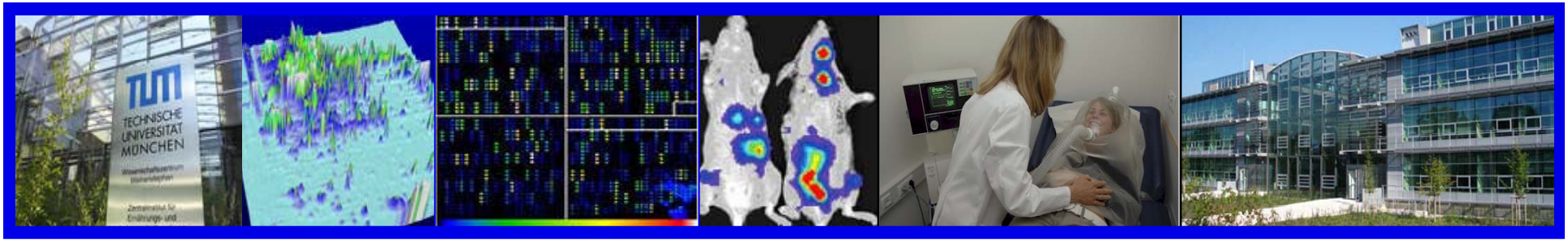
center for diet and disease
www.cdd-tum.de



Genetic & nutrient determinants of the Metabolic Syndrome (Nutrigenomics)

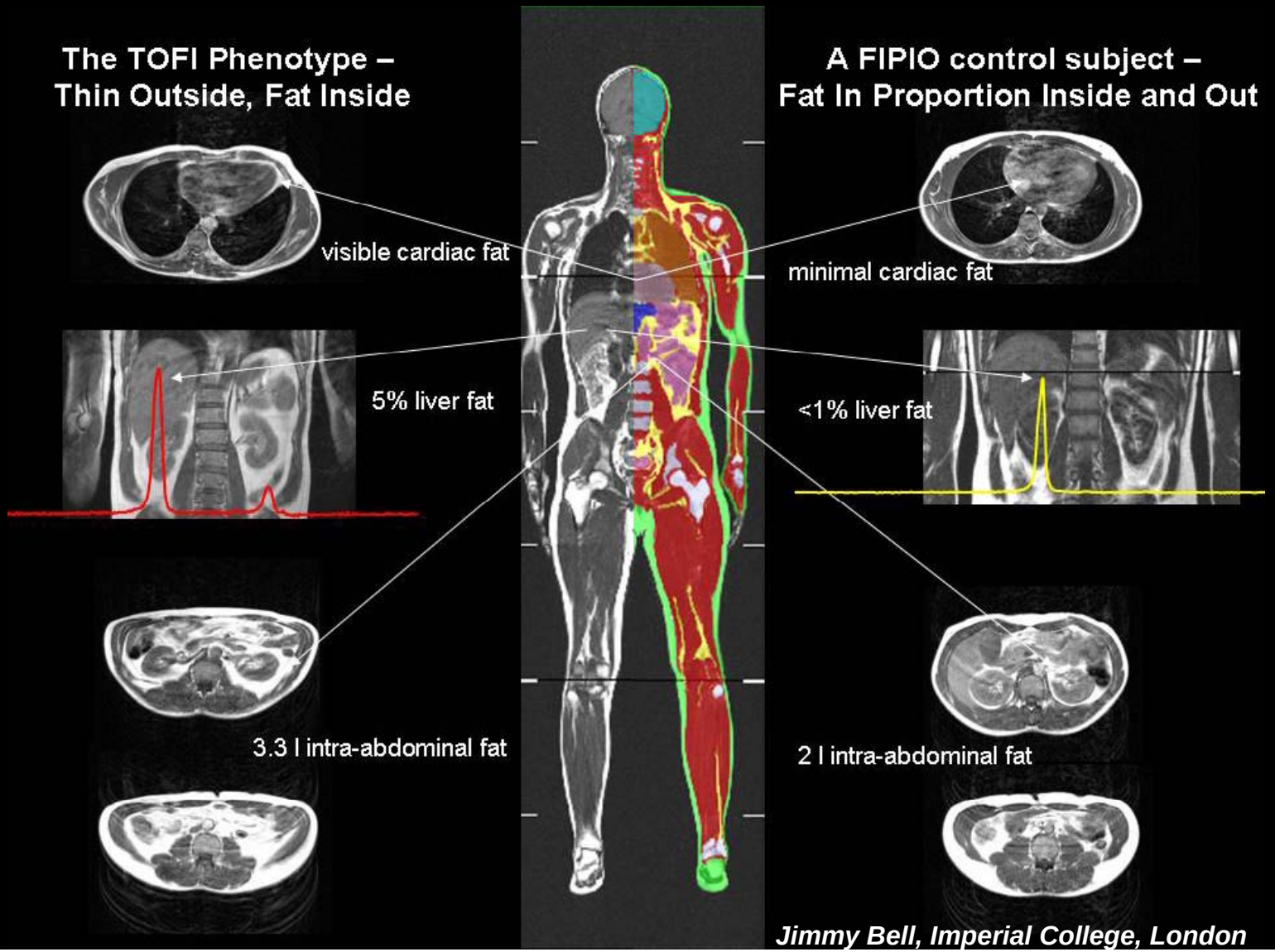
A (my) definition of Nutrigenomics

Nutrigenomics **seeks to understand the molecular basis of how diet and dietary constituents affect gene and protein functions and metabolism on basis of an individuals genetic make up.**

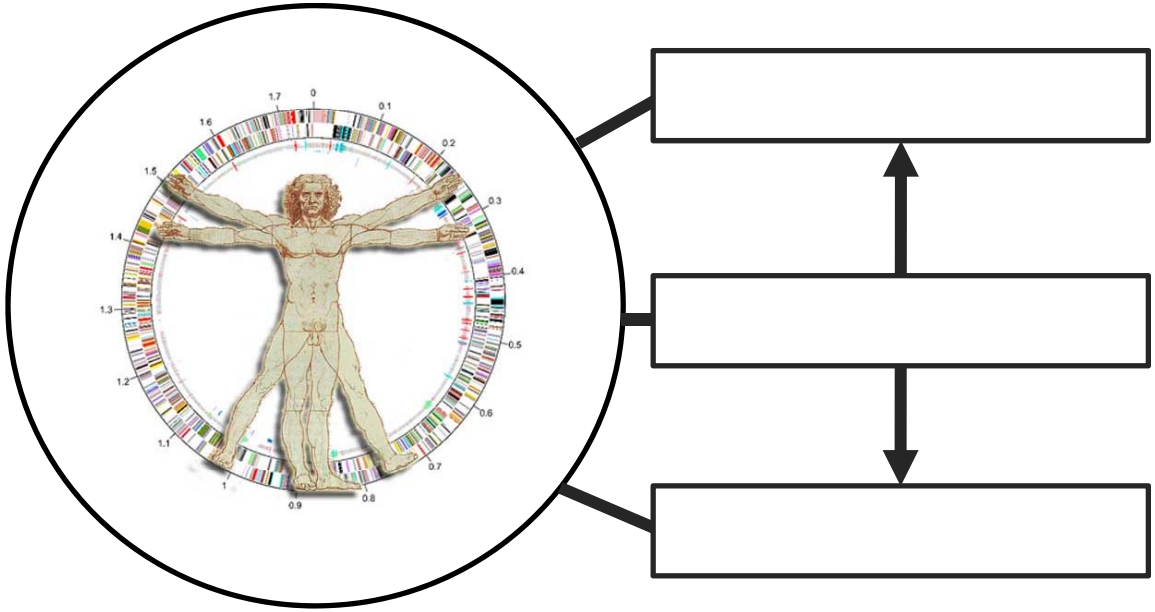
Nutrigenomics **employs various profiling techniques and uses model systems for the most comprehensive description of the interplay of genes and nutritional factors that make up human metabolism in health and disease.**

humans are different – outside and inside

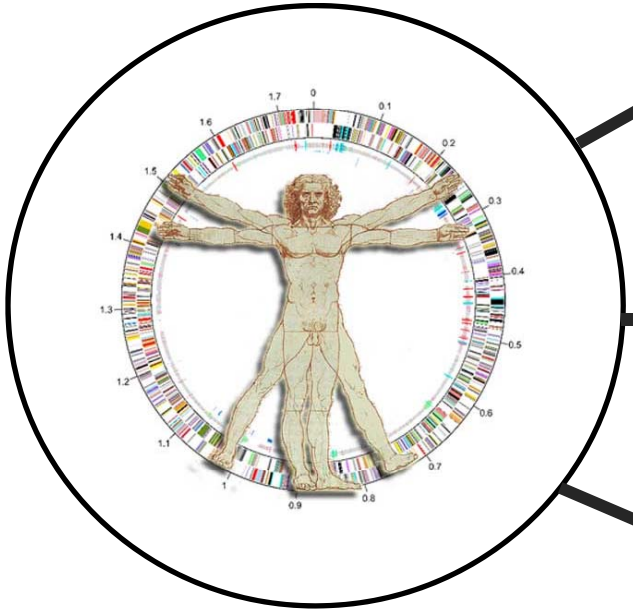
humans are different – outside and inside



What determines „normal“ human metabolism ?



What determines „normal“ human metabolism ?

