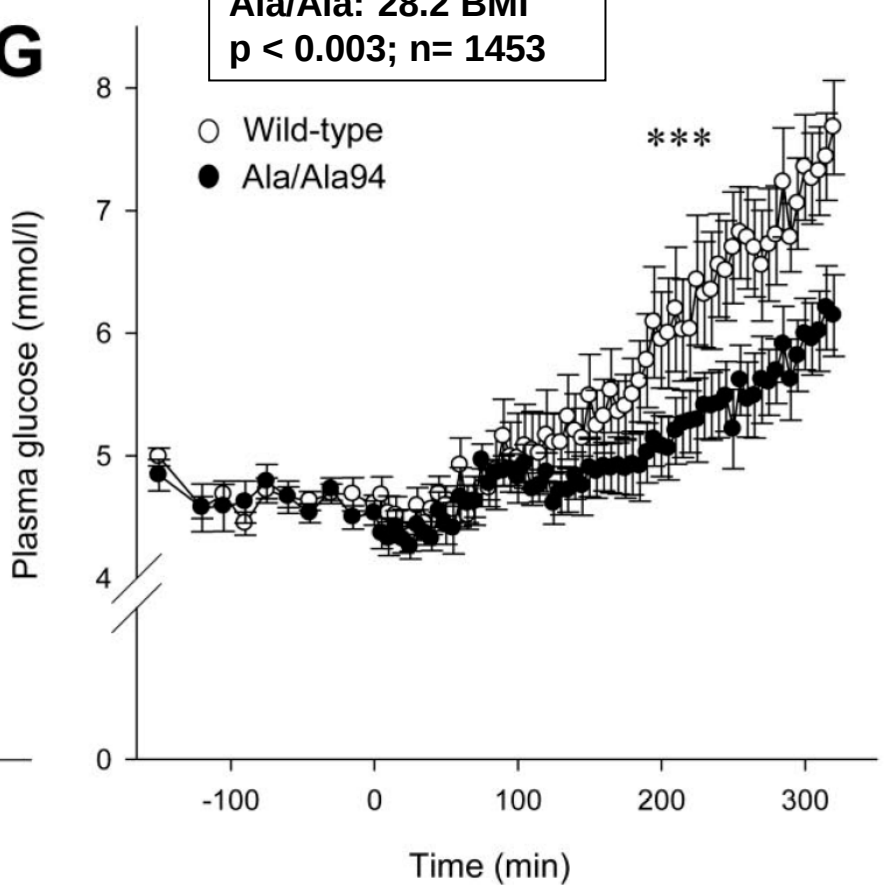
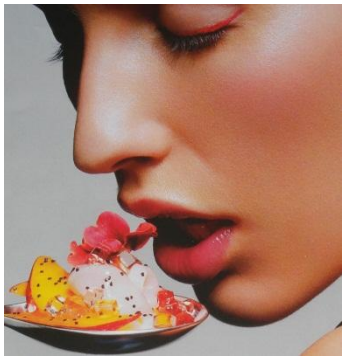




Nutrigenomics und Nutrigenetics:



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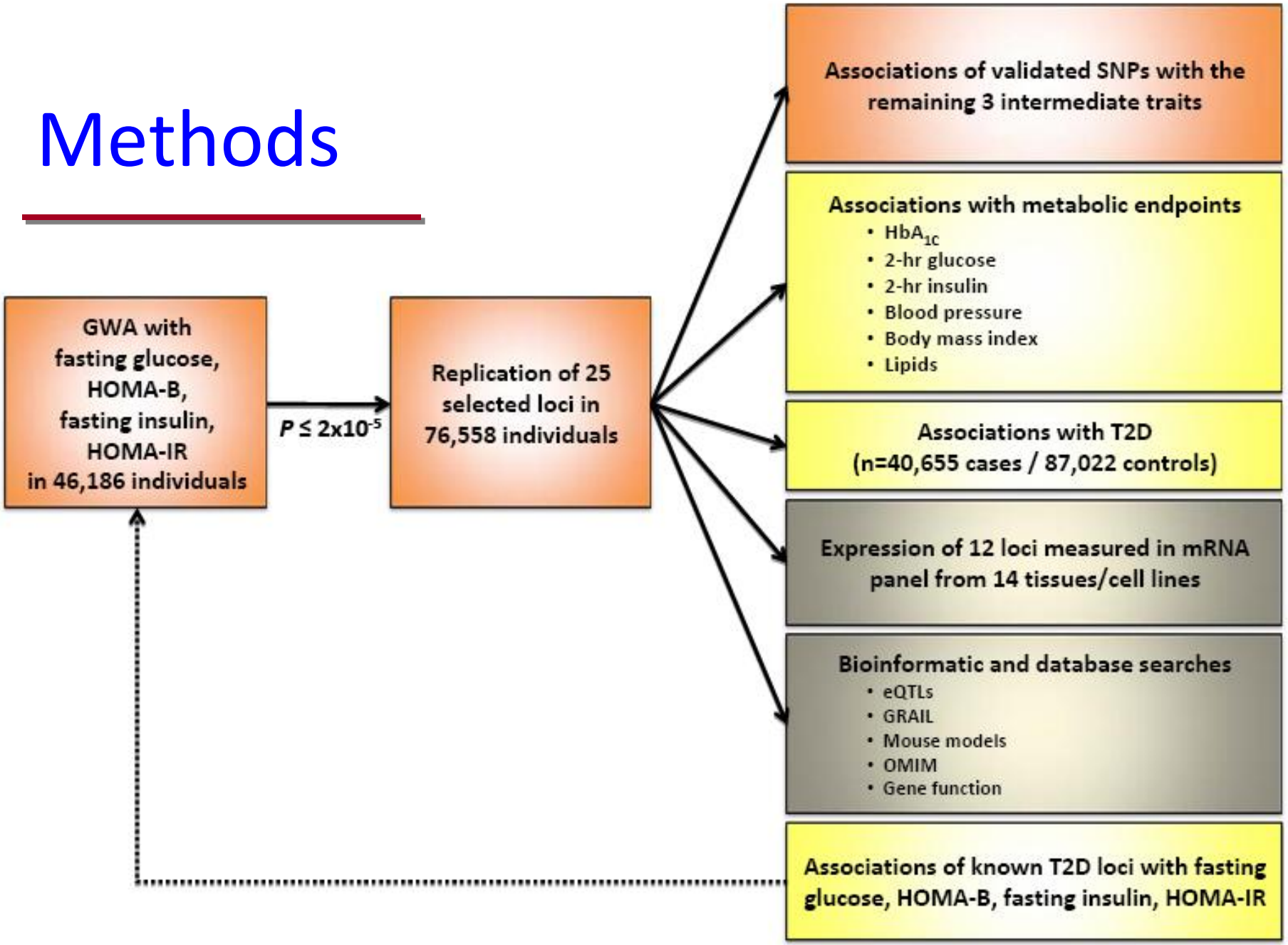
Genome Wide Association Searches
GWAS

Meta-Analysis of Glucose and Insulin-related traits Consortium

- MAGIC: large-scale meta-analyses of genome-wide association studies (GWAS) in persons without diabetes
- Aims:
  - identify genetic loci influencing fasting glycemic traits:
    - fasting glucose (FG)
    - fasting insulin (FI)
    - fasting indices of β-cell function (HOMA-B) and insulin resistance (HOMA-IR)
  - investigate additional metabolic impact of these loci
  - understand variation in the physiological range and describe the overlap with variants that influence pathological variation and T2D risk

