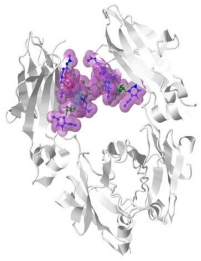
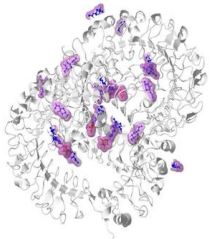
Visokoprotočna glikomika u molekularnoj dijagnostici

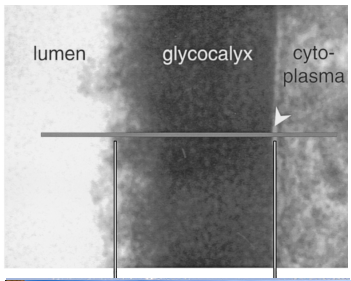
Gordan Lauc
University of Zagreb &
Genos Glycoscience Research Laboratory

WO2014203010; US2016103137, WO2012042020; WO2011015944; WO2009044213

Glycans are important structural component of nearly all proteins





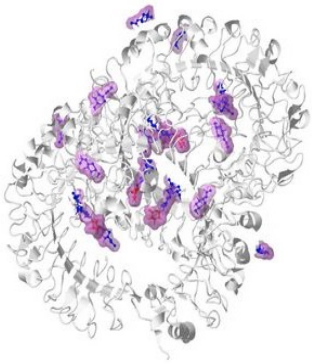


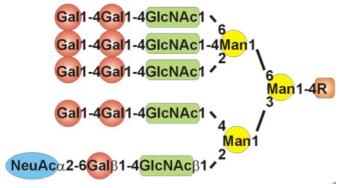
Genome does not contain templates for synthesis of glycan parts of glycoproteins

DNA ⇄ RNA → proteins

↓ ???

glycoproteins



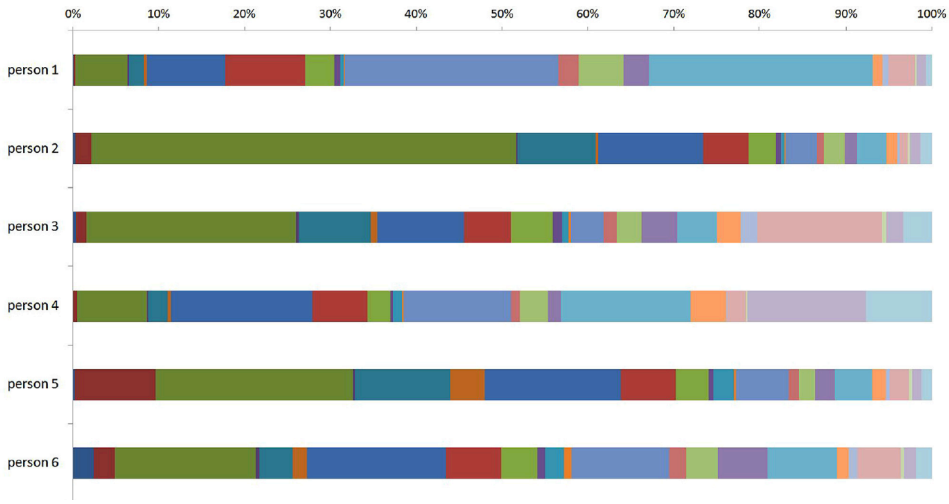


Cohort	Plasma glycome	IgG Glycome
10001 Dalmatian	2,000	4,000
Orcades	2,000*	2,000
TwinsUK	4,000	4,500
KORA	–	2,000
SABRE	2,000	–
Global population study	–	2,700
FINNRISK	–	1,200
Estonian biobank	–	1,300
China	1,000	1,000
CRC	2,000*	2,000
IBD	3,000	5,700
SLE	–	1,200
Type 1 Diabetes	1,000	1,000
Type 2 Diabetes	–	3,000
Down syndrome	–	800
PTSD	600	600
Total	17,600	33,000