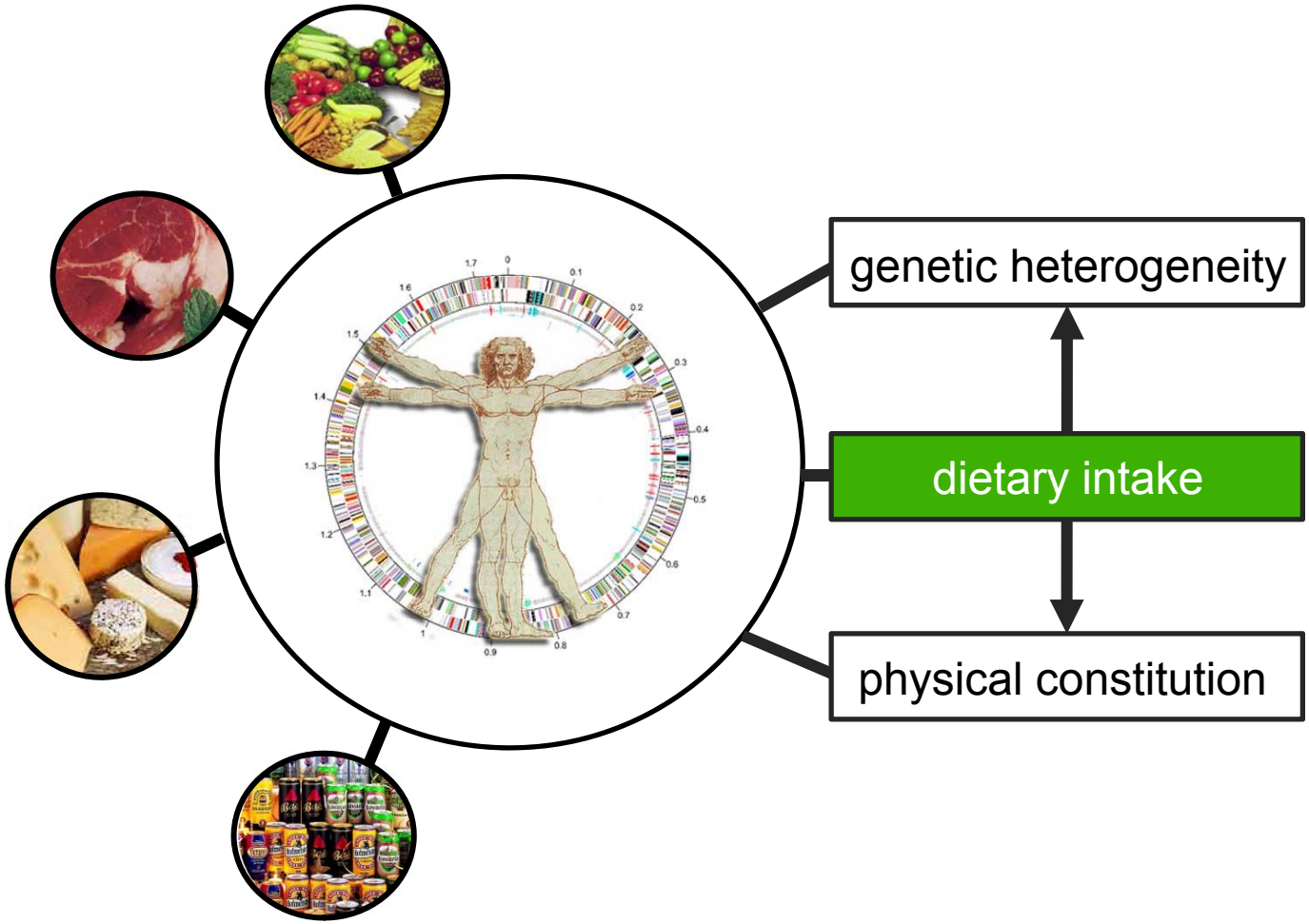


genetic heterogeneity

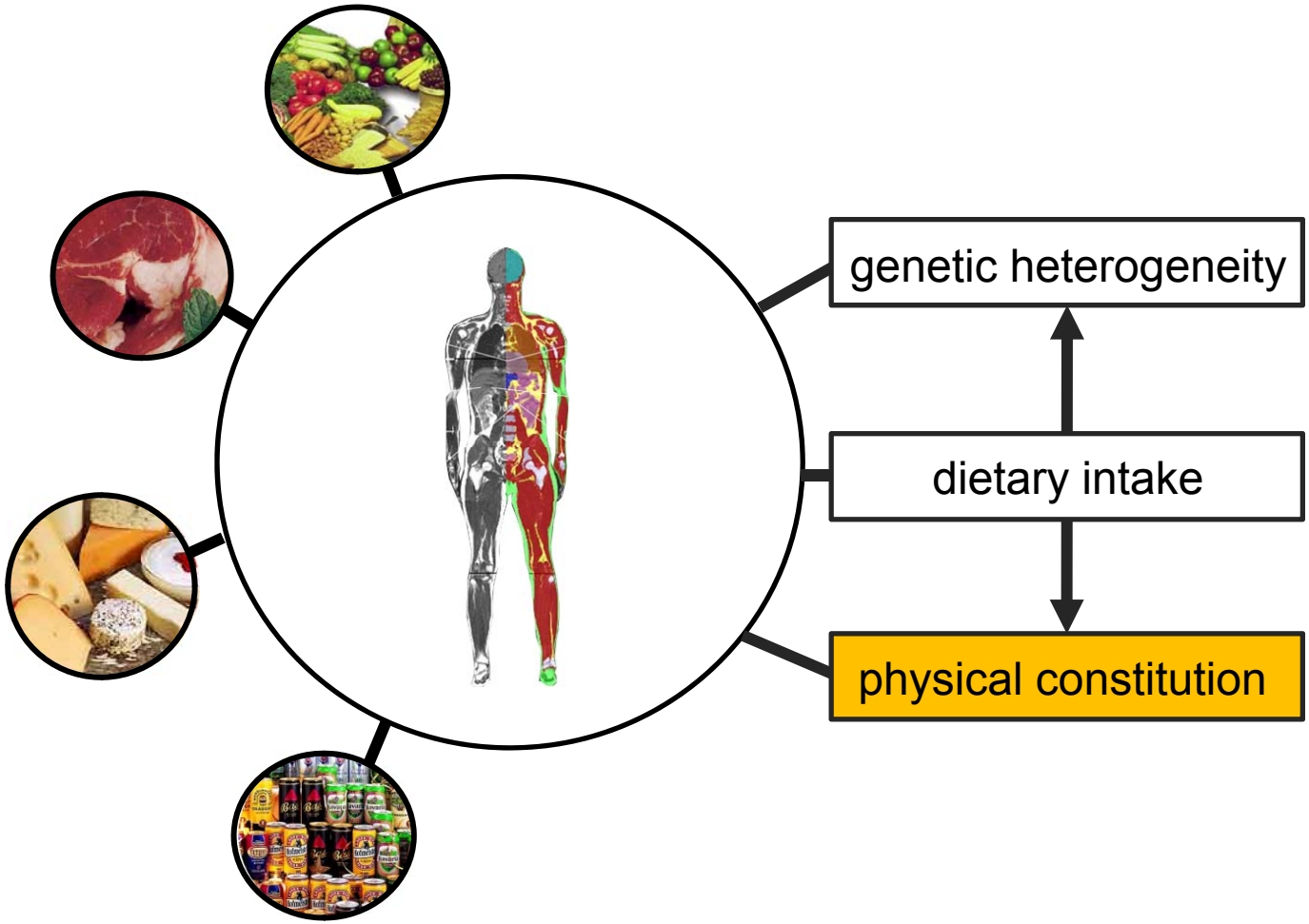
dietary intake

physical constitution

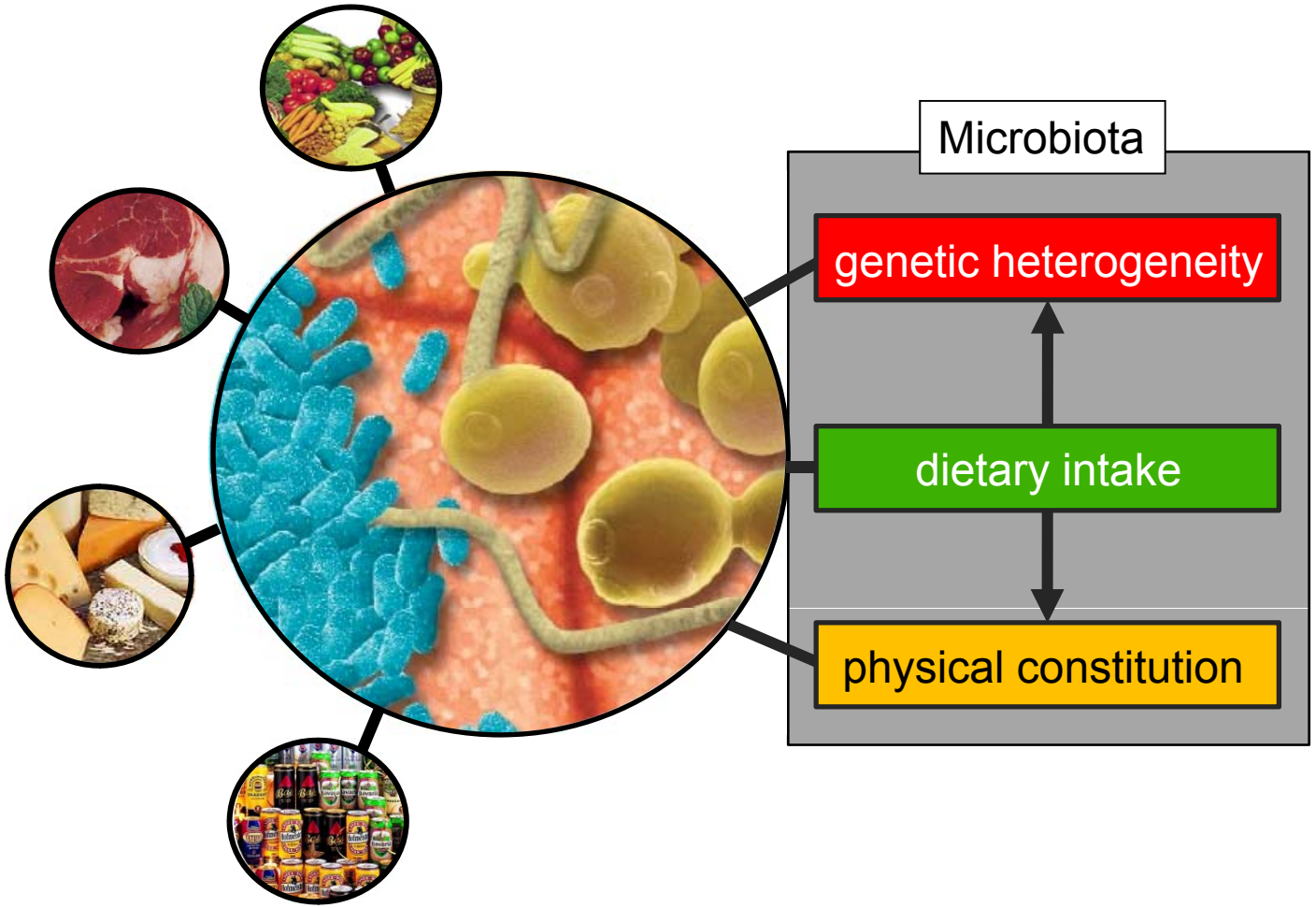
What determines „normal“ human metabolism ?



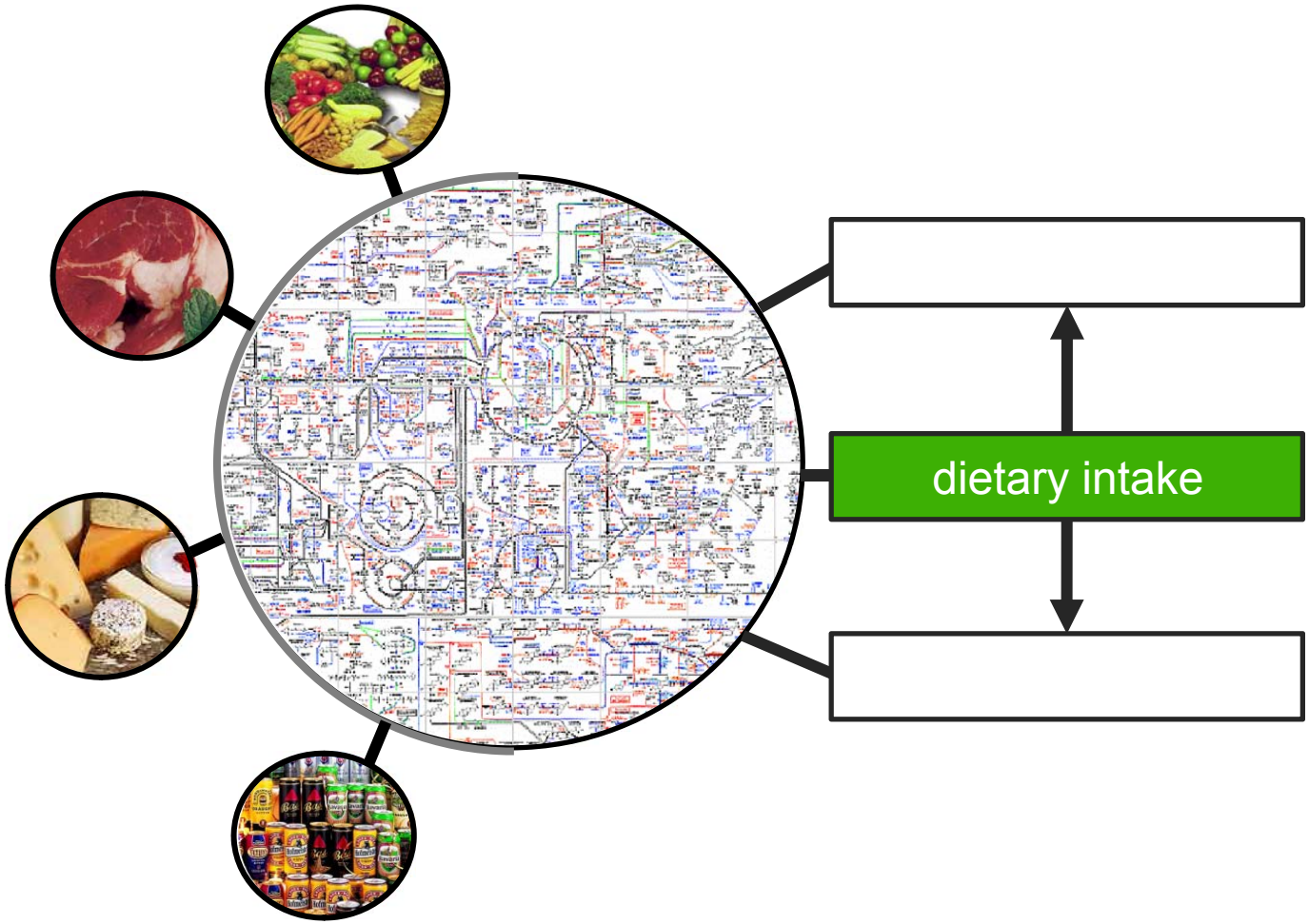
What determines „normal“ human metabolism ?

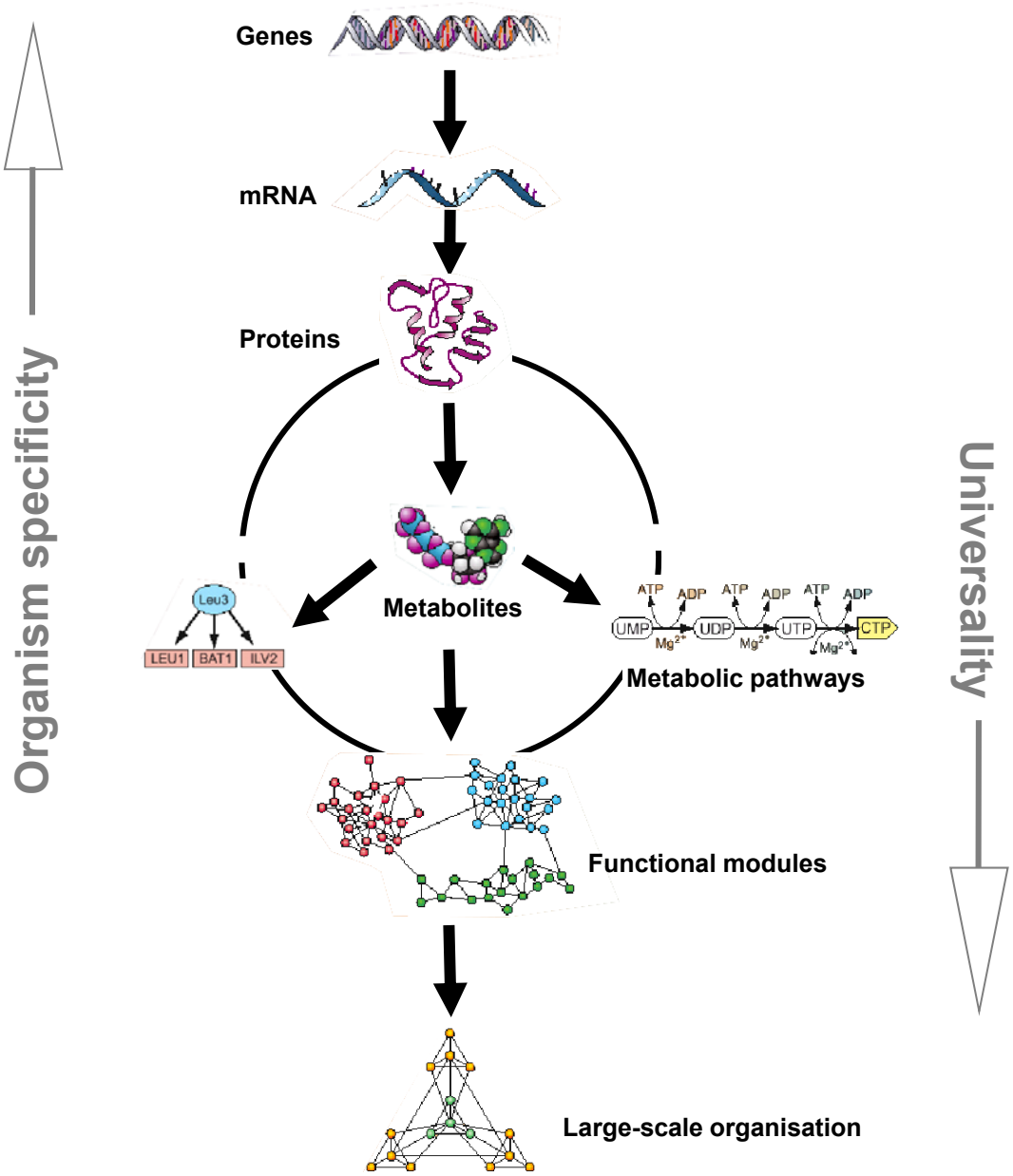


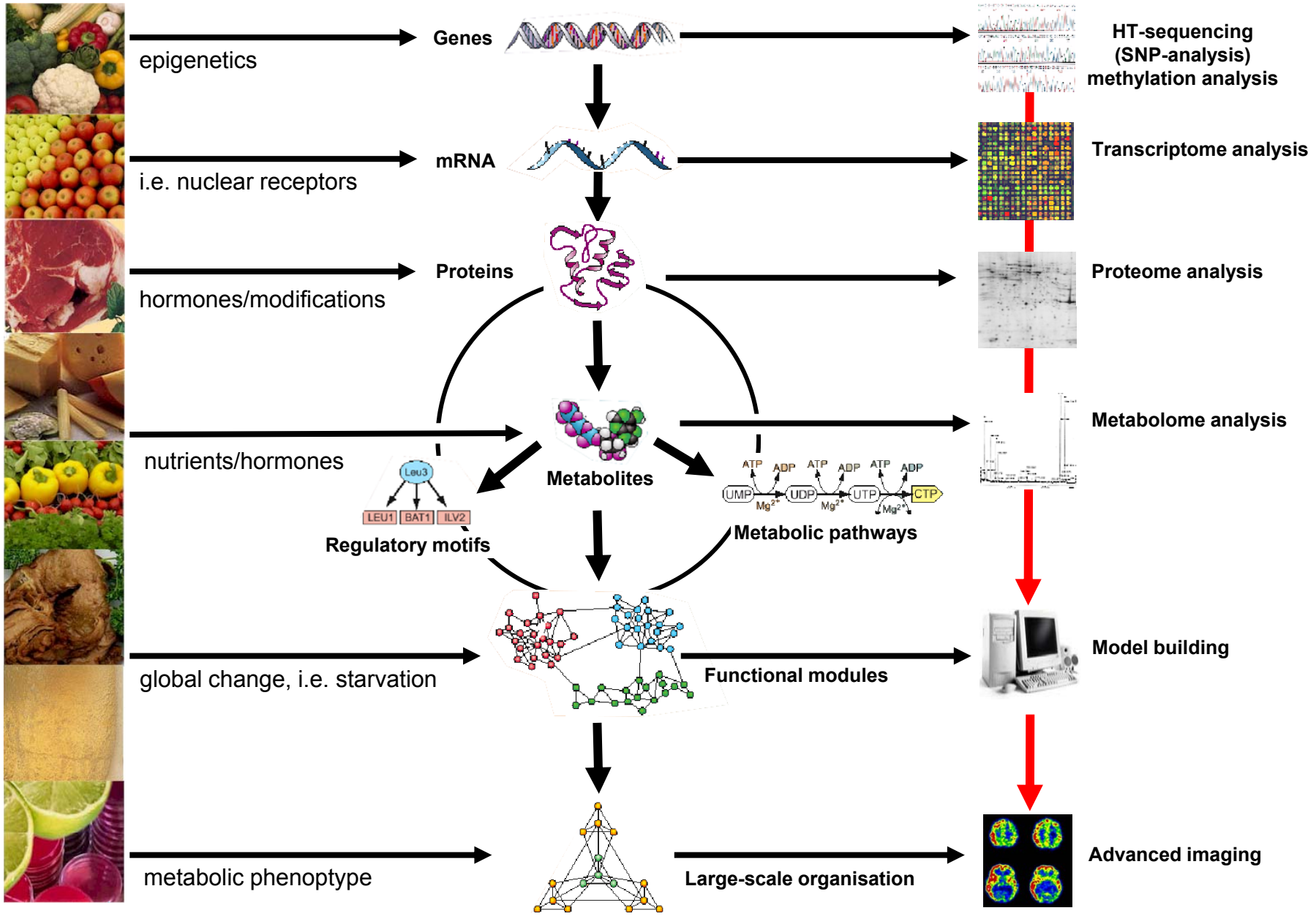
What determines „normal“ human metabolism ?