Methods


GWA with fasting glucose, HOMA-B, fasting insulin, HOMA-IR in 46,186 individuals
P ≤ 2x10-5
Replication of 25 selected loci in 76,558 individuals
Associations of validated SNPs with the remaining 3 intermediate traits
Associations with metabolic endpoints
• HbA1c
• 2-hr glucose
• 2-hr insulin
• Blood pressure
• Body mass index
• Lipids
Associations with T2D (n=40,655 cases / 87,022 controls)
Expression of 12 loci measured in mRNA panel from 14 tissues/cell lines
Bioinformatic and database searches
• eQTLs
• GRAIL
• Mouse models
• OMIM
• Gene function
Associations of known T2D loci with fasting glucose, HOMA-B, fasting insulin, HOMA-IR

Replication in ~77,000 samples

Amish (n~1,000)
ARIC (n~7,300)
BHS (n~4100)
BotniaPPP (n~3,600)
BWHHS (n~3,500)
Caerphilly (n~1,000)
deCODE (n~8,000)
DIAGEN (n~1,360)
EFSOCH (n~1,300)
Ely (n~1,600)
FamHS (n~550)
Fenland (n~1,400)
French (n~700)
FUSIONs2 (n~1,000)
GHRAS (n~800)
GenomeEUtwin (n~800)
Hertfordshire (n~2,100)
Health2000 (n~6,400)
Inter99 (n~5500)
NHANES (n~2,000)
MesyBePo (n~1,600)
METSIM (n~3,500)
OBB (n~1,300)
Partners/Roche (n~630)
PIVUS (n~900)
SEGOVIA (n~2,100)
SUVIMAX (n~1,600)
TwinsUK (n~1,800)
UKT2DGC (n~3,600)
ULSAM (n~950)
Umea (n~3,000)
WASHS (n~900)
Whitehall II (n~5,500)
French children (n~600)
GENDAI (n~1,000)

- Joint meta-analysis: discovery and replication samples
- Included a total of
  - 122,743 participants for FG
  - 98,372 for FI, HOMA-IR and HOMA-B
- Established genome-wide significant ($P<5x10^{-8}$) associations

Many thanks to many authors

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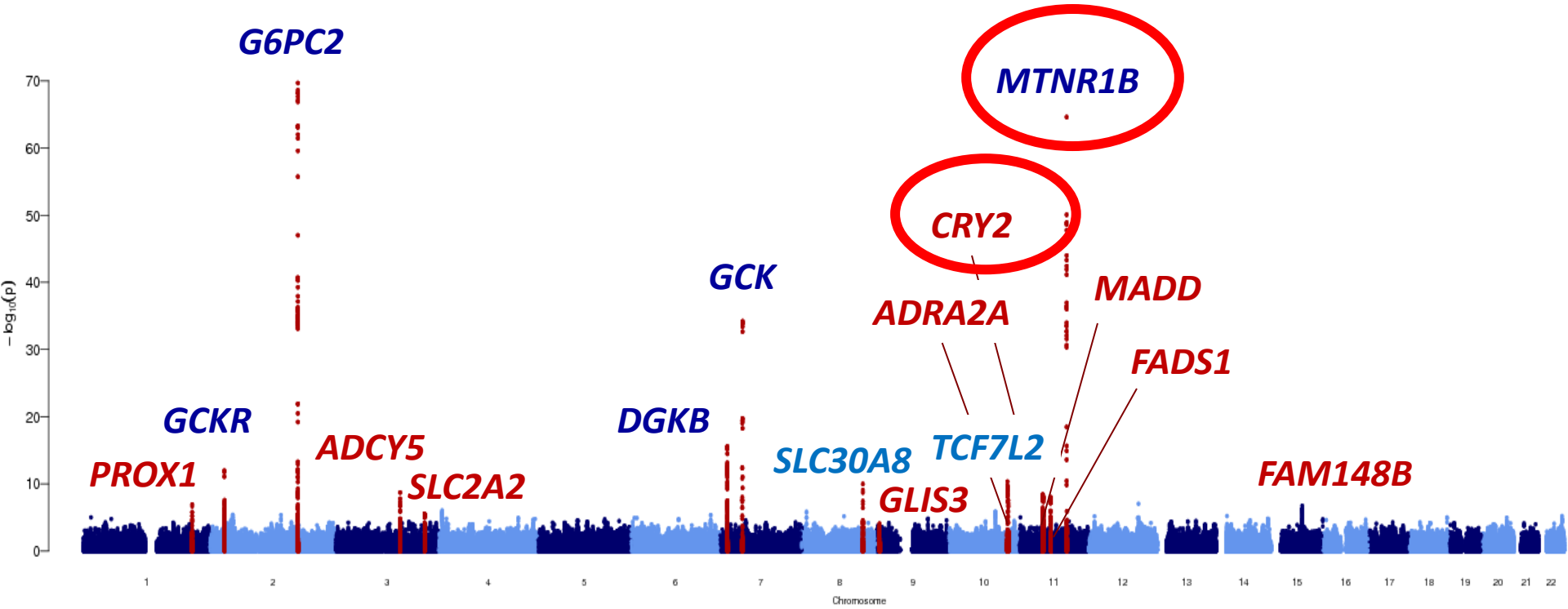
Fasting glucose meta-analysis

- 9 novel loci identified



Note: Hits represented by closest mapping gene, but this does not imply causality

Dupuis*, Langenberg*, Prokopenko*, Saxena*, Soranzo* *et* 302 for MAGIC, *Nat Genet* (in press)

~10% of FG heritability explained

0.4 mmol/L (7.2 mg/dl)

Dupuis* et al., 2010

Associations of Common Genetic Variants With Age-Related Changes in Postload Glucose

Evidence From 18 Years of Follow-Up of the Whitehall II Cohort

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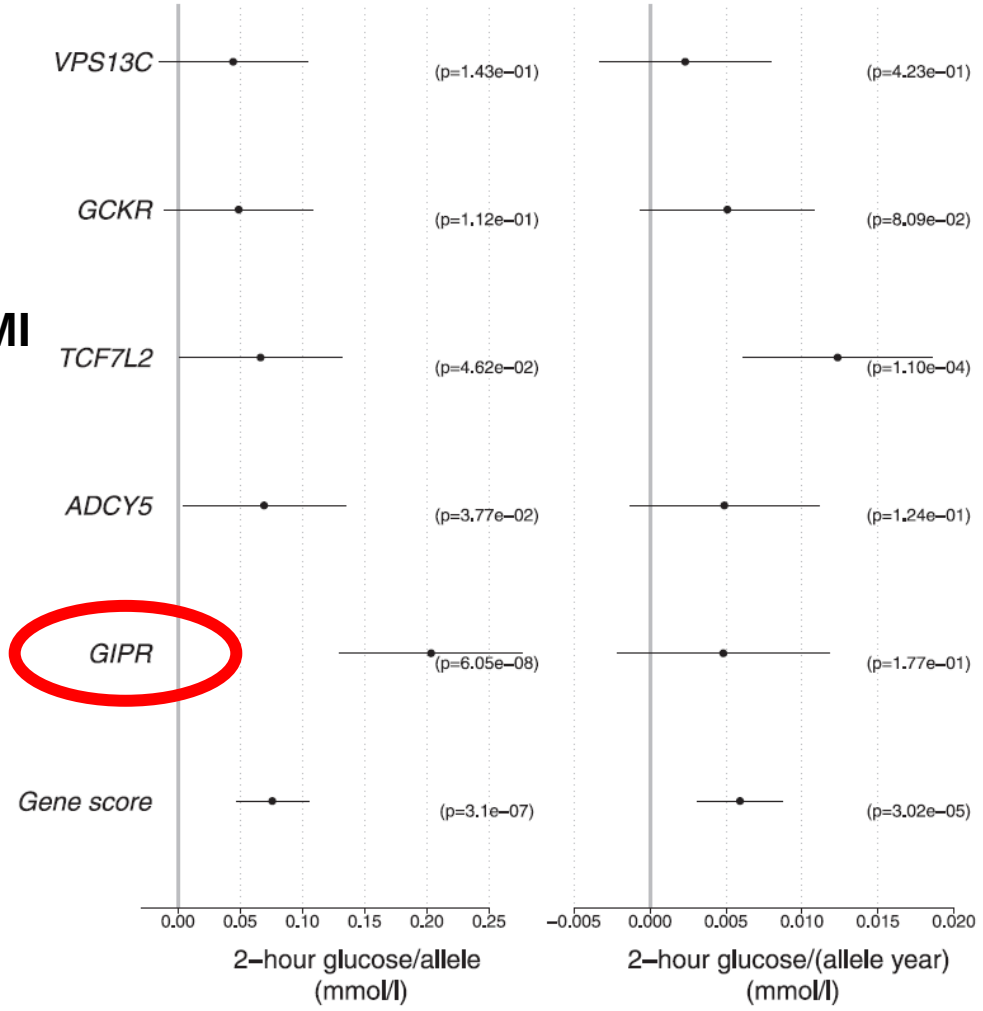
Jensen et al., Diabetes 2011