* Analysed in NIBRT

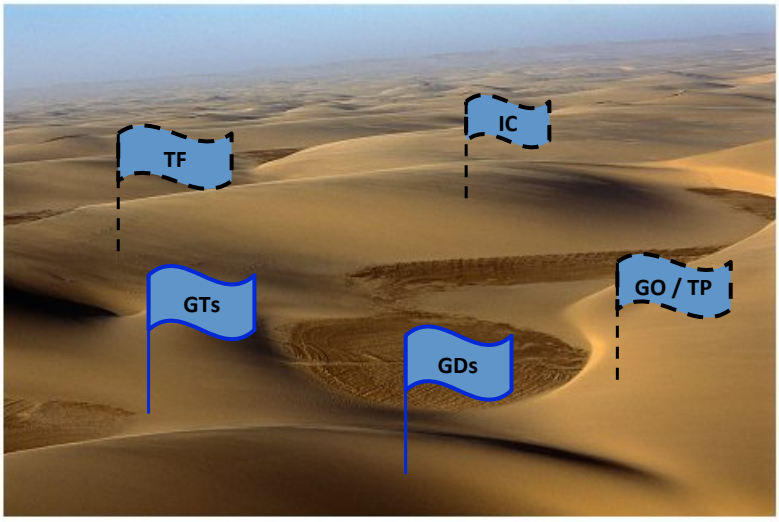
Mining the gold from big glycomics datasets

Composition of IgG glycome differs significantly between individuals

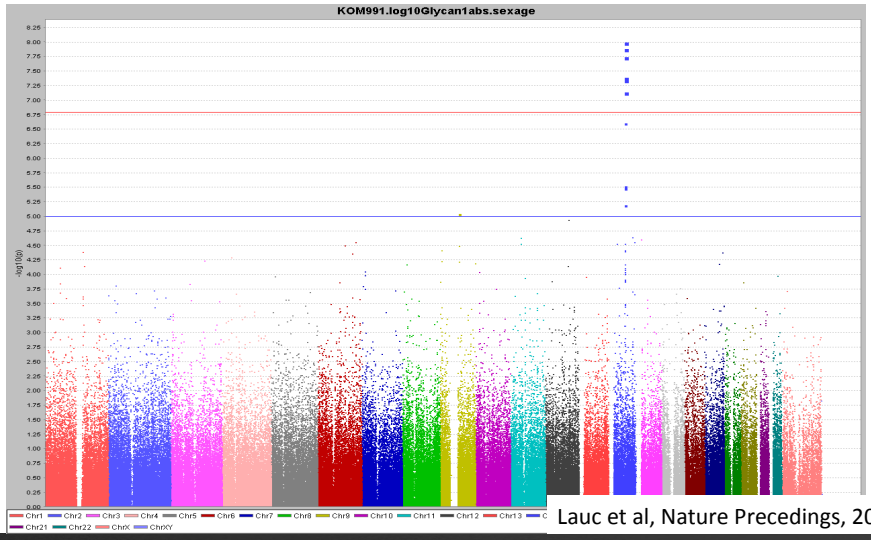


Lauc et al, Front Genet, 2014

The majority of genes that affect IgG glycosylation are still not known



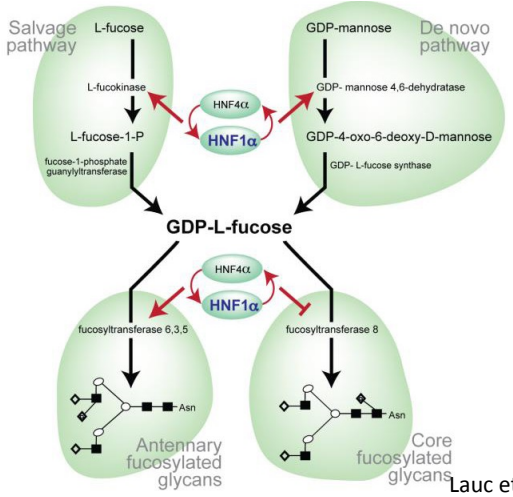
Genome-wide association (GWA) studies can be used to map genes involved in glycosylation



Lauc et al, Nature Precedings, 2009

The first GWAS study of human glycome identified HNF1A as a master regulator of plasma protein fucosylation