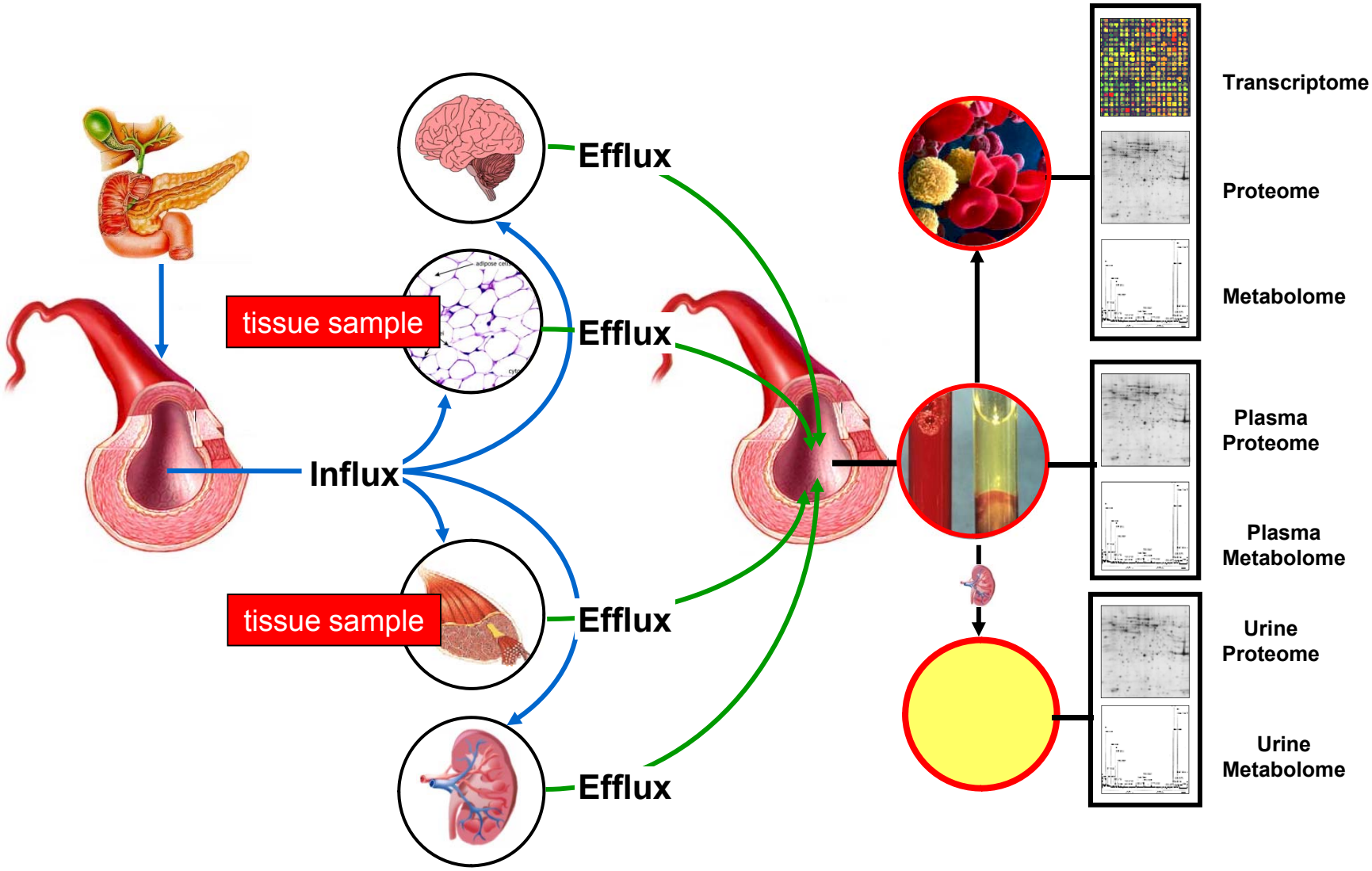
What determines „normal“ human metabolism ?



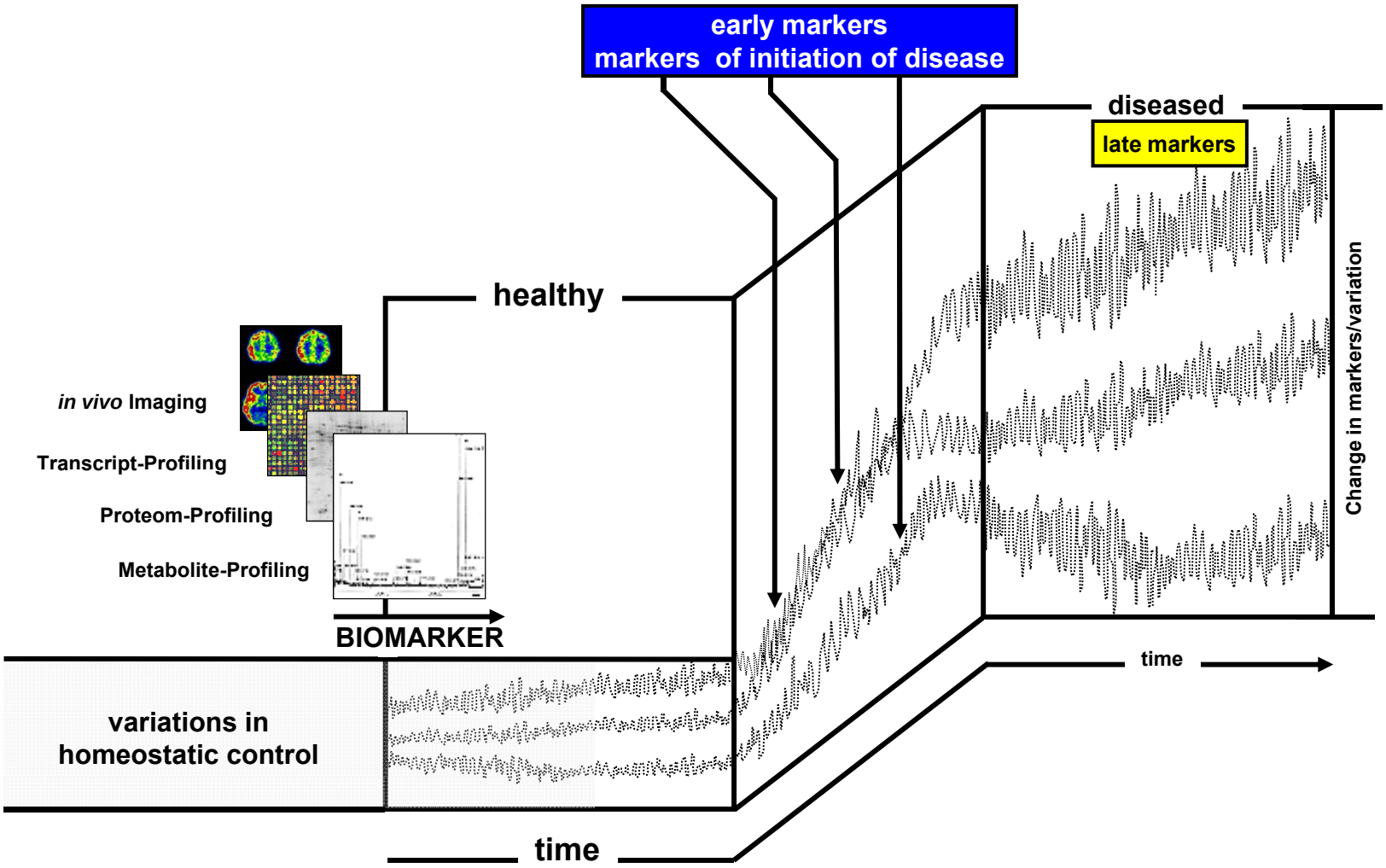

Organism specificity
Genes
mRNA
Proteins
Metabolites
Leu3
LEU1
BAT1
ILV2
ATP
ADP
UMP
UDP
UTP
CTP
Mg2+
Metabolic pathways
Functional modules
Large-scale organisation
Universality


epigenetics
Genes
HT-sequencing
(SNP-analysis)
methylation analysis
i.e. nuclear receptors
mRNA
Transcriptome analysis
hormones/modifications
Proteins
Proteome analysis
nutrients/hormones
Metabolites
Metabolome analysis
Leu3
LEU1
BAT1
ILV2
Regulatory motifs
ATP
ADP
UMP
UDP
UTP
CTP
Metabolic pathways
global change, i.e. starvation
Functional modules
Model building
metabolic phenoptype
Large-scale organisation
Advanced imaging

Limitations when applying the profiling tools in human studies



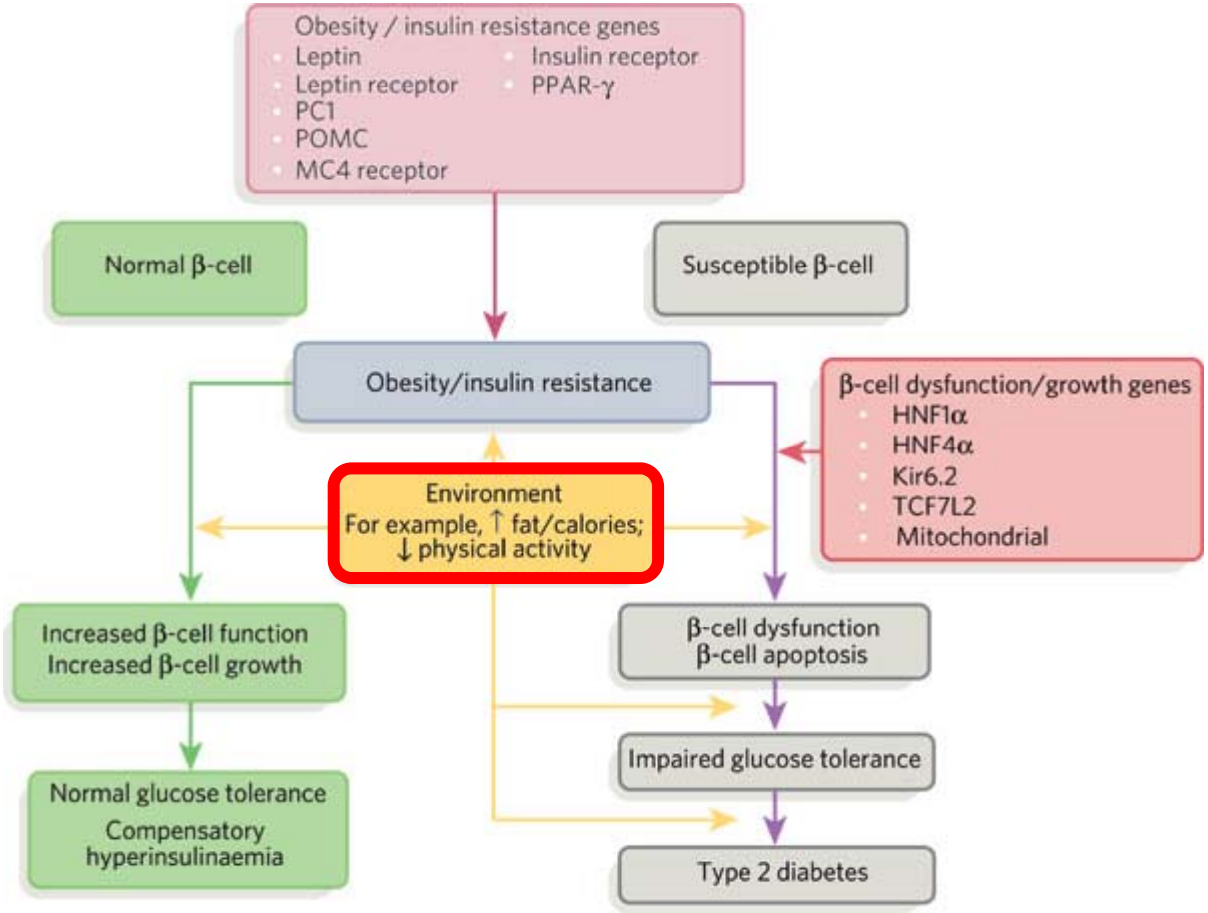
With profiling techniques to biomarkers of disease



What is „the state of the art“ ?

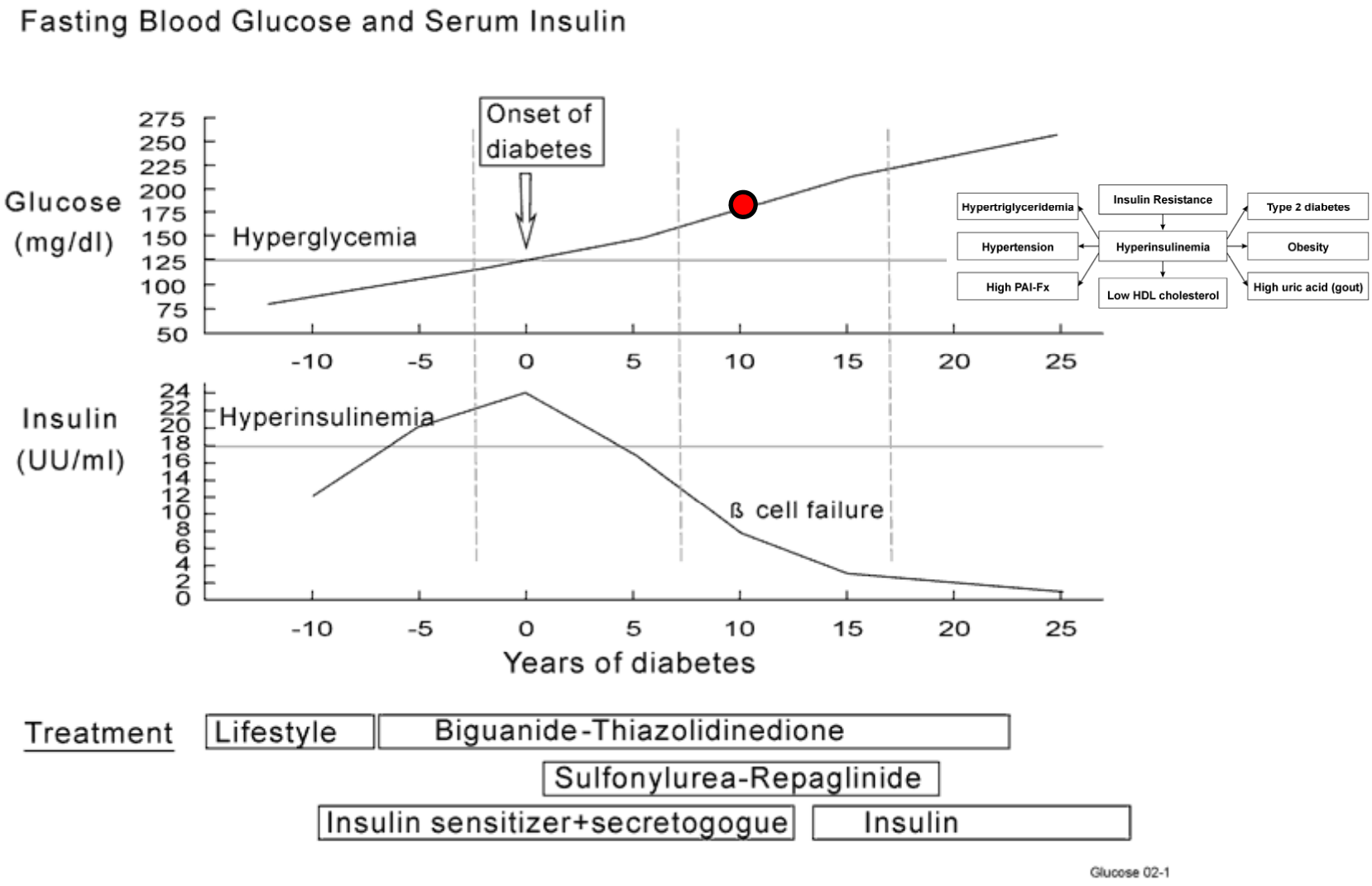
EXAMPLE: non-insulin-dependent diabetes (NIDDM)

The interplay of genetics and environment in the development of NIDDM



Genes responsible for obesity and insulin resistance interact with environmental factors (increased fat/caloric intake and decreased physical activity), resulting in the development of obesity and insulin resistance. These increase secretory demand on ß-cells. If the ß-cells are normal, their function and mass increase in response to this increased secretory demand, leading to compensatory hyperinsulinaemia and the maintenance of normal glucose tolerance. By contrast, susceptible ß-cells have a genetically determined risk, and the combination of increased secretory demand and detrimental environment result in ß-cell dysfunction and decreased ß-cell mass, resulting in progression to impaired glucose tolerance, followed, ultimately, by the development of type 2 diabetes. HNF, hepatocyte nuclear factor.