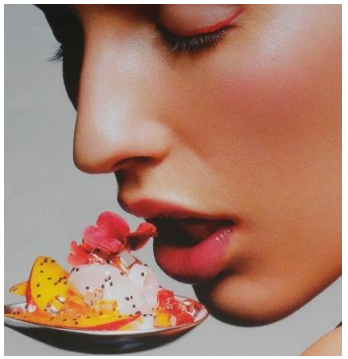
DIfE

Impact at age 55
Corrected for BMI



Increase per year

Nutrigenomics und Nutrigenetics: current situation



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- Studies show numerous gene variants affecting metabolic regulation
- Effects of single variants are small
- Studies do not allow nutritional recommendations based on gene variants yet
- Functional studies needed

GIP-receptor gene variants are highly associated with 2h glucose in oGTT and risk of Type 2 Diabetes

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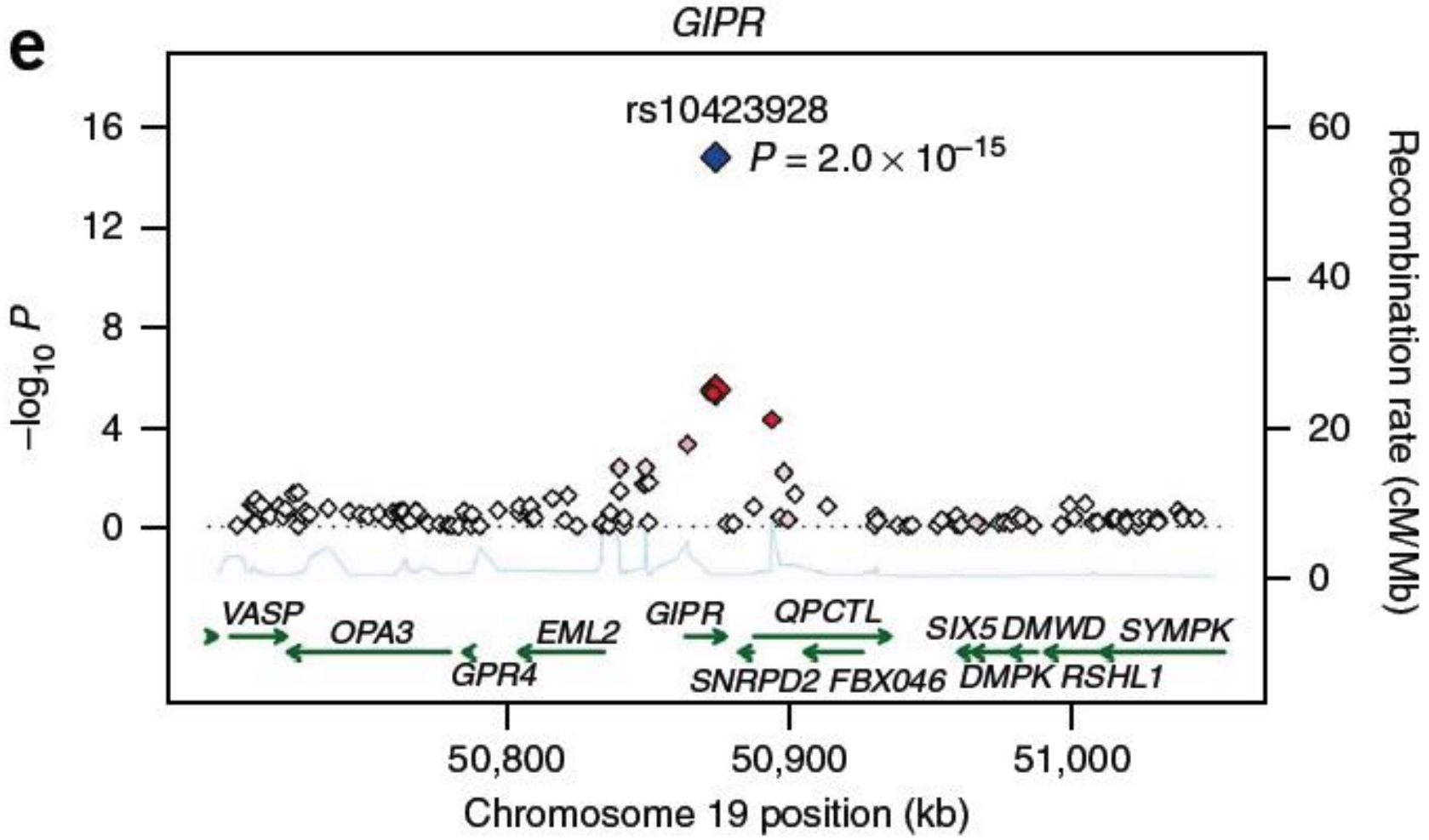
Saxena et al., Nat Genetics 2010

DIfE



What is the role of GIP (glucose induced insulinotropic peptide) in human adipose tissue ?

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Gögebakan, Osterhoff, Rudovich, Isken & Pfeiffer