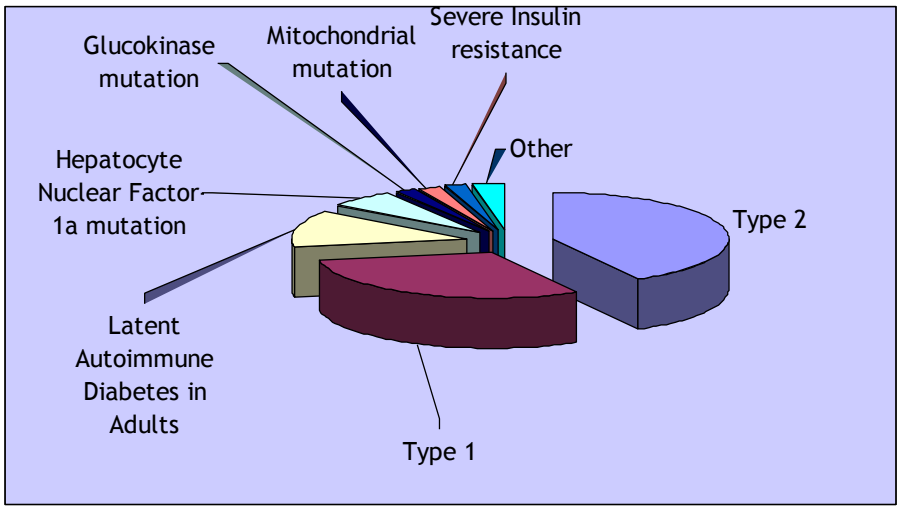
Ana Mužinić



Lauc et al, *PLoS Genetics*, 2010

GENOS www.genos-glyco.com UNI-ZG

Mutations in *HNF1A* cause Maturity Onset Diabetes of the Young (HNF1A-MODY)



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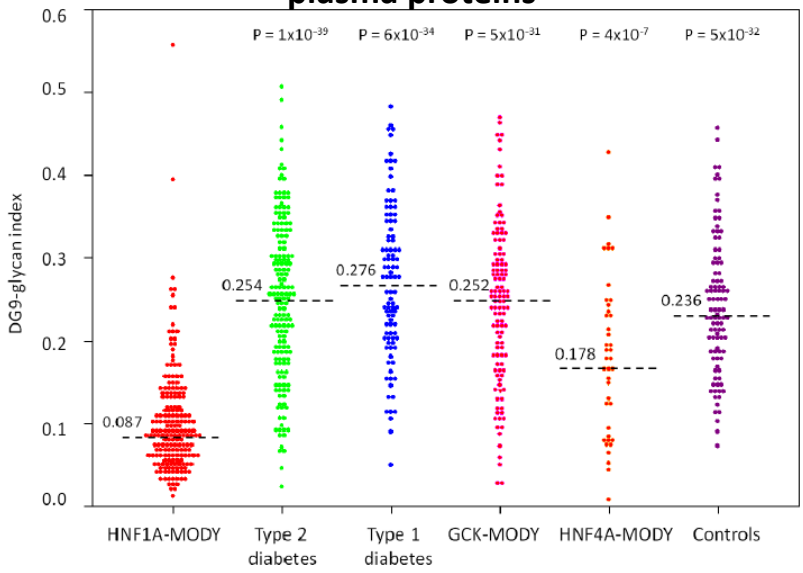
Mutations in HNF1A result in decreased fucosylation of plasma proteins



Glycan ratio (DG9 - index) is a robust biomarker for HNF1A-MODY

Mislav Novokmet

Thanabalasingham et al, *Diabetes, 2013*

Analysis in a prospective setting

- 1100 young onset diabetics recruited in Zagreb and Oxford
- Plasma glycome analysed by UPLC
- Sequencing of the entire HNF1a gene
  - 32 mutations (11 known to be pathological)
- Classification