The natural history of NIDDM



Genotyping/identification of NIDDM susceptibility genes

Identified susceptibility genes for NIDDM

EXT2	Exostosin 2 pancreas development
WFS1	Wolfram syndrome 1/wolframin survival signal beta cells
CDKN2A/2B	Cyclin-dependent kinase inhibitor 2A/2B Tumorsuppressorgene
SCL30A8	Solute carrier family 30 [zinc transporter], member 30 insulin secretion
TCF2/HNF1B	HNF1 homoeobox B associated with T2D and (invers) prostata cancer
CDKAL1	Cyclin-dependent kinase 5 regulatory subunit associated protein 1-like 1:OR 1.39 per allele (p = 0.0004) Mechanism: Reduced insulin incretion
HHEX	Homoeobox, haematopoietically expressed: OR 0.81 per allele (p = 0.009) Mechanism: Reduced insulin incretion
IGF2BP2	Insulin-like growth factor 2 binding protein 2: OR 1.15 per allele (p = 0.049) Mechanism: pancreas development?, reduced insulin secretion
PPARG	*peroxisome proliferator-activated receptor* OR 0.76 per Allel (p = 0.010) Mechanism: fat regulation
FTO	Fat mass and obesity associated OR 1.15 per allele (p = 0.047) Mechanism: Appetite regulation?
DGKB	isotype of catalytic domain of DAG-kinase pancreas: DAG/PKC-dependent insulin secretion
ADCY5	adenylate cyclase 5 cAMP-dependent insulin secretion from beta cells
MADD	mitogen-activated protein kinase activating death domains control of ß-cell mass
SCL39A13	Solute carrier family 30 [zinc transporter], member 30) TGF-ß signalling
ADRA2A	α2A adrenergic receptor in ß-cell outward potassium channel – modifying insulin release
FADS1	Fatty acid desaturase synthesis of PUFA
CRY2	cryptochrome 2 circadian pacemaker
SLACA2	GLUT2-transporter mediates glucose uptake into ß-cells, liver and other cells
IGF1	insulin-like growth factor 1

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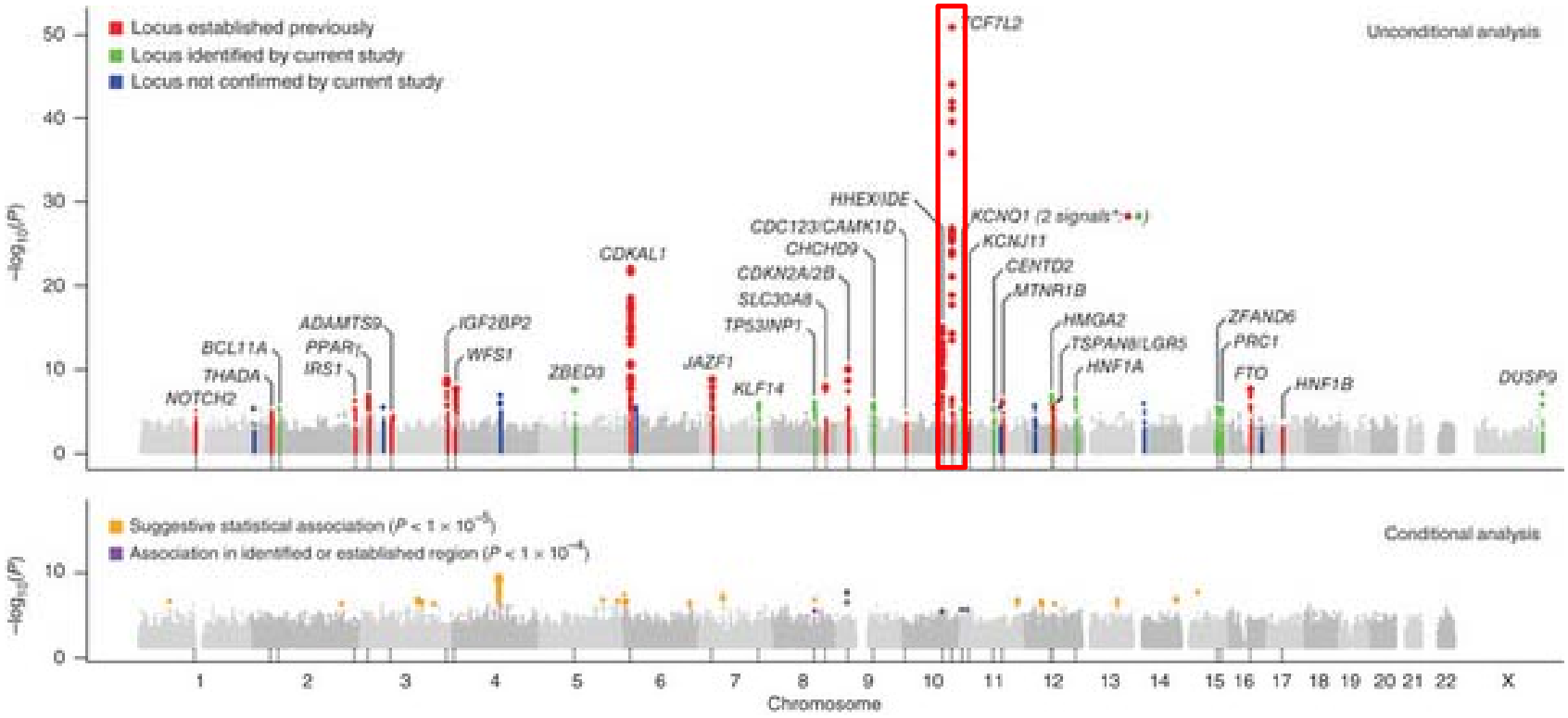
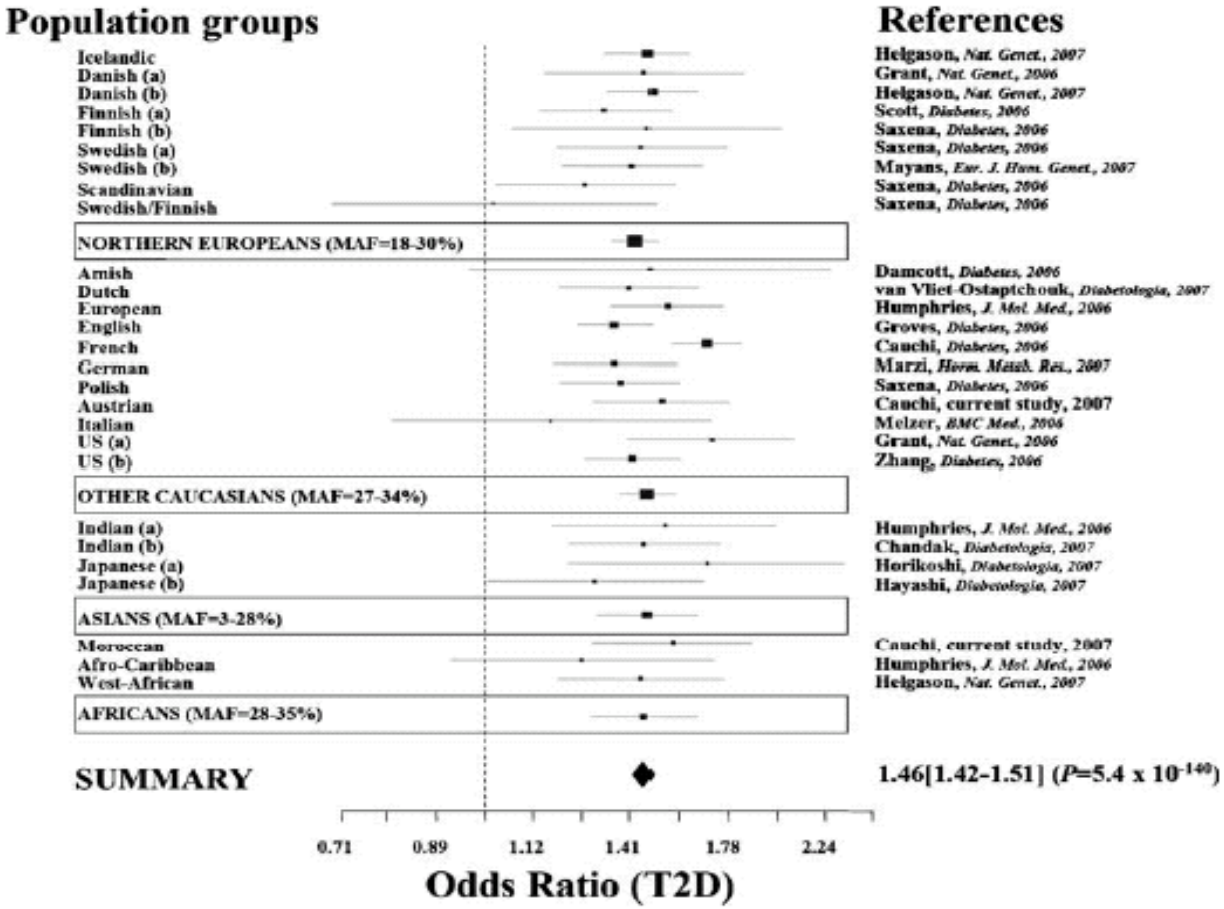
Identified susceptibility genes for NIDDM



Identified susceptibility genes for NIDDM

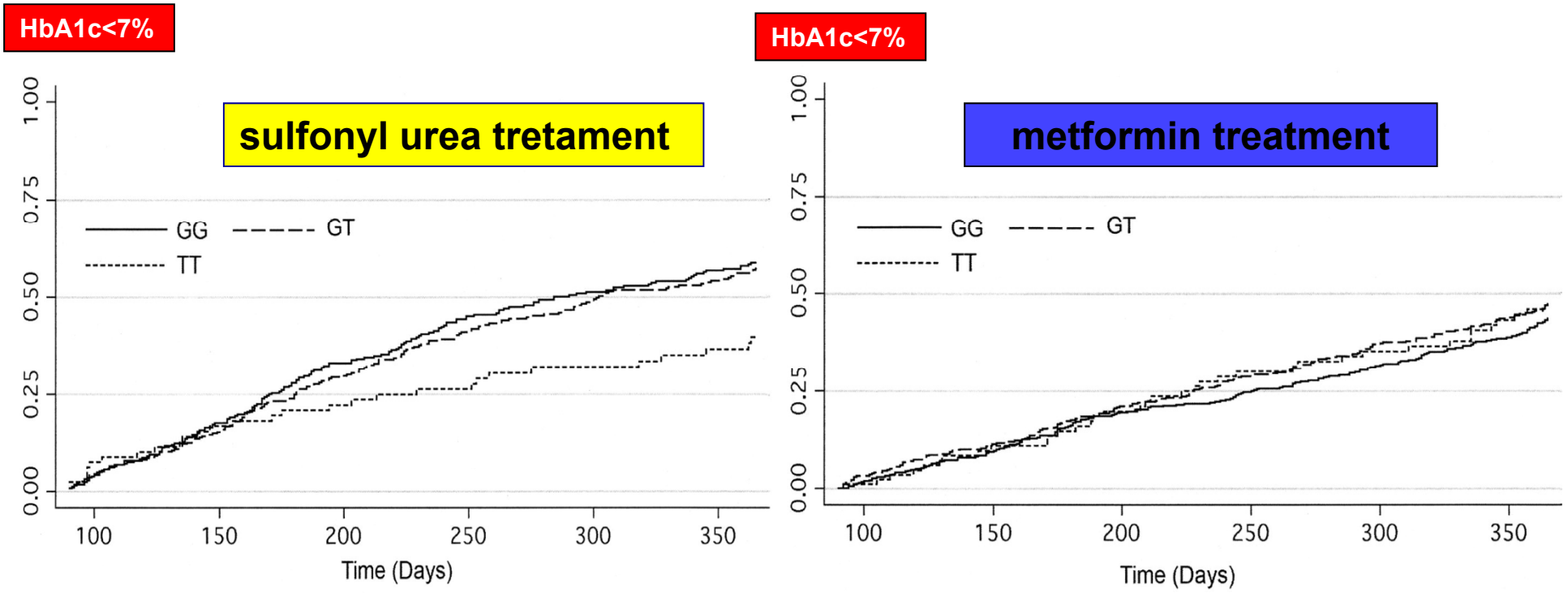
TCF7L2: Replication in ~ 50 Populations



S Cauchi, J Mol Med 2007;85:777

TCF7L2 and pharmacotherapy

GoDARTS (Scotland):
***TCF7L2*-risk variant associated with therapy failure with sulfonyl area and no association with metformin**



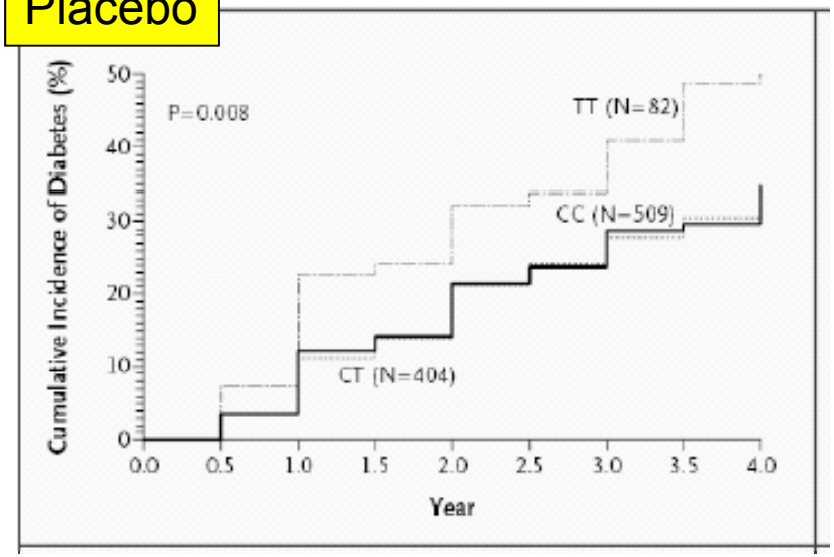
Kaplan-Meier plots showing the proportion of patients, by genotype at rs1225372, who achieve a target HbA1C <7% after being initiated on treatment with a sulfonylurea or metformin.

Diabetes 56:2178-2182, 2007

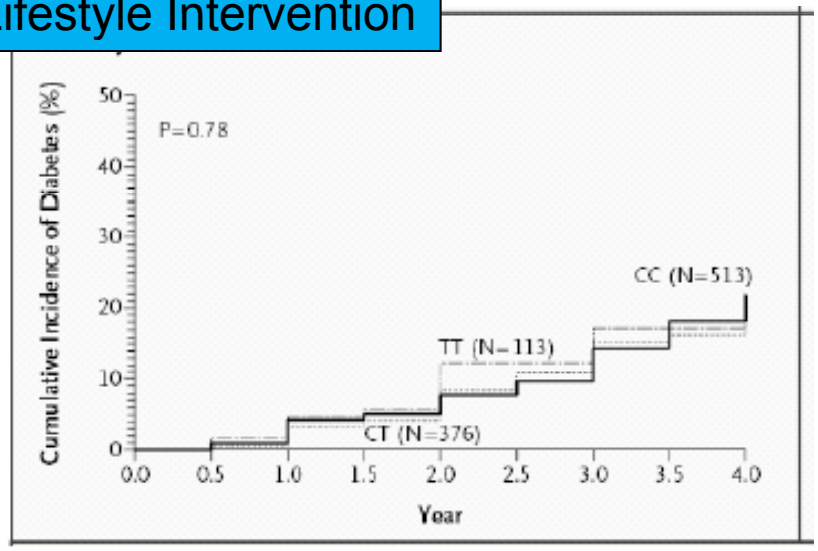
TCF7L2 and lifestyle intervention

DPP (Diabetes Prevention Program)

Placebo



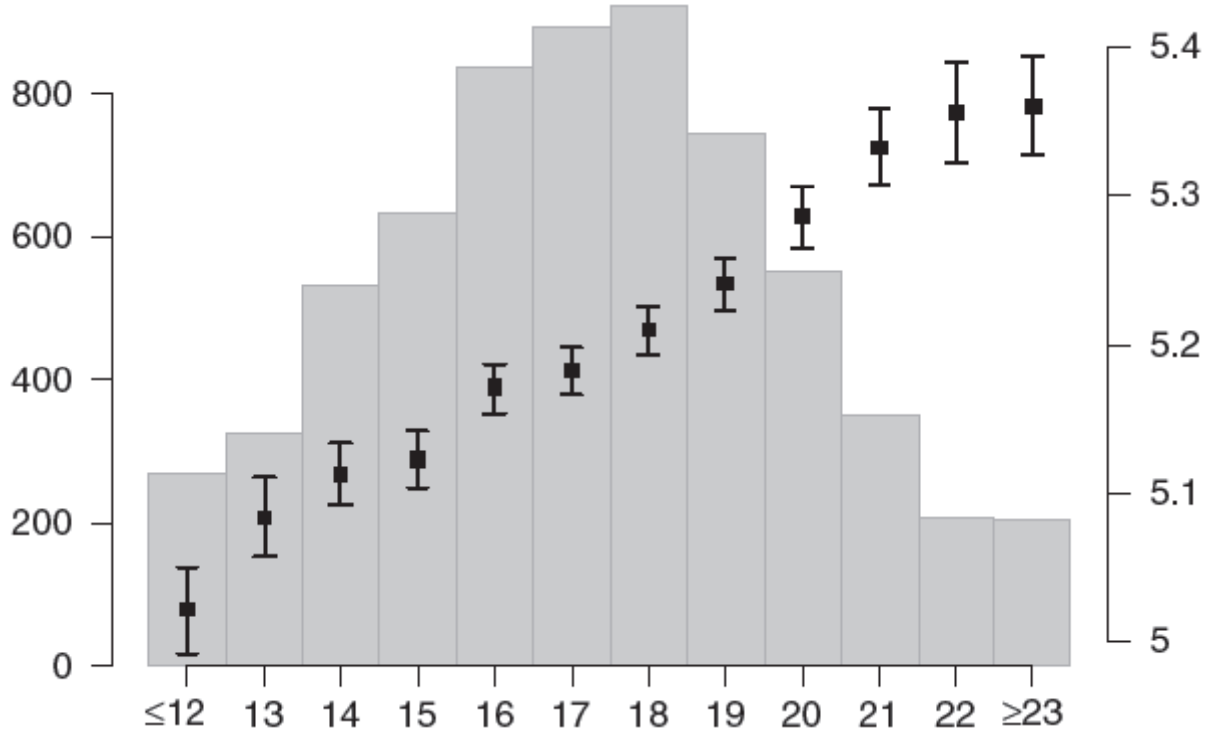
Lifestyle Intervention



Incidence of Diabetes According to Treatment Group and Genotype at Variant rs7903146

JC Florez: NEJM 2006;355:241

New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes



Variation in levels of fasting glucose depending on the number of risk alleles at newly identified loci, weighted by effect size in an aggregate genotype score for the Framingham Heart Study. The bar plots show the average and standard error of fasting glucose in mmol/l for each value of the genotype score based on the regression coefficient (right *y* axis), and the histogram denotes the number of individuals in each genotype score category (left *y* axis). Comparable results were obtained for the NFBC 1966 and ARIC cohorts. On average, the range spans ~0.4 mmol/l (~7.2 mg/dl) from low to high genotype score.