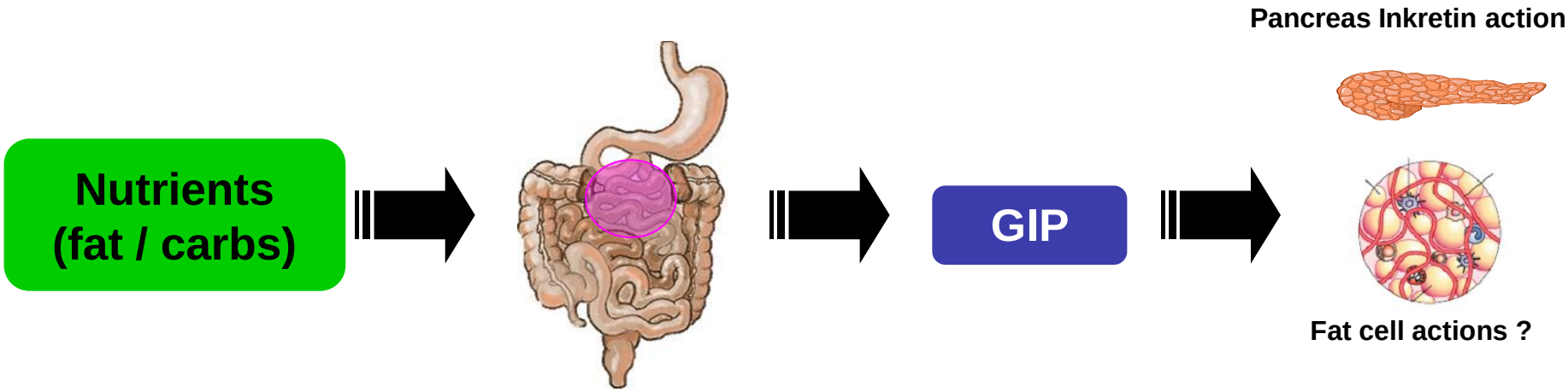
DIfE

YAEGTFISDYSIAMDKIHQ

WDNKKGKQALLWNVFDQ

KHNITQ

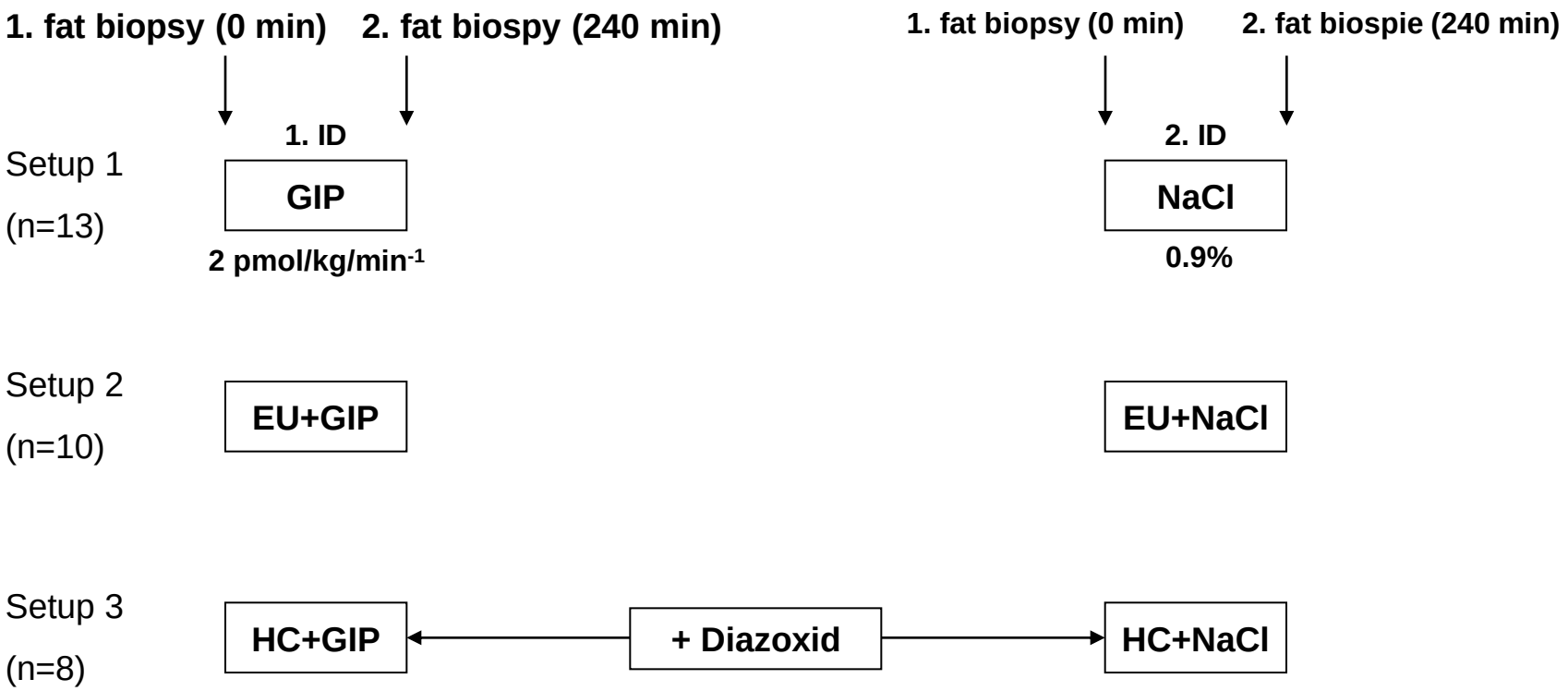
GI tract



GIP treatment of volunteers

Clinical, randomized, placebo-controlled cross over study

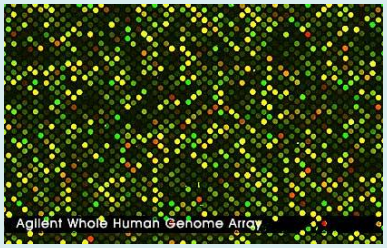
Subjects: 17 healthy overweight men, BMI 28-40 kg/m^2, age 30-65 years with normal glucose tolerance



Insulin infusions: 40 mU/kg/min^{-1}
ID: intervention day
EU: euglycaemic-hyperinsulinaemic clamp
(blood glucose concentration: 80 mg/dl)
HC: hyperglycaemic-hyperinsulinaemic clamp
(blood glucose concentration: 140 mg/dl)

Acute effects after 240 min intervention

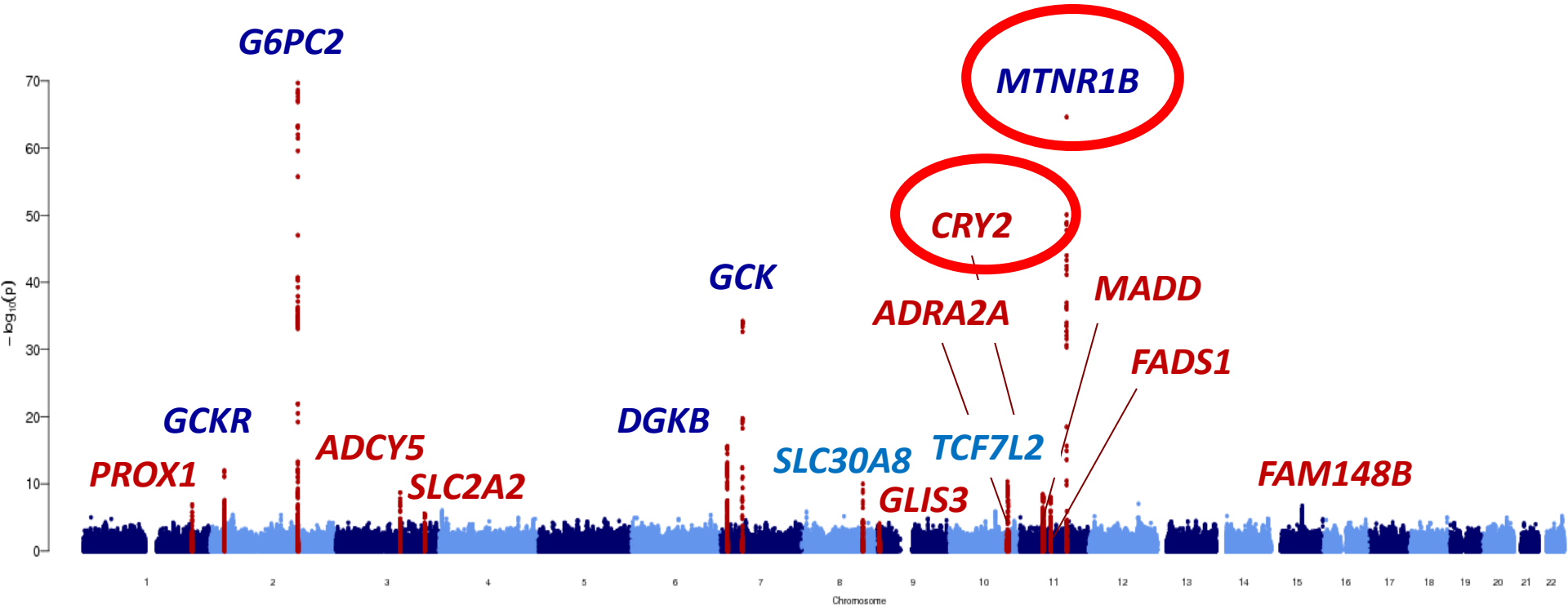
GIP treatment of human volunteers



- Fat biopsy => processing for analysis of transkriptome
- Hybridization to a total number of 100 Agilent 60-mer Whole Human Genome (4x44K) single-color DNA microarrays
- Calculation of gene expression fold changes with Agilent GeneSpring GX software
- Statistical evaluation by iterative group analysis method to determine regulated pathways