Prof. Olga Gornik


Frano Vučković


Tamara Pavić

EFSD European Foundation for the Study of Diabetes

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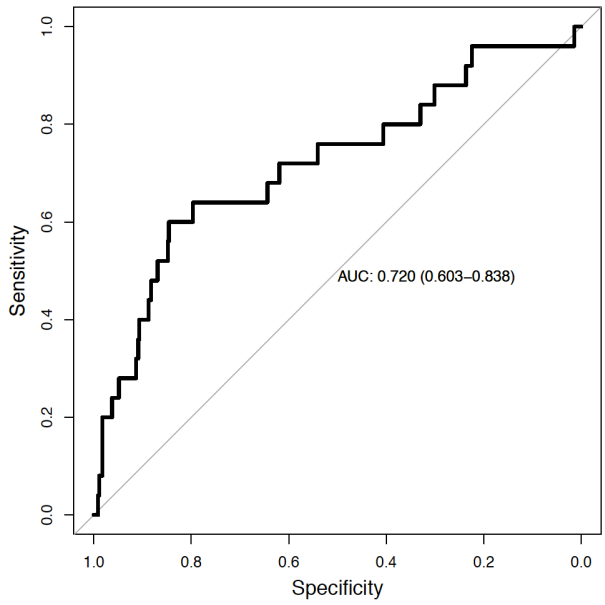
All HNF1a mutations



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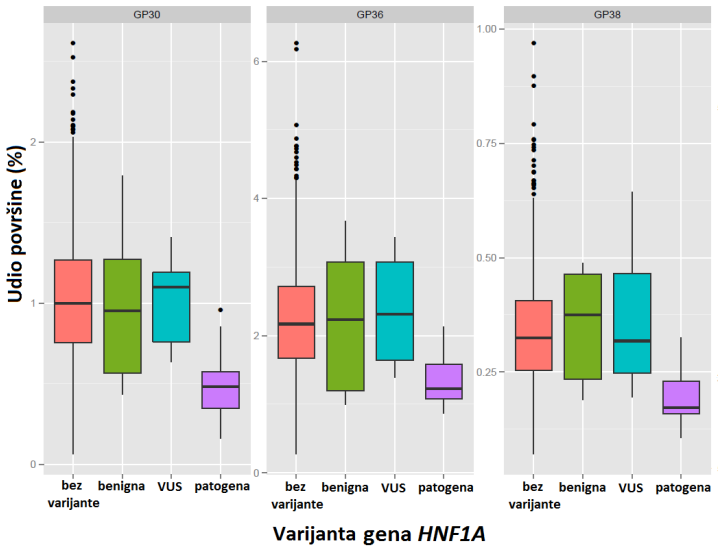
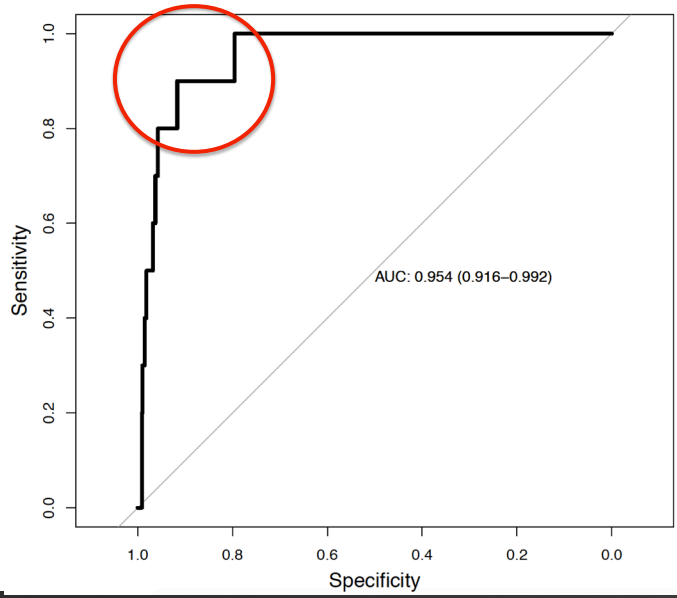
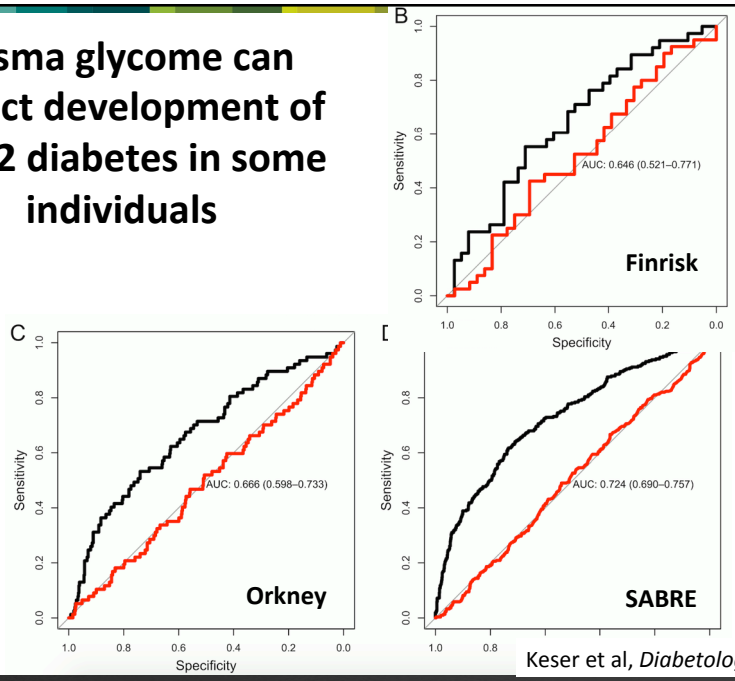
Glycan profiling can identify pathogenic mutations