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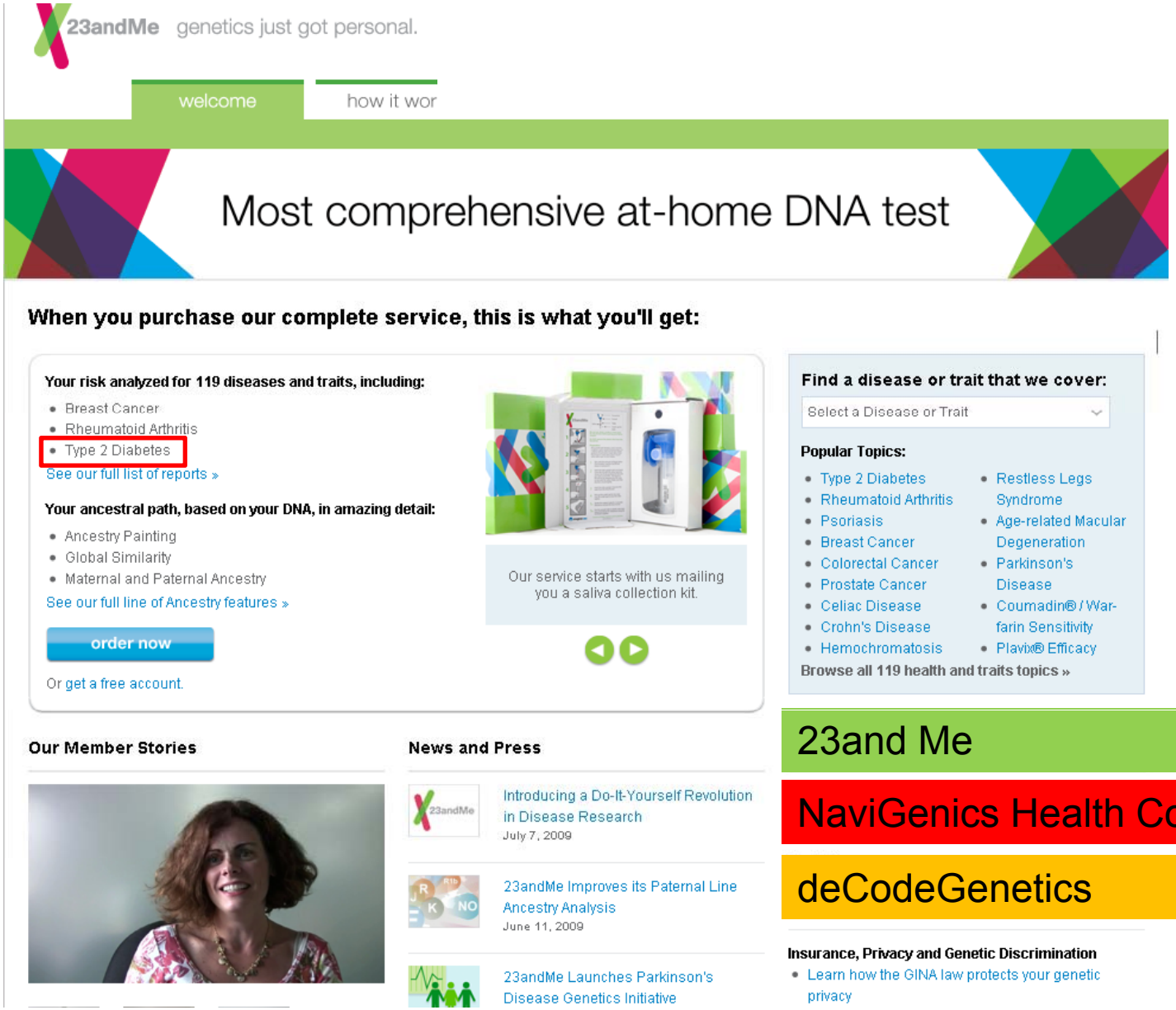
Genotyping and NUTRITION in the commercial environment



23and Me

NaviGenics Health Compass

deCodeGenetics

Nature Medicine | Commentary

Christopher B Newgard & Alan D Attie

Getting biological about the genetics of diabetes

The first round of genome-wide association studies has not accounted for common human diseases to the extent that was expected. New phenotyping approaches and methods of data integration should bring these studies closer to their promised goals.

Nature Medicine Volume: 16, pages: 388–391 Year published: (2011)

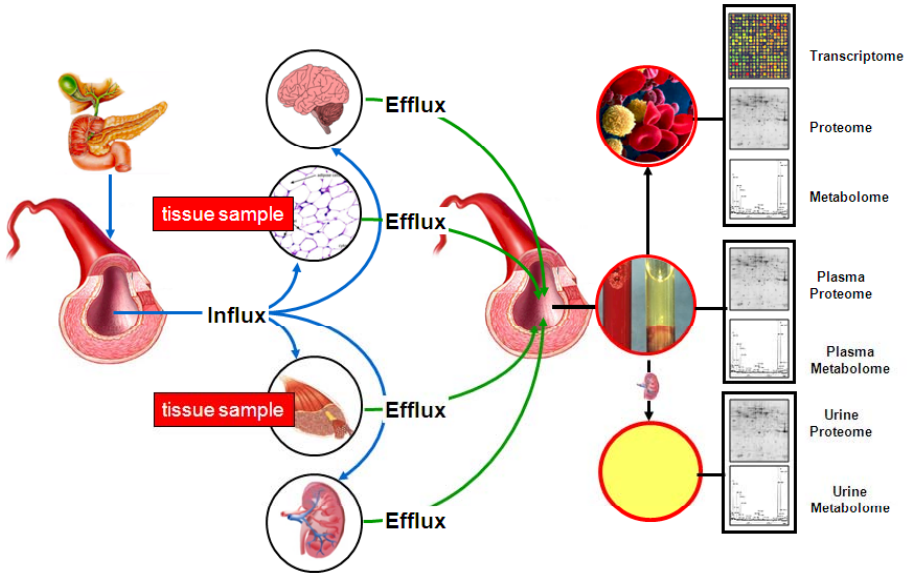
Applications of the profiling techniques to identify NIDDM-dependent changes

transcriptomics

proteomics

metabolomics

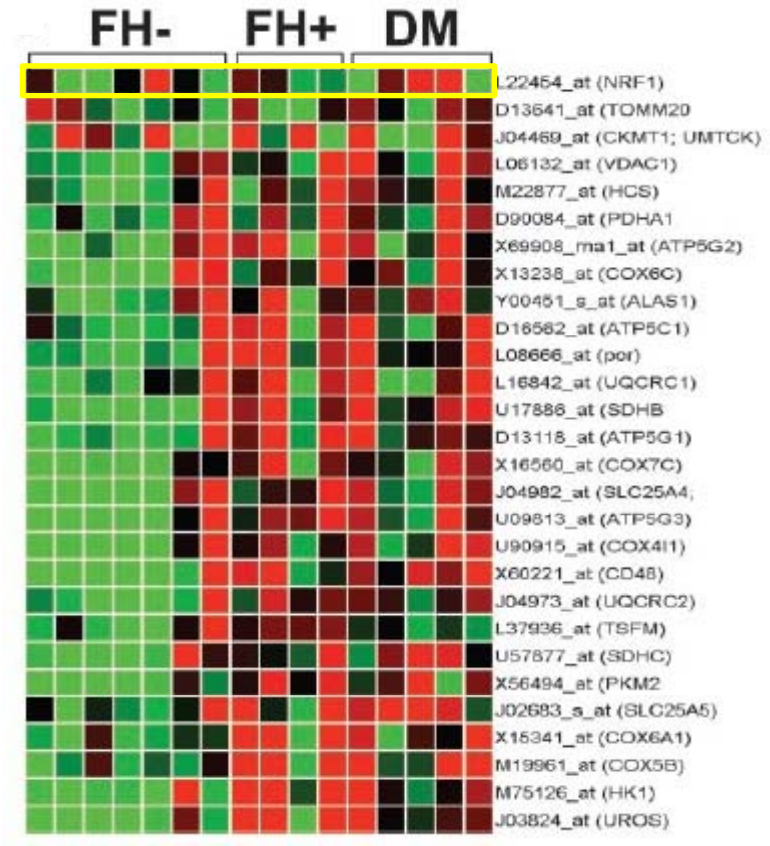
systems approach

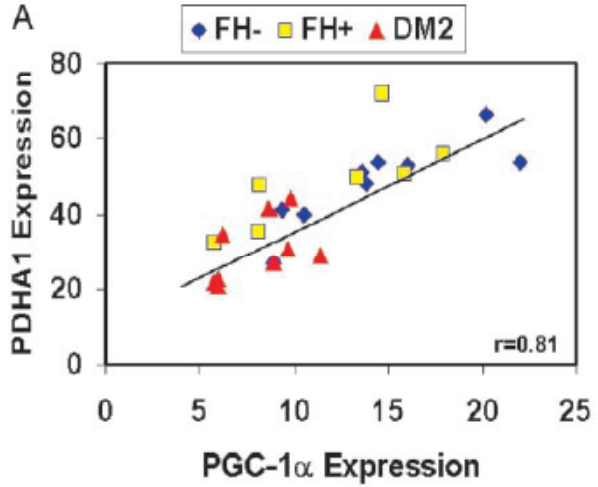


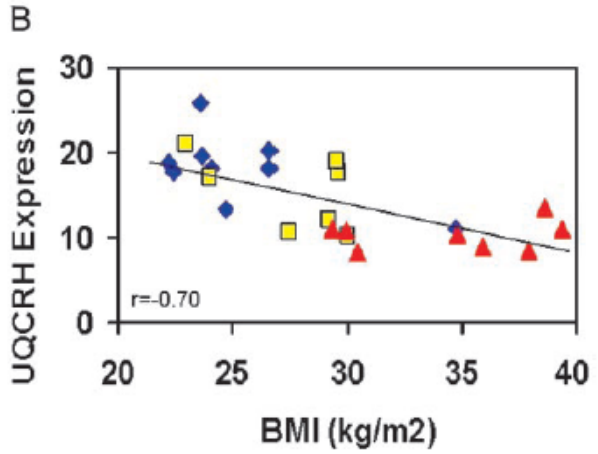
transcriptomics

Coordinated reductions of genes of oxidative metabolism in humans with insulin resistance and diabetes: potential roles of PGC1-α and NRF1

muscle tissue samples







Expression of many oxidative metabolism genes is reduced in FH insulin-resistant nondiabetic and type 2 DM subjects. Hierarchical clustering was performed (GENESPRING, algorithm similar to that of Eisen *et al. (51) by using* glycolysis, tricarboxylic acid cycle, and electron transport gene groups (GENMAPP). Genes known to be regulated by NRF transcription in humans or rodents are indicated by an asterisk. Colors represent gene expression values in individual subject expression changes relative to the mean (normalized to 1 for each gene), with red and green representing decreases or increases in expression, respectively by 50%. (*B) Expression of genes regulated by NRF* transcription is decreased in FH and DM2. The gene tree was created by compiling a list of NRF-regulated genes (52) as in *A*.

Transcriptional profiling of myotubes from patients with type 2 diabetes: no evidence for a primary defect in oxidative phosphorylation genes

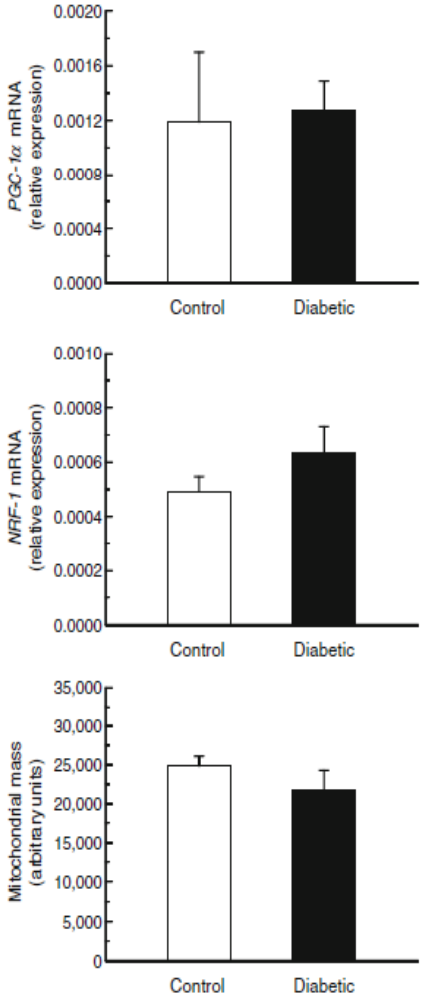


Table 3 The ten most up- and downregulated gene sets analysed with MAPPFinder

MAPP name	Changed (n)[a]	Measured (n)[b]	On MAPP (n)[c]	Changed (%)[d]	z score	Permuted p value	FWER p value
Downregulated in diabetic myotubes							
Integrin-mediated_cell_adhesion	7	87	99	8.0	2.9	<0.01	0.59
Fatty_acid_omega_oxidation	2	15	15	13.3	2.4	0.08	0.87
Focal_adhesion	10	169	187	5.9	2.4	0.02	0.87
Nucleotide_metabolism	2	16	17	12.5	2.3	0.08	0.91
Pentose_phosphate_pathway	1	5	7	20.0	2.3	0.15	0.94
RNA_transcription_reactome	3	32	40	9.4	2.2	0.05	0.95
Nuclear_receptors_in_lipid_metabolism_and_toxicity	3	32	33	9.4	2.2	0.05	0.95
S1P_signaling	2	20	25	10.0	1.9	0.12	0.99
Heme_biosynthesis	1	9	9	11.1	1.5	0.24	1.00
MAPK_signaling_pathway	7	145	162	4.8	1.4	0.21	1.00
Upregulated in diabetic myotubes							
Smooth_muscle_contraction	11	138	156	8.0	3.3	<0.001	0.41
Triacylglyceride_synthesis	3	18	24	16.7	3.3	0.02	0.44
Irinotecan_pathway	2	12	12	16.7	2.7	0.06	0.73
Oxidative_stress	3	24	28	12.5	2.6	0.03	0.74
Calcium_regulation_in_cardiac_cells	9	127	149	7.1	2.6	0.01	0.74
Fatty_acid_omega_oxidation	2	15	15	13.3	2.3	0.08	0.90
Biogenic_amine_synthesis	2	15	15	13.3	2.3	0.08	0.90
Prostaglandin_synthesis_regulation	3	30	31	10.0	2.2	0.07	0.91
Synthesis_and_degradation_of_ketone_bodies	1	5	5	20.0	2.2	0.17	0.94
Small_ligand_GPCRs	2	17	18	11.8	2.0	0.10	0.97

A fold change >1.05 or less than −1.05 and a p value <0.05 (unadjusted) were used as the criteria for gene expression changes between diabetic and control myotubes. Among the 2,544 genes linked to local MAPPS, R=74 and R=80 genes met the criteria for up- and downregulation, respectively (see "Methods")