Fasting glucose meta-analysis

- 9 novel loci identified



Note: Hits represented by closest mapping gene, but this does not imply causality

Dupuis*, Langenberg*, Prokopenko*, Saxena*, Soranzo* *et* 302 for MAGIC, *Nat Genet* (in press)

Clock genes – the meter of metabolism (Green et al.,Cell 2008)

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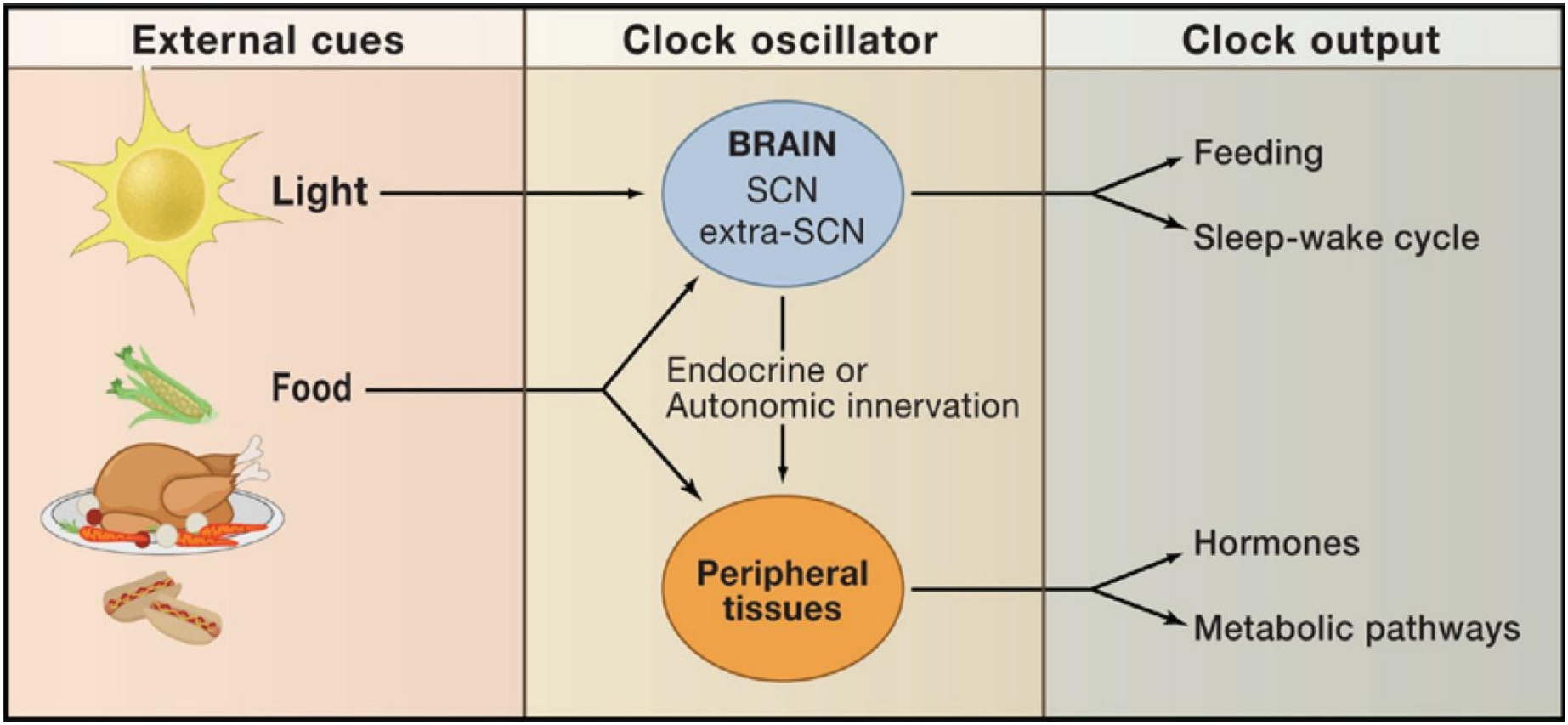

Disruption of clock gene expression causes obesity and metabolic disturbances

Core Clock Circadian Genes Coordinate Metabolism

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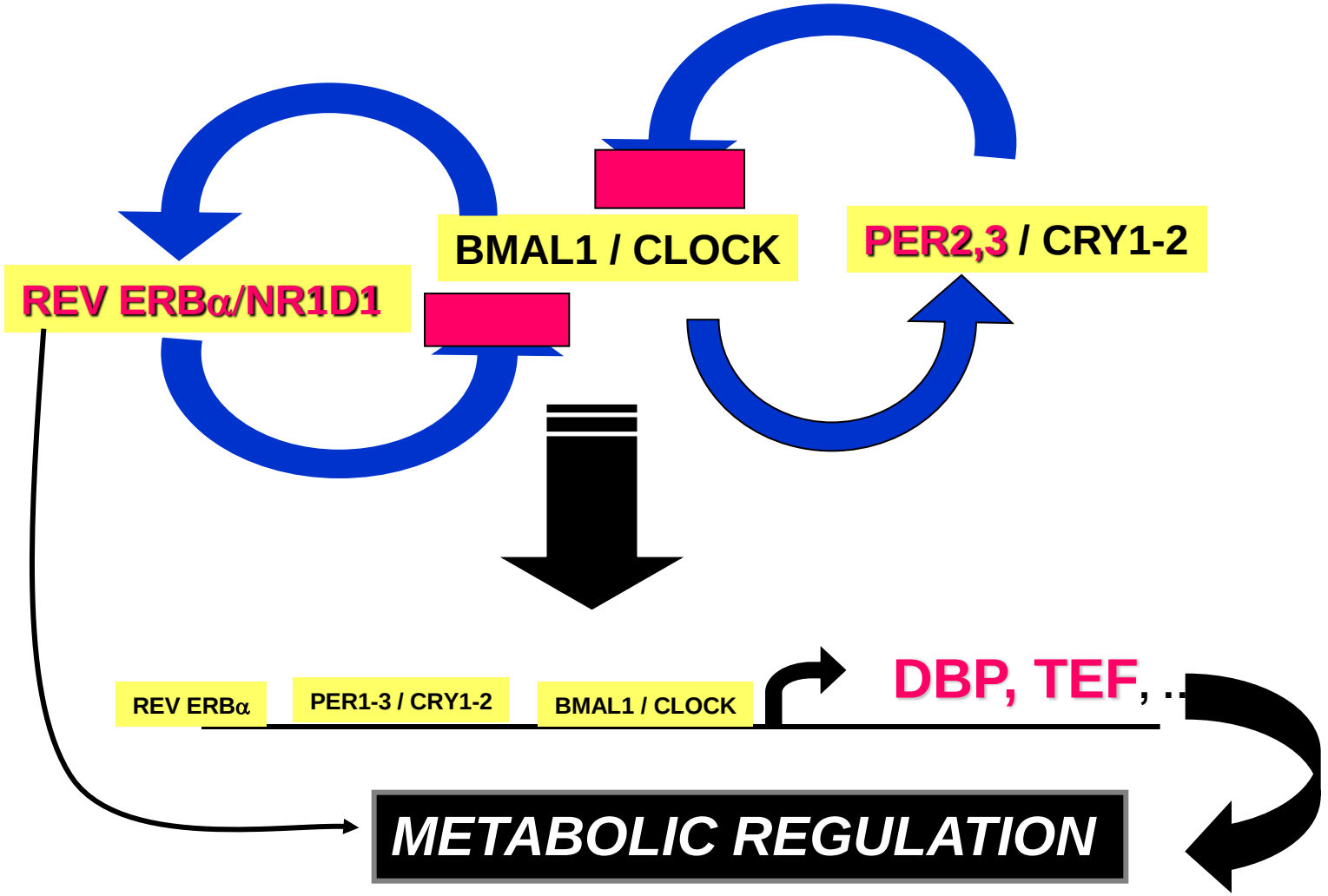
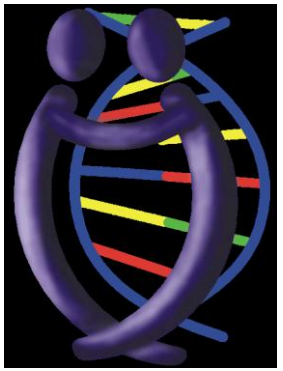