Known pathogenic mutations

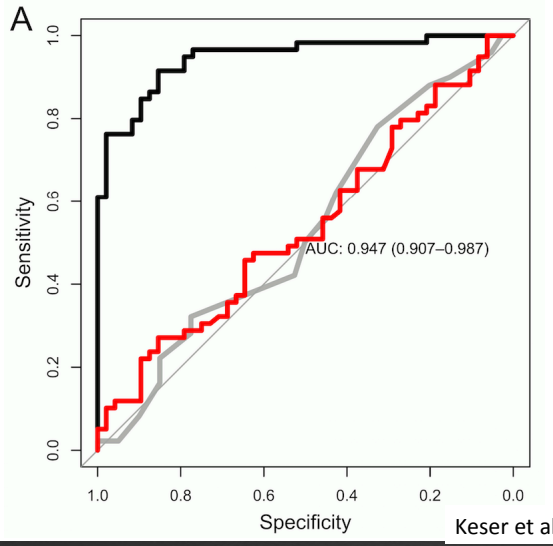


Plasma glycome can predict development of type 2 diabetes in some individuals



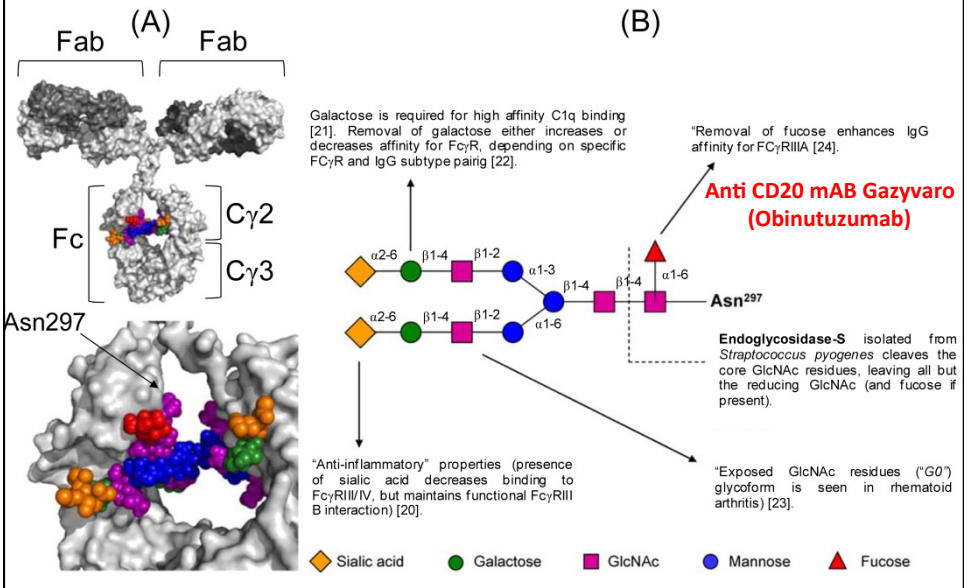
Keser et al, *Diabetologia, 2017*

Plasma glycome is a very good predictor for hyperglycemia in acute disease