[a]Number of genes changed

[b]Number of genes measured on the chip

[c]Number of genes on the MAPP

[d]Number changed divided by number measured

Diabetologia (2008) 51:2068–2077

Using pre-existing microarray datasets to increase the experimental power: applications to insulin resistance (adipose tissue)

Insulin resistance genes identified from 3 different mi
(singular value decomposition augmented ge

Symbol	Description	Direc
FOSB*	FBJ murine osteosarcoma viral oncogene homolog B	Up
ACTG2	actin, gamma 2, smooth muscle, enteric	Down
FADS1*	fatty acid desaturase 1	Down
PMP2	**peripheral myelin protein 2**	**Dow**
ATP1A2*	**ATPase, Na^+/K^+ transporting, alpha 2**	**Dow**
CNN1	calponin 1, basic, smooth muscle	Down
CSN1S1	casein alpha s1	Down
SELE*	selectin E (endothelial adhesion molecule 1)	Up
CASQ2	calsequestrin 2 (cardiac muscle)	Down
FAM150B	family with sequence similarity 150, member B	Down
FASN*	**fatty acid synthase**	**Dow**
FOS*	**v-fos FBJ osteosarcoma viral oncogene homolog**	**Up**
SRGN	**serglycin**	**Up**
CILP	cartilage intermediate layer protein	Up
CXCR4*	**chemokine (C-X-C motif) receptor 4**	**Up**
PPBP*	pro-platelet basic protein (chemokine ligand 7)	Down
AADAC	arylacetamide deacetylase (esterase)	Up
ELOVL6*	**long chain fatty acid elongation**	**Dow**
*IL6**	*interleukin 6 (interferon, beta 2)*	*Up*

4440 arrays from Affymetrix, Ilumina, Agilent platforms

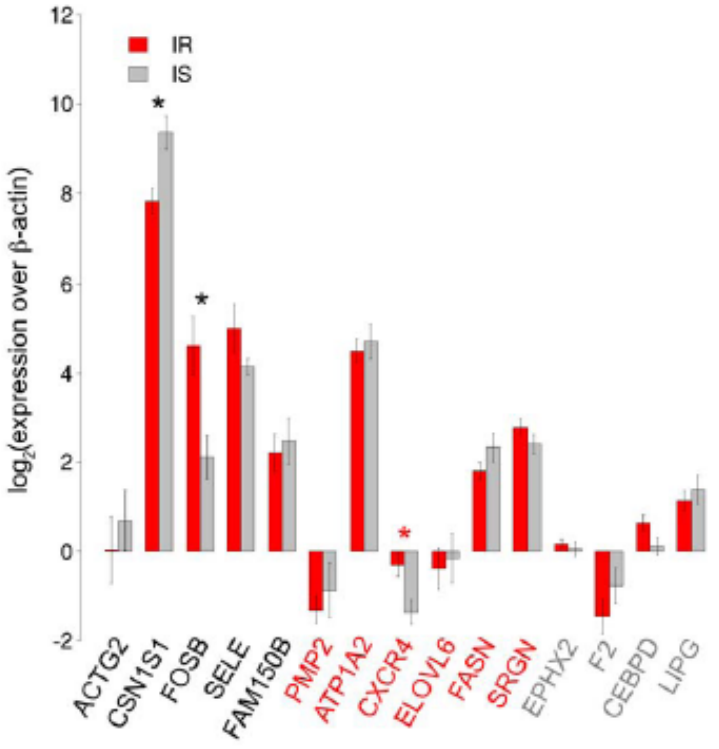
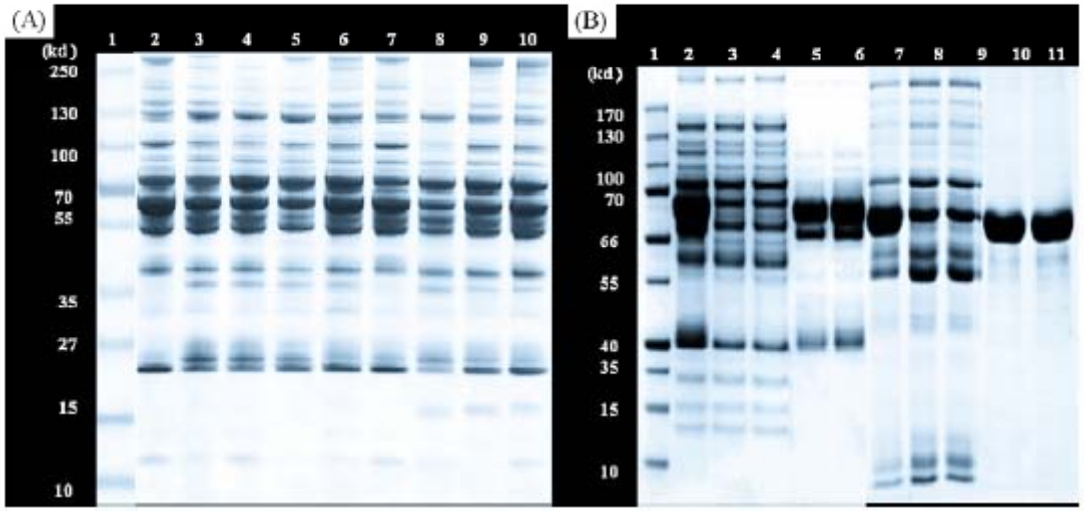


Figure 6. Quantitative PCR validation of insulin resistance candidate genes. Fifteen genes were tested for differential expression between 11 out of the original 12 insulin resistant samples and all 12 original insulin sensitive samples using TaqMan Real-time PCR. The first five genes came from predictions of both fold change and SAGAT, the next six were suggested by SAGAT only, and the last four genes served as negative controls. The directionality of differential expression of all non-control genes was in agreement between the microarray and qPCR data. Three DE genes were statistically significant according to qPCR: CSN1S1, FOSB, and CXCR4.

Proteomic identification of human plasma biomarkers in diabetes mellitus type 2

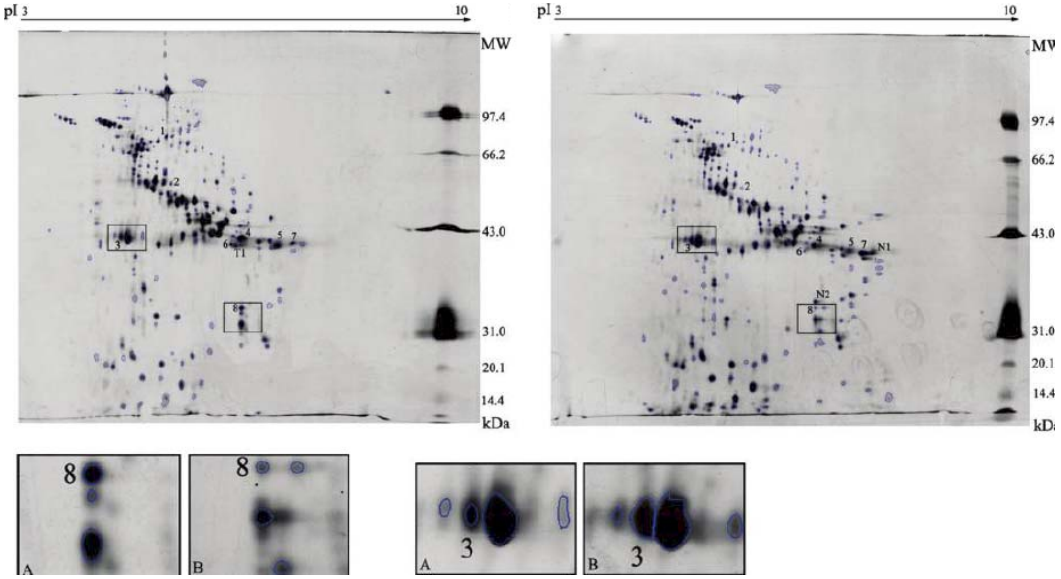


Identification of protein biomarkers in diabetes type 2 by 2D liquid chromatography and Mass Spectrometric (MALDI-TOF) analysis.

CF fractions p*I*	Protein identified	Quantification of identified biomarker proteins after proteomics by ELISA assay in the control and diabetic groups.			Matched peptides no. (%)	Sequence coverage	% age change
		Variable*	Control	Diabetic			
6.05–5.91	Apolipoprotein A-I	C-reactive protein (μg/ml)	6.5 ± 1.30	64.2 ± 28.3[a]	66/67(98)	98%	+872
6.05–5.91	Apolipoprotein E	Apolipoprotein A-I (g/l)	1.76 ± 0.67	1.4 ± 0.68	20/23(87)	86%	−6.4
5.91–5.67	C reactive protein	Apolipoprotein E (g/l)	1.05 ± 0.55	9.47 ± 2.56[a]	12/24(50)	80%	+802
5.67–5.43	Leptin (precursor)	Leptin (ng/ml)	1.348 ± 0.5	12.7 ± 1.74[a]	18/27(67)	70%	+842
		*[a] $P < 0.001$, control baseline compared with diabetic baseline.					

S. Riaz et al. / Journal of Pharmaceutical and Biomedical Analysis 51 (2010) 1103–1107

Proteomics-based identification of differentially expressed proteins including galectin-1 in the blood plasma of type 2 diabetic patients



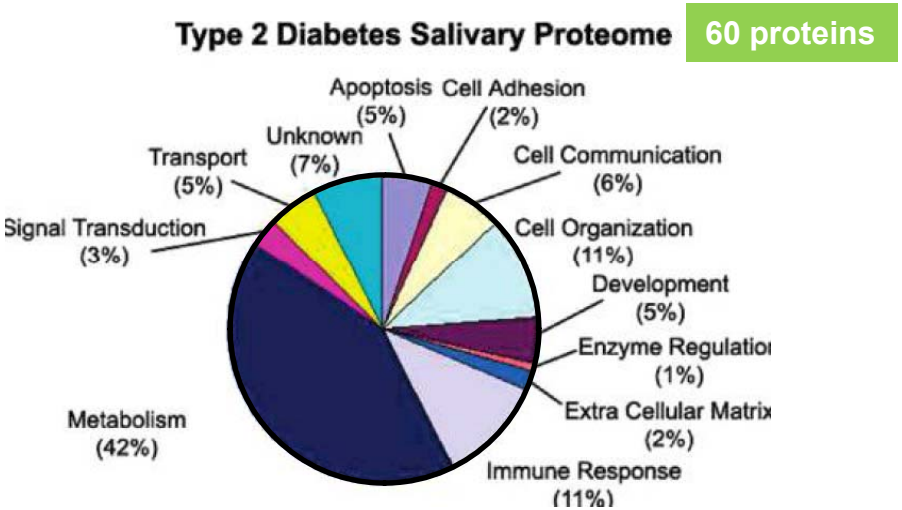
spot number	protein identified	accession number	MASCOT score	sequence coverage (%)	molecular weight (Da)	isoelectric point (p*I*)	peptide identified/ peptide simulated	matched peptides	position	fold change
1	PRO2044	gi|6650826	141	45	30084	6.97	11/26	RHPDYSVVLLLR	9−20	3.866
2	Hypothetical protein	gi|7269700	48	60	6200	9.69	3/13	MVSLFFVEHVVVPAAAGR	1−18	3.48
3	Pro-apolipoprotein	gi|178775	234	63	28944	5.45	19/38	VKDLATVYVDVLK	17−29	−4.152
4	Unknown Protein	gi|15679996	115	36	23322	8.00	7/8	QNCELFEQLGEYKFQNALLVR	6−26	3.389
5	Chain M, Crystal	gi|48425	86	30	23948	8.96	6/14	EIVLTQSPGTLSLSPGER	1−18	2.416
6	Hypothetical protein	gi|41410097	62	53	9865	5.89	4/13	MDPAALADAVQR Oxidation (M)	1−12	2.577
7	PRO2675	gi|77702	51	19	33466	6.14	5/20	DVFLGMFLYEYAR Oxidation (M)	27−39	−5.7
8	Chain A, X-Ray Human Galectin-1	gi|42542977	81	41	14868	5.34	5/12	VRGEVAPDAK	19−28	4.833

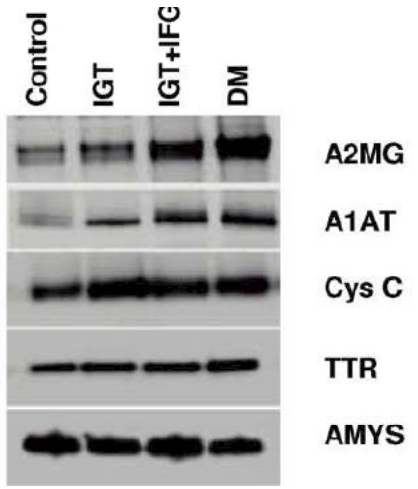
Proteomic identification of salivary biomarkers of type 2 diabetes

Table 2. Salivary Proteins Showing Differential Abundance in Subjects with Type-2 Diabetes and Controls[a]

function	Swiss-Prot accession	protein name	diabetes vs control: fold change	diabetes vs control: *p*-value
Metabolism	P23280	Carbonic anhydrase 6	3.84	<0.0001
	P14618	Pyruvate kinase isozymes M1/M2	3.47	0.0002
	P06737	Glycogen phosphorylase, liver form	3.32	0.0105
	Q549C7	Transthyretin	2.4	0.0246
	P22894	Neutrophil collagenase	2.36	0.0039
	P00491	Purine nucleoside phosphorylase	−2.08	0.0032
	O60235	Transmembrane protease, serine 11D	−2.13	0.012
	P30838	Aldehyde dehydrogenase, dimeric NADP-preferring	−2.19	0.0034
	Q13231−3	Isoform 2, 3 and 4 of Chitotriosidase-1	−2.2	0.0263
	Q9UBR2	Cathepsin Z	−2.85	0.0361
	P00558	Phosphoglycerate kinase 1	−3.18	<0.0001
	O60218	Aldo-keto reductase family 1 member B10	−3.32	0.0127
	Q13787	Apolipoprotein B-100	−4.13	<0.0001
	P00915	Carbonic anhydrase 1	−4.36	<0.0001
	P00918	Carbonic anhydrase 2	−5.54	0.0002
	Q86U62	Proteasome (prosome, macropain) subunit, beta type, 7	−6.11	0.0184
	P27824	Calnexin	−7.74	0.0005
Immune response	Q6FHH3	Uteroglobin	10.43	<0.0001
	Q4VAX6	Serpin peptidase inhibitor, clade B	6.05	0.0101
	Q9NP55	Protein Plunc	5.48	<0.0001
	P13671	Complement component C6	4.75	0.036
	P01009	Alpha-1-antitrypsin	3.24	<0.0001
	P01034	Cystatin-C	2.22	0.0007
	P30740	Leukocyte elastase inhibitor	2.03	0.011
	P01040	Cystatin-A	−2.42	0.0042
	P04083	Annexin A1	−3.57	<0.0001
Development	Q4VB24	Histone cluster 1, H1e	6.05	0.0101
	Q09666	Neuroblast differentiation-associated protein AHNAK	3.08	0.0472
	Q9NZT1	Calmodulin-like protein 5	−2.17	0.0151
	Q01469	Fatty acid-binding protein, epidermal	−2.55	<0.0001
	Q06830	Peroxiredoxin-1, −2 and −6	−2.59	<0.0001
	Q96RM1	Small proline-rich protein 2F	−2.85	0.0361
	P31151	Protein S100-A7	−2.94	0.003
	Q5TCI8	Lamin A/C	−3.26	<0.0001
	P07355	Annexin A2	−4.25	0.0014
	P15924	Desmoplakin	−5.88	<0.0001
	P30043	Flavin reductase	−6.11	0.0003
Extracellular matrix protein	P07998	Ribonuclease pancreatic	3.78	0.0015
	A2RTY6	Interalpha (Globulin) inhibitor H2	3.16	0.0102
	P19827	Interalpha-trypsin inhibitor heavy chain H1	2.8	0.0042
	P36222	Chitinase-3-like protein 1	2.65	0.0173
	Q14624	Interalpha-trypsin inhibitor heavy chain H4	2.59	0.006
	P80303	Nucleobindin-2	2.05	0.005
	Q9UKR3	Kallikrein-13	−4.48	0.0265
	O43240	Kallikrein-10	−4.99	0.0024
Signal transduction	Q7M4Q5	Basic proline-rich peptide IB-8a	5.4	0.019
	P39687	Acidic leucine-rich nuclear phosphoprotein 32 family	3.32	0.0105
	Q5VY30	Retinol binding protein 4, plasma	2.15	0.0143
	P23528	Cofilin-1	2.11	0.0464
	P62258	14−3−3 protein epsilon	−2.25	0.01
	P12429	Annexin A3	−2.68	0.008
	Q04917	14−3−3 protein eta	−2.95	0.0438
Cell organization and biogenesis	O15511	Actin-related protein 2/3 complex subunit 5	6.05	0.0101
	P60953−2	Isoform 2 of P60953 Cell division control protein 42 homologue precursor	4.75	0.036
	P01023	Alpha-2-macroglobulin	2.23	<0.0001
	P28676	Grancalcin	−7.09	0.0083
Cell motility	P61160	Actin-like protein 2	3.36	0.0476
	P26038	Moesin	2.04	0.0006
	O95274	Ly6/PLAUR domain-containing protein 3	−2.3	0.0236
	P67936−2	Isoform 2 of P67936 Tropomyosin alpha-4 chain	−3.75	0.0006