NUGAT:
NUtriGenomic Analysis in Twins



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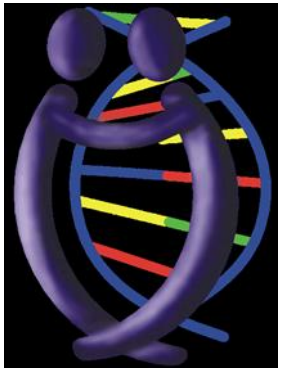
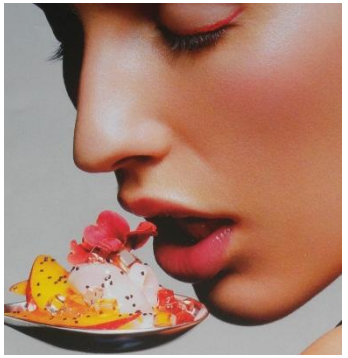
DIfE

- **Estimation of genetic effect size on nutrition induced genetic & metabolic responses**
- **45 twin pairs (mono- und dizygotic)**
- **Sequential controlled nutritional intervention for 6 weeks:**
  1. **High carb (55%) low fat (30%) healthy pattern,**
  2. **High saturated fat diet (45%) high GI carbs**
  3. **High protein, high fiber**
- **Extensive phenotyping of nutritional responses: IVGTT, fat biopsy, monocyte preps, ^{1}H MRI spectroscopy liver fat, gene expression arrays, epigenetics analysis, biomarkers**

NUGAT: NUtriGenomic Analysis in Twins





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DIfE

- **Primary hypothesis: nutrition will affect insulin sensitivity in a genetically determined manner differing between twin pairs (ivGTT and MTT)**
- **Secondary/explorative hypothesis: Nutritional interventions will result in genetically determined responses of biomarkers that differ between individual twin pairs but not witin twin pairs**
  - **Hormone responses**
  - **Hepatic fat**
  - **Cytokines / chemokines**
  - **Transcriptome in fat and monocytes**
  - **Metabolome**

The NUGAT study

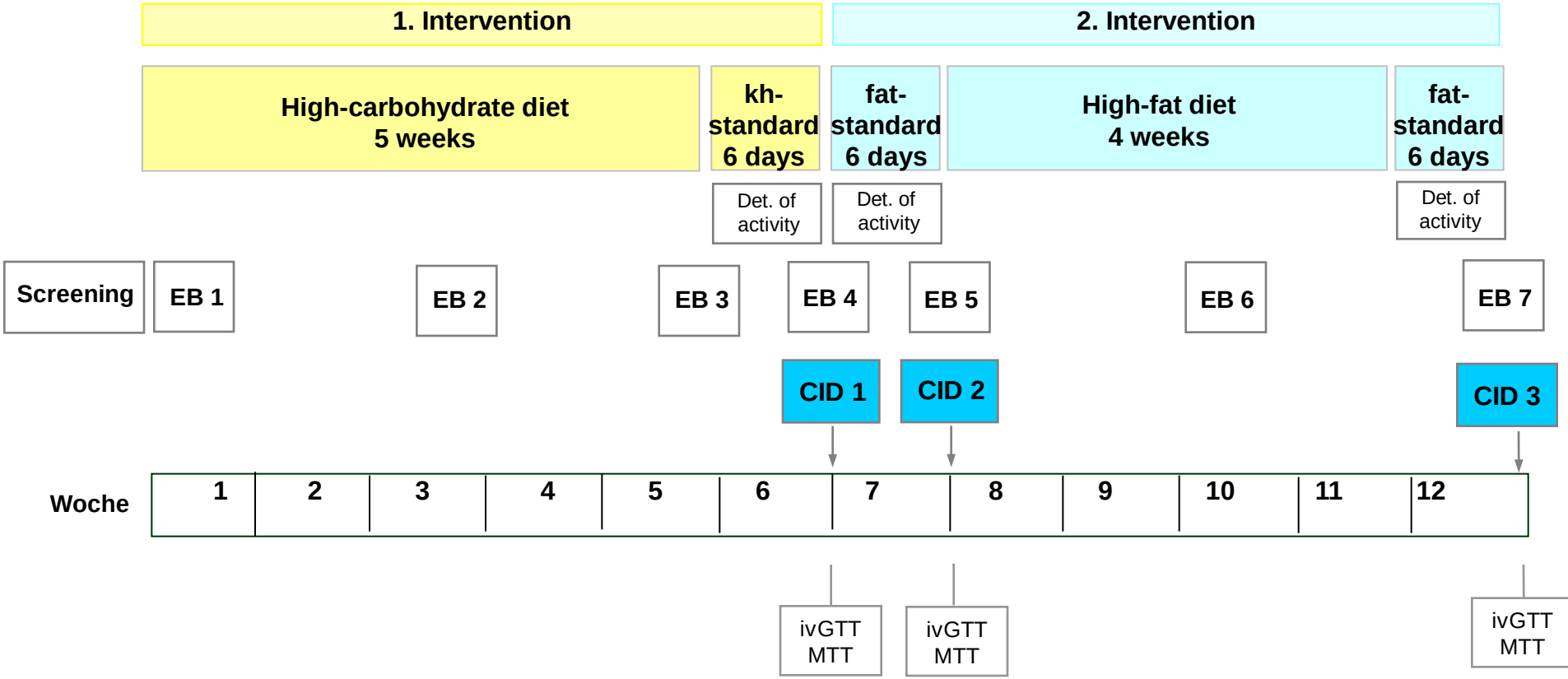
= **NU**tri**G**enomics **A**nalysis in **T**wins (NUGAT)

High-carbohydrate diet: 55% carboh., 15% prot., 30% fat
High-fat diet: 40% carboh., 15% prot., 45% fat

CHARITÉ

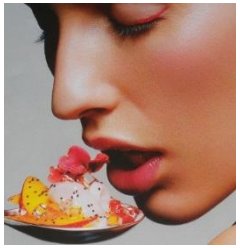
DIFE

Isocaloric diet !!