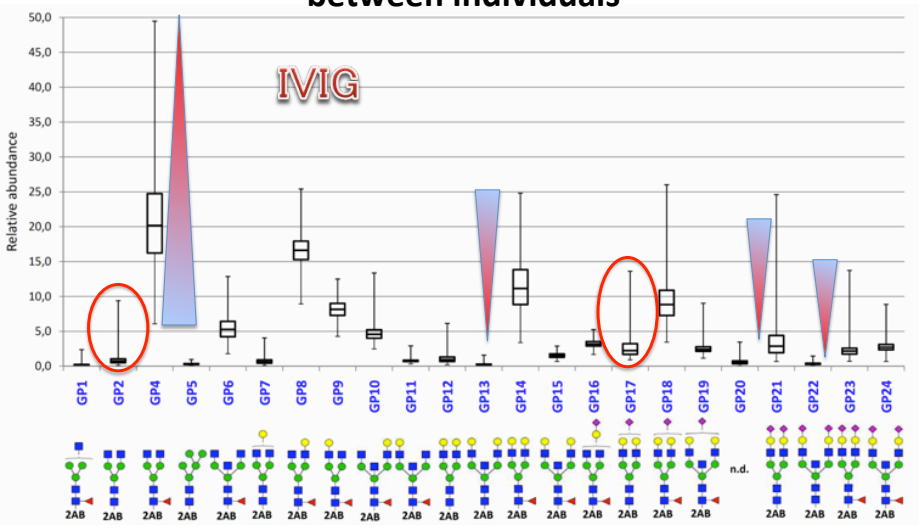


Keser et al, *Diabetologia, 2017*

IgG glycosylation is functionally important



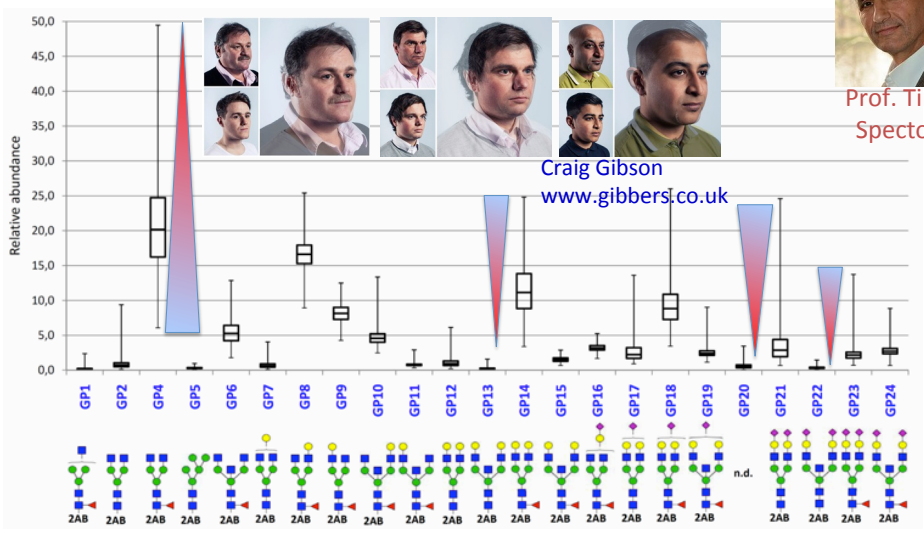
Composition of IgG glycome differs significantly between individuals