[a] Spectral counts of human salivary proteins with 3 or more unique peptide identifications were subjected to label-free quantification. Proteins that were significantly differentially abundant (p-value ≤0.05) by at least ±2.0-fold are shown above. Proteins are grouped according to their function. Fold change between the groups was quantified using equation described by Old et al.[12]

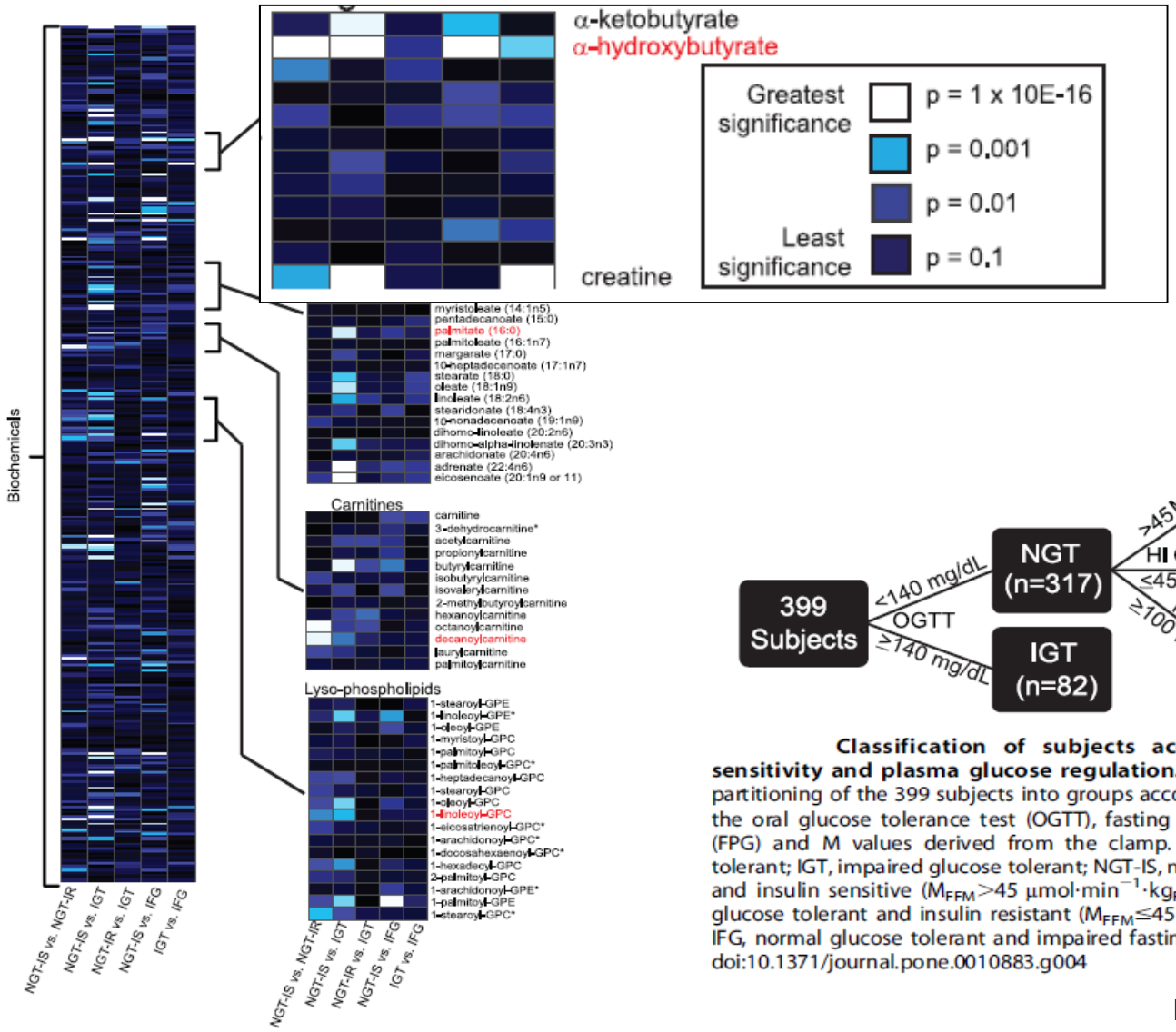




Western blot analysis of alpha-2 macroglobulin (A2MG), alpha-1-antitrypsin (A1AT), cystatin C (Cys C), transthyretin (TTR), and salivary alpha-amylase (AMYS).

Metabolite profiling in non-diabetic human volunteers with insulin resistance

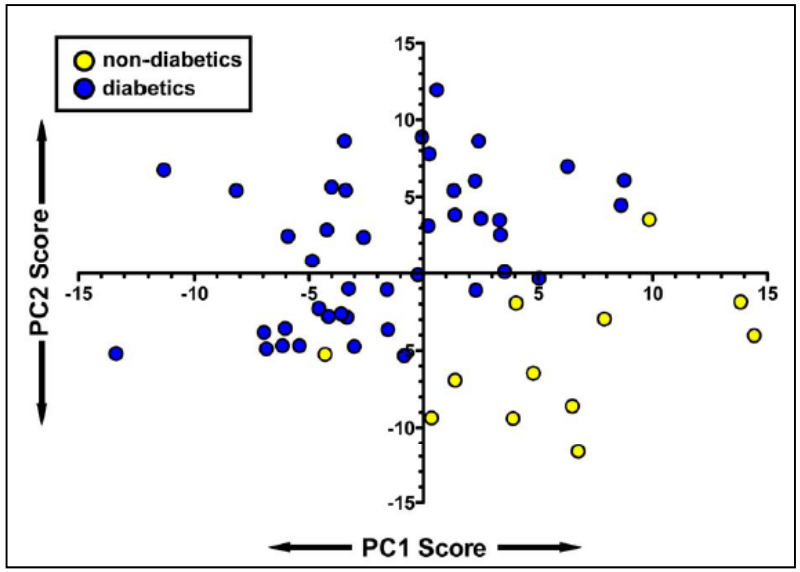
α-hydroxybutyrate is an early biomarker of insulin resistance and glucose intolerance in a nondiabetic population.

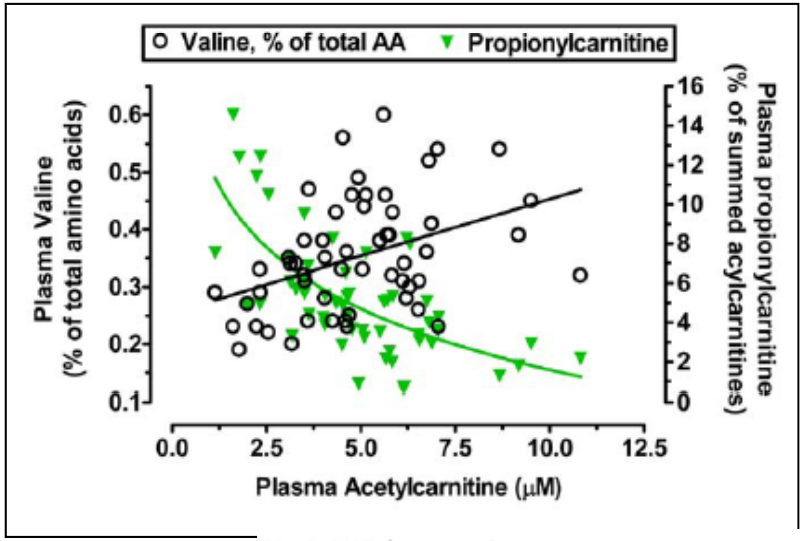


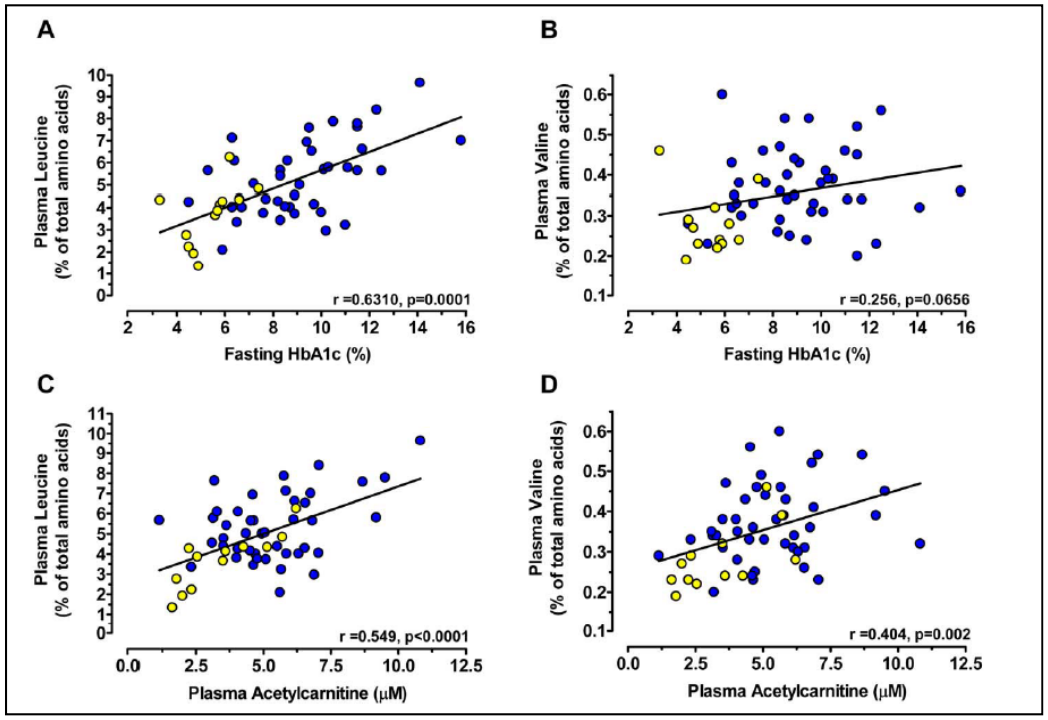
Classification of subjects according to insulin sensitivity and plasma glucose regulation. Schema showing the partitioning of the 399 subjects into groups according to the results of the oral glucose tolerance test (OGTT), fasting plasma glucose levels (FPG) and M values derived from the clamp. NGT, normal glucose tolerant; IGT, impaired glucose tolerant; NGT-IS, normal glucose tolerant and insulin sensitive (M_{FFM}>45 μmol·min^{-1}·kg$_{FFM}^{-1}$); NGT-IR, normal glucose tolerant and insulin resistant (M_{FFM}≤45 μmol·min^{-1}·kg$_{FFM}^{-1}$); IFG, normal glucose tolerant and impaired fasting glucose.
doi:10.1371/journal.pone.0010883.g004

PLoS One. 2010 May 28;5(5):e10883.

Plasma metabolomic profiles reflective of glucose homeostasis in non-diabetic and type 2 diabetic obese African-American women.

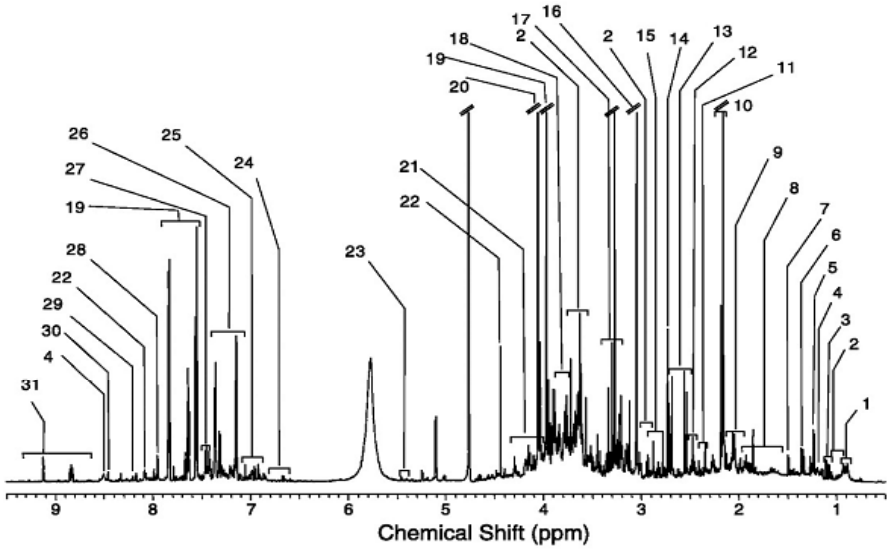






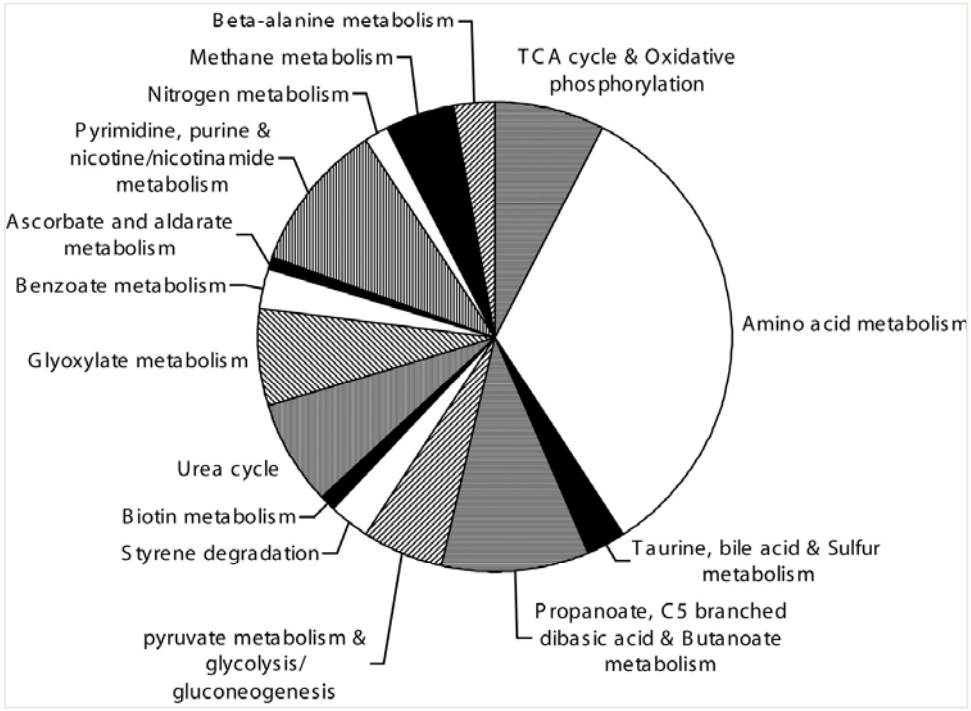
A metabolomic comparison of urinary changes in type 2 diabetes

Metabolomic analysis of human urine



A: high-resolution 700-MHz ^{1}H-NMR spectrum of an aqueous urine sample from a healthy control volunteer with the relevant resonance assignments shown. Each resonance corresponds to a chemical moiety within a particular metabolite with the intensity proportional to the concentration of that metabolite. *1*, -hydroxybutyrate/valerate; *2*, amino acids; *3*, valerate; *4*, unassigned; *5*, ß-hydroxybutyrate; *6*, lactate; *7*, alanine; *8*, amino acids/ornithine; *9*, *N*-acetyl groups/aspartate/glutamate; *10*, methionine; *11*, oxalacetate/pyruvate; *12*, ß-hydroxybutyrate/glutamine/glutamate; *13*, citrate; *14*, DMA; *15*, TMA/DMG; *16*, creatine/creatinine; *17*, taurine; *18*, PAG; *19*, hippurate; *20*, creatine/creatinine; *22*, uridine bases; *22*, NMN acid; *23*, allantoin; *24*, unassigned pyrimidine; *25*, 3-hydroxypropionic acid/tyrosine; *26*, meta-hydroxyphenyl-propionic acid (mHPPA) sulfate/indoxyl sulfate; *27*, PAG; *28*, *N*-methyl-2-pyridone-5-carboxamide (2PY); *29*, NMN amide; *30*, formate; *31*, NMN amide/NMN acid.