CID: Clinical Investigation Day
EB: Ernährungsberatung / dietary consultation
ivGTT: intravenous glucose tolerance test
MTT: meal time test

Epigenetic mechanisms modify DNA



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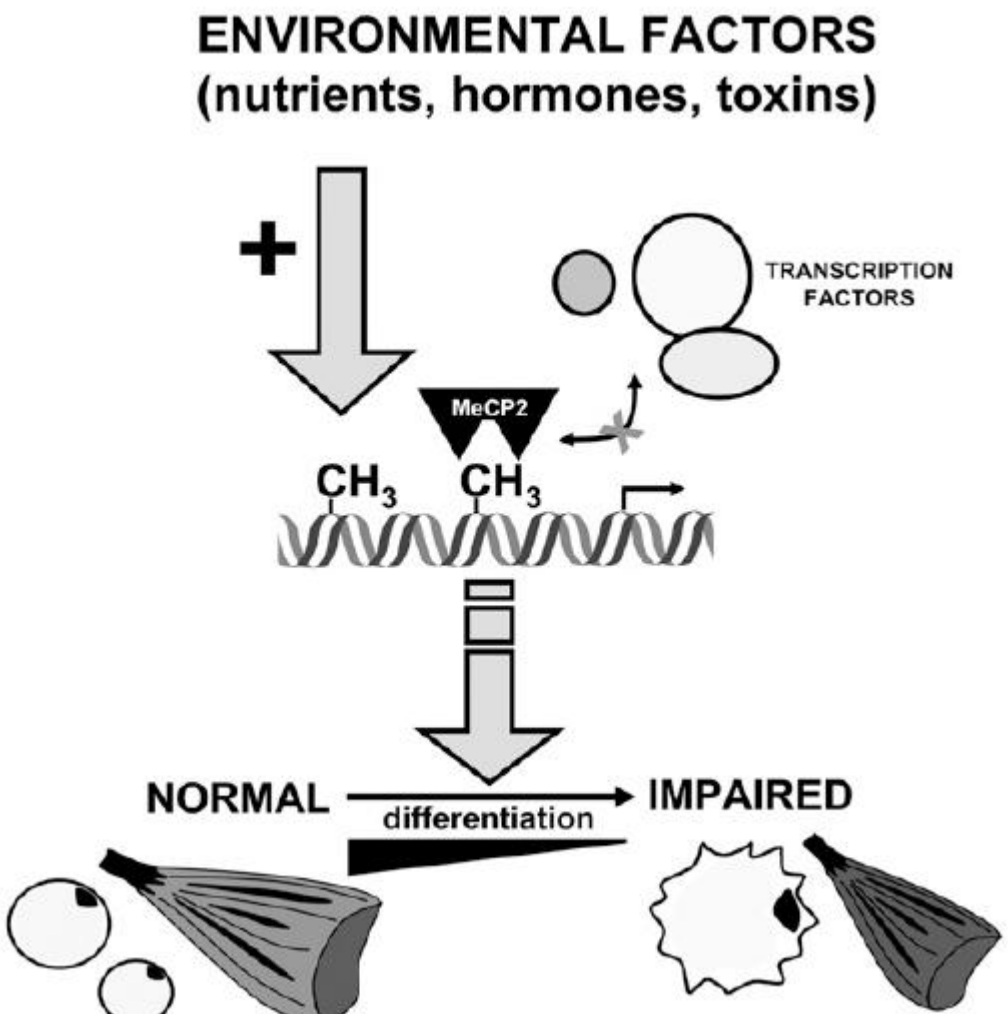
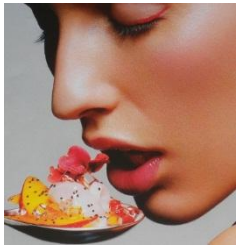
Barres & Zierath, AJCN 2011

DIfE



Estimated global association between a summary score reflecting a dietary pattern with a high content of fruit and dairy products, and low content of white bread, processed meat, margarine, and soft drinks and annual change in ‘‘waist circumference for a given body mass index (DWCBMI, cm/y)’’



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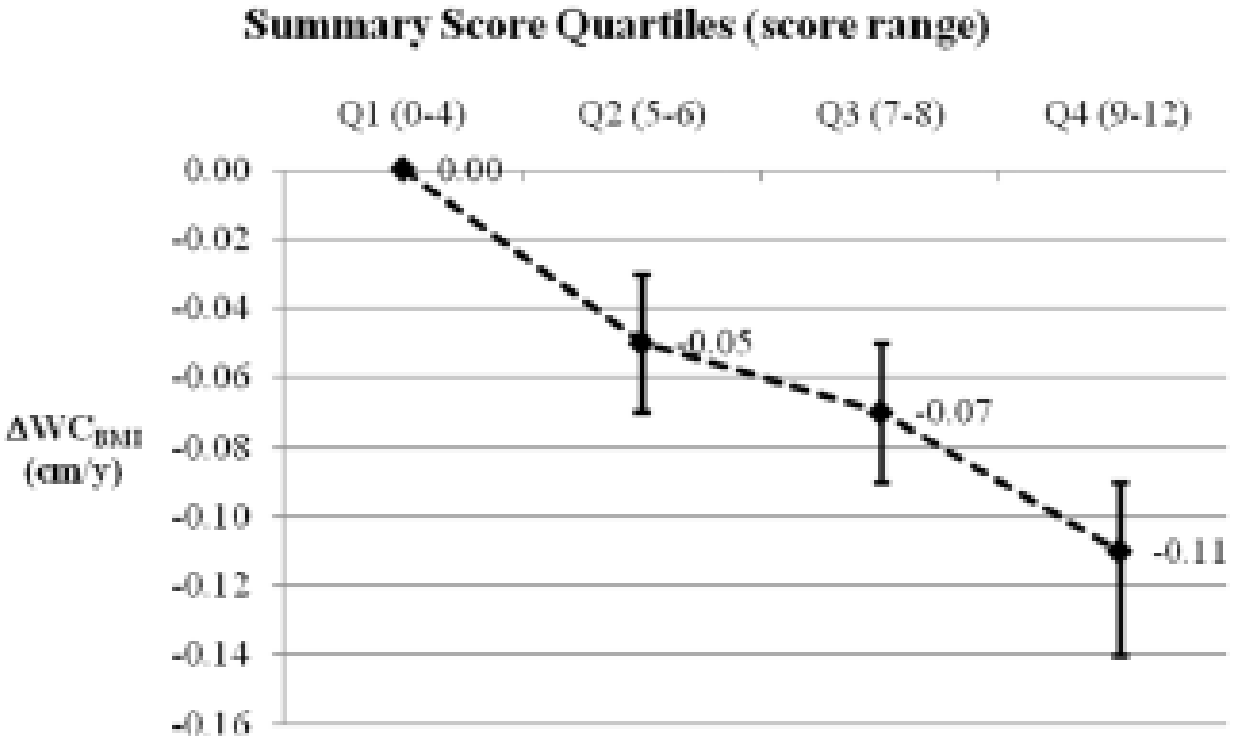
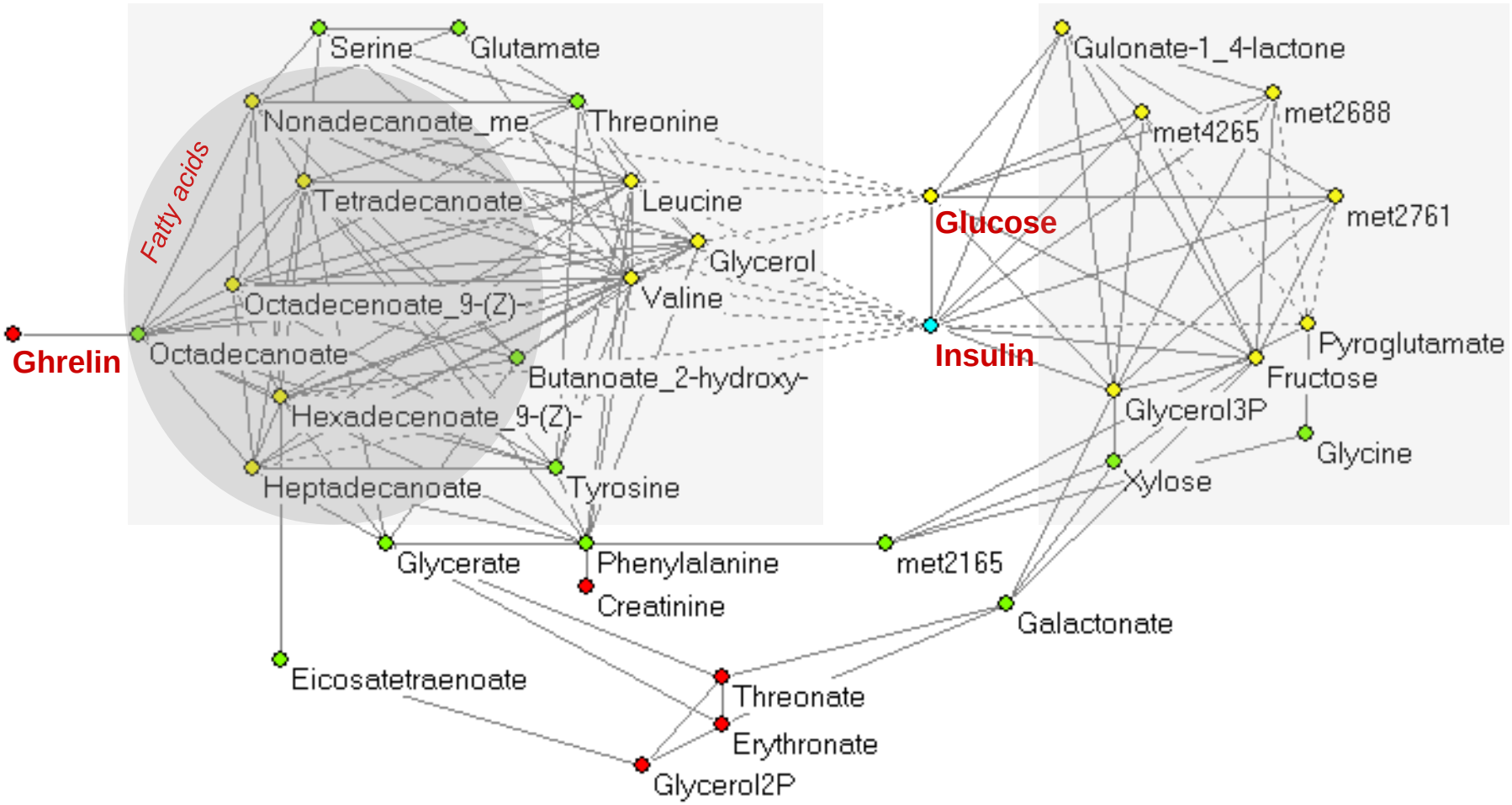
Romaguera et al., PLOS one 2011

DIfE

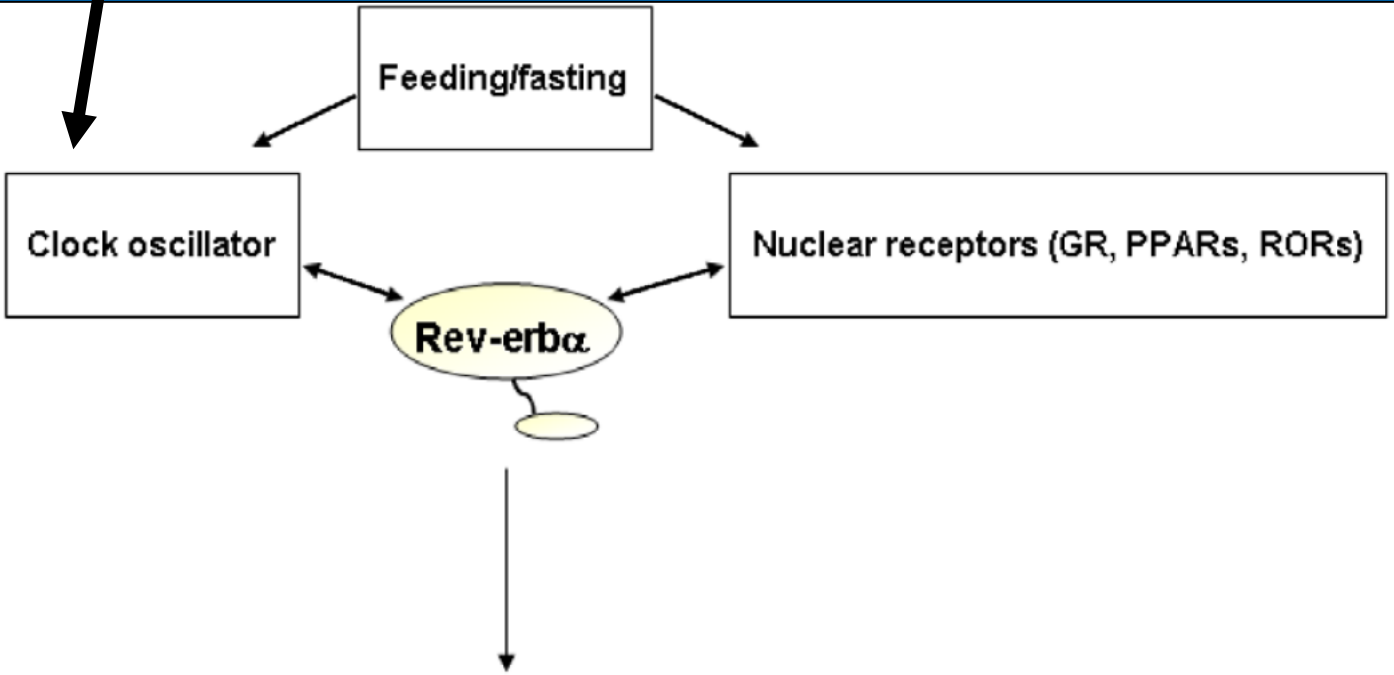


GIP dependent metabolome and hormone correlations network



Rudovich N, Nikiforova VJ,.... Pfeiffer AFH, AJP 2011

Hypothesis: FOOD => GIP / Clocks / Transkriptome / Metabolome



Lipid metabolism (apoA-I (rat), apoC-III)

Adipogenesis, adipocyte lipid metabolism (aP2, c/EBPα)

Muscle fiber type

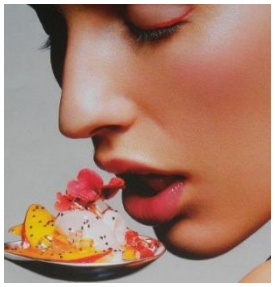
Inflammatory reaction (cox-2, IL-6)

Circadian rhythm (Bmal1)

B.Staehls et al., FEBS lett 2008


Freilandhaltung

Summary



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DIfE

- Genetic variation determines responses to food but the effect size and the individual differences need to be determined
- Effects of single variants appear to be small.
- Clock genes may integrate nutritional responses
- Interaction of environment (food choice and intake) and genetic variation needs to defined
- Energy balance may have greater effects than food choice?
- How important are epigenetic influences?
- “Several encouraging trials suggest that prevention and therapy of age- and lifestyle-related diseases by individualised tailoring to optimal **epigenetic diets** or drugs are conceivable”