PLS-DA score plot of the healthy subjects compared with the type 2 diabetes mellitus (T2DM) patients.



Physiol. Genomics 29: 99-108, 2010

Metabolic network topology reveales transcriptional regulatory signatures of type 2 diabetes

muscle tissue metabolite profiling

Reporter metabolites for Mexican-American dataset.

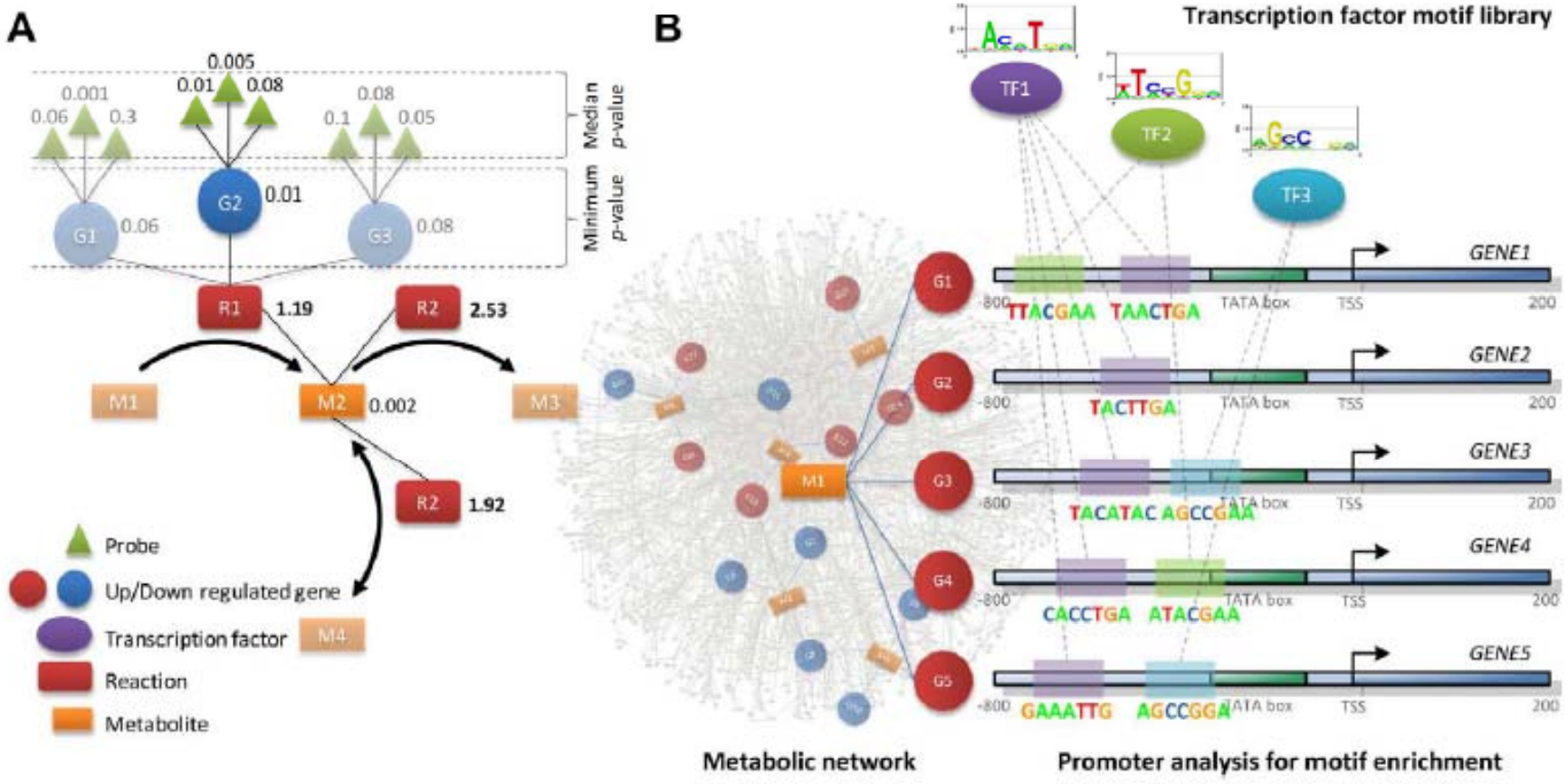
Reporter metabolite	P-values		Enzyme neighbors (Up-regulated:Down-regulated)		
	T2DM/FH−	FH+/FH−	T2DM/FH−	FH+/FH−	
2-Oxoglutarate	**0.001**	**0.001**	2:7	2:7	TCA cycle
L-Malate	0.098	**0.029**	1:4	2:3	
Succinyl-CoA†	**0.011**	**0.009**	0:5	0:5	
Ferrocytochrome C;Ferricytochrome C	**0.008**	**0.007**	0:3	0:3	Oxidative phosphorylation
Fumarate	**0.019**	**0.025**	0:2	0:2	
Ubiquinone-10†;Ubiquinol-10†	**0.040**	**0.021**	1:3	1:3	
2,3-Disphospho-D-glycerate†	**0.021**	**0.004**	0:1	0:1	Glycolysis
2-Phospho-D-glycerate*	**0.038**	**0.006**	0:2	1:1	
beta-D-Fructose*	**0.049**	**0.038**	0:2	0:2	
D-Fructose 2,6-bisphosphate	**0.037**	0.136	0:2	0:1	
D-Fructose 6-phosphate	**0.013**	0.119	4:6	3:7	
D-Glucose*	**0.037**	0.066	0:7	1:5	
D-Glucose 6-phosphate	**0.009**	**0.014**	1:3	1:3	
D-Glycerate 2-phosphate	**0.026**	**0.003**	0:2	1:1	
L-Lactate	**0.048**	0.067	1:2	1:2	
Phosphoenolpyruvate	0.079	**0.048**	2:2	3:1	
Pyruvate	**0.042**	0.202	1:6	1:6	
2-Oxoadipate*	**0.002**	**0.004**	0:1	0:1	Amino acid metabolism
beta-Alanine	**0.031**	**0.027**	1:1	1:1	
L-Glutamate†	**0.025**	**0.009**	1:1	1:1	
(R)-2-Methyl-3-oxopropanoyl-CoA*	**0.043**	0.118	0:2	0:1	Lipid metabolism
*1,2-Diacyl-sn-glycerol (DAG)**	**0.036**	0.117	3:2	5:1	
1D-myo-Inositol 1,4-bisphosphate	**0.025**	0.054	1:2	1:2	
3-cis-Dodecenoyl-CoA*	**0.009**	**0.039**	0:3	0:3	
Acylglycerol*; 2-Acylglycerol*	**0.035**	**0.018**	1:1	1:1	
Glutaryl-CoA†	**0.007**	**0.015**	0:2	0:2	
Glycerol	**0.020**	**0.001**	1:1	1:1	
Glycerol 3-phosphate	0.051	**0.005**	2:1	2:1	
Lipoamide*	**0.014**	**0.006**	0:5	0:5	
Phosphatidylinositol	**0.017**	0.128	1:5	1:5	
trans-3-decenoyl-CoA*	**0.026**	0.076	0:2	0:2	
ADP	**0.047**	0.174	16:31	20:27	Other
CO_2	**0.041**	**0.004**	1:11	3:9	
Coenzyme A†	**0.007**	**0.014**	4:8	3 10	
Creatine;Phosphocreatine†	**0.032**	**0.048**	0:1	0:1	
NAD+†; NADH†	**0.003**	0.095	3:17	17:4	
Trichloroethanol*	**0.021**	**0.006**	2:1	3:0	

Reporter metabolites for Swedish male dataset.

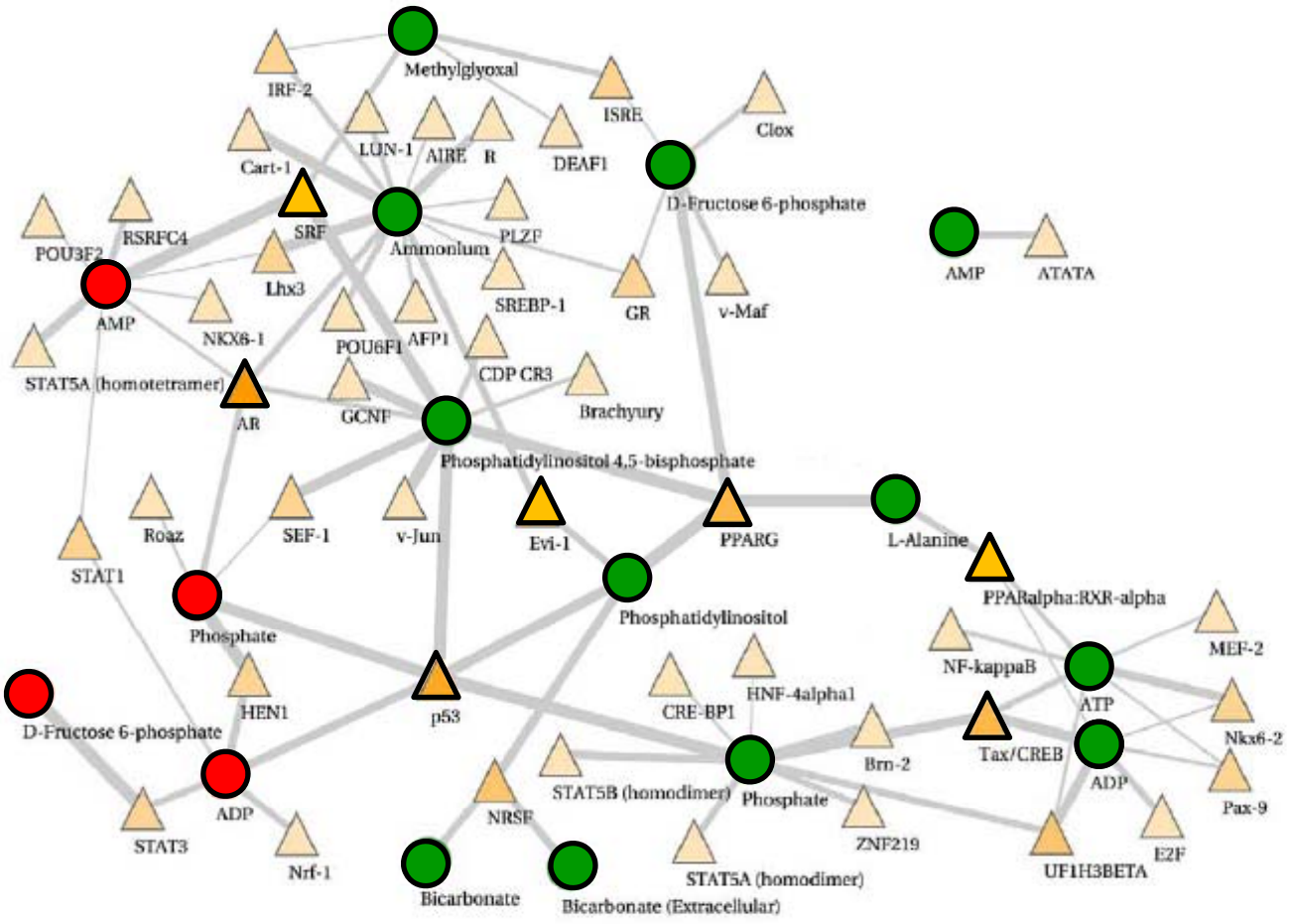
Reporter Metabolite	P-values		Enzyme neighbors (Up-regulated:Down-regulated)		
	T2DM/NGT	IGT/NGT	T2DM/NGT	IGT/NGT	
Citrate	**0.047**	0.646	1:0	1:0	TCA cycle
Succinyl-CoA	**0.013**	0.285	2:3	2:3	
2-Hydroxyglutarate*	**0.002**	**0.023**	0:1	0:1	
*2-Oxoglutarate**	**0.049**	**0.047**	8:11	8:11	
Ferrocytochrome C; Ferricytochrome C	**0.006**	**0.032**	1:2	0:3	Oxidative phosphorylation
Ubiquinone-10	**0.017**	0.769	0:5	1:4	
Ubiquinol-10	**0.022**	0.484	0:4	1:3	
Phosphoenolpyruvate*	0.196	**0.037**	1:3	1:3	Glycolysis
D-Glyceraldehyde*	0.083	**0.017**	2:1	3:0	
D-Alanine	**0.016**	0.330	0:3	0:3	Amino acid metabolism
L-Alanine	**0.047**	0.319	3:7	3:7	
3-Methylglutaconyl-CoA†	**0.038**	0.816	0:2	1:1	
*L-Leucine**	**0.047**	0.109	1:3	1:3	
*1,2-Diacyl-sn-glycerol (DAG)**	**0.022**	**0.049**	2:5	2:5	Lipid metabolism
1D-myo-Inositol 1,4-bisphosphate†	0.060	0.151	0:3	2:1	
3-Dehydrosphinganine*	0.232	**0.035**	1:1	2:0	
Acetoacetyl-CoA*	**0.009**	0.462	1:4	2:3	
Butanoyl-CoA†	0.365	**0.038**	0:2	1:1	
*Decanoyl-CoA; Lauroyl-CoA**	0.268	**0.033**	1:2	2:1	
Fatty acid*	**0.021**	0.756	3:4	3:4	
Lophenol*‖	**0.007**	0.749	0:1	0:1	
*Palmitoleoyl-CoA**	0.238	**0.019**	1:3	2:2	
*Palmitoyl-CoA**	0.179	**0.014**	3:4	6:1	
Phosphatidyl glycerol phosphate	**0.047**	0.316	0:1	0:1	
Phosphatidylinositol 4,5-bisphosphate	0.097	**0.001**	1:5	2:4	
Propanoyl-CoA*	0.259	**0.016**	2:5	2:5	
Prostaglandin E2	**0.036**	**0.032**	0:3	1:2	
Sphinganine*	**0.038**	0.283	1:3	2:2	
(Gal)3 (GalNAc)1 (Glc)1 (Cer)1*	**0.023**	**0.034**	1:2	1:2	Other
AMP†	**0.041**	0.218	7:17	6:17	
ATP†	**0.003**	**0.010**	28:60	27:60	
cAMP†	**0.033**	**0.049**	2:0	2:0	
CDPcholine	**0.020**	0.122	0:2	0:2	
Choline phosphate	**0.030**	0.573	0:2	1:1	
NAD+*	0.333	**0.020**	29:34	34:34	
Phosphocreatine	**0.025**	0.176	0:1	1:0	
Trichloroethanol*	**0.020**	**0.038**	1:2	3:0	

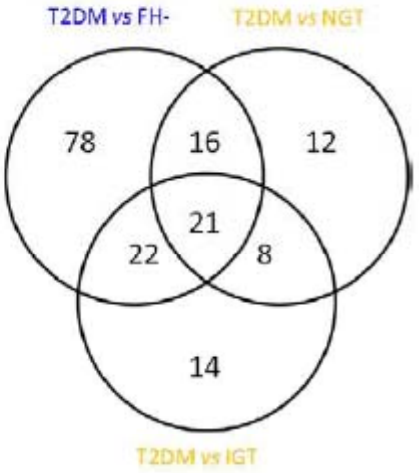
Metabolic network topology reveales transcriptional regulatory signatures of type 2 diabetes

motive enrichment analysis



Metabolic network topology reveales transcriptional regulatory signatures of type 2 diabetes





reporter molecules UP

reporter molecules DOWN

transcription factor binding motifs

Summary of the main results from the motif enrichment analysis. A) Motif enrichment analysis for the genes associated with reporter metabolites from the T2DM vs NGT comparison. Reporter metabolites with up-regulated neighboring gene set are shown as red circles, whereas reporter metabolites with down-regulated neighboring gene set are represented as green circles. Transcription factor binding motifs (shown as triangles) are colored according to the number of enzyme sets in which they are enriched, ranging from light yellow (enriched in few sets) toorange (enriched in as many as 6 sets). Edges are scaled according to q-values signifying the confidence of the motif enrichment. B) Venn diagramshowing the overlap of transcription factor binding motifs across the comparisons

SUMMARY

Nutrigenomics/genetics applications in biomarker discovery for NIDDM/metabolic syndome

- **The GWAS have not delivered SNP´s/haplotypes with prognostic/ diagnostic values that are superior to „classical“ diagnosis tools.**
- **The applications of the profiling techniques to characterise the molecular changes induced by insulin resistance or NIDDM have not yet revealed any robust and specific markers for early diagnosis of metabolic impairments.**
- **It needs many more well controlled and large-scale studies in which profiling techniques are combined with excellent phenotyping approaches and robust clinical endpoints.**


Thank you for your attention !