Pučić et al, *Mol Cell Proteomics*, 2011

Heritability of glycome composition is up to 80%

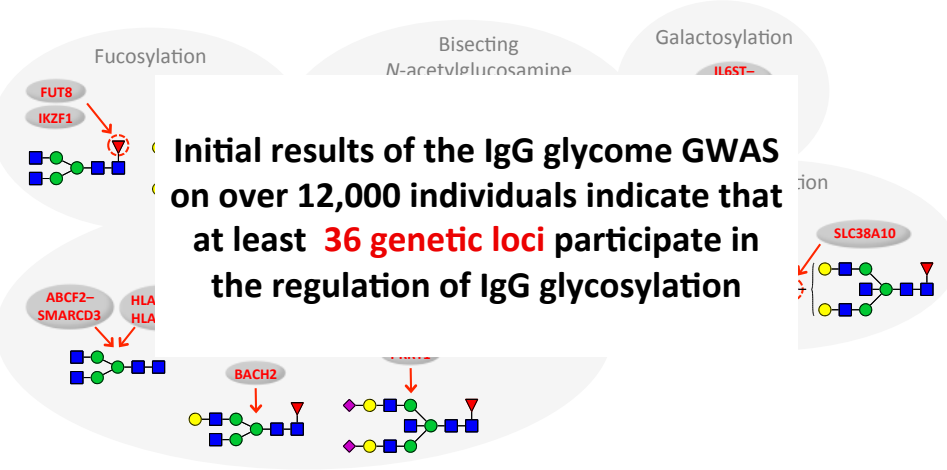
Prof. Tim Spector



Craig Gibson
www.gibbers.co.uk

Menni et al, *PLoS ONE*, 2013

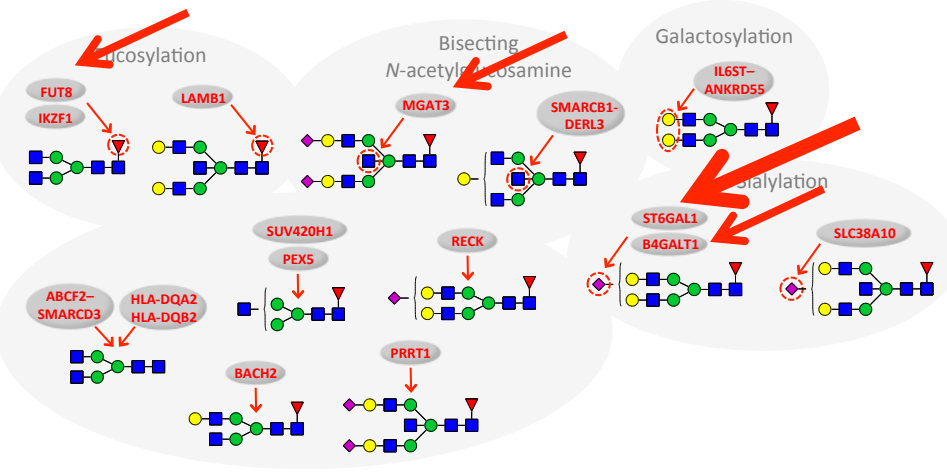
GWAS of IgG glycome performed on 2247 individuals identified 16 genome wide significant associations



Initial results of the IgG glycome GWAS on over 12,000 individuals indicate that at least 36 genetic loci participate in the regulation of IgG glycosylation

Lauc et al, *PLoS Genetics*, 2013

Out of 37 loci that associate with IgG glycans, only 4 contain known glyco-genes

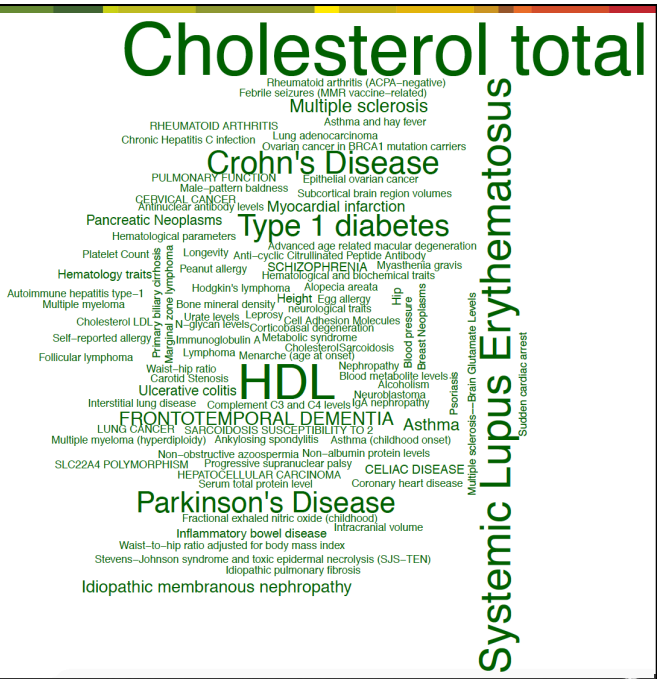


Lauc et al, *PLoS Genetics*, 2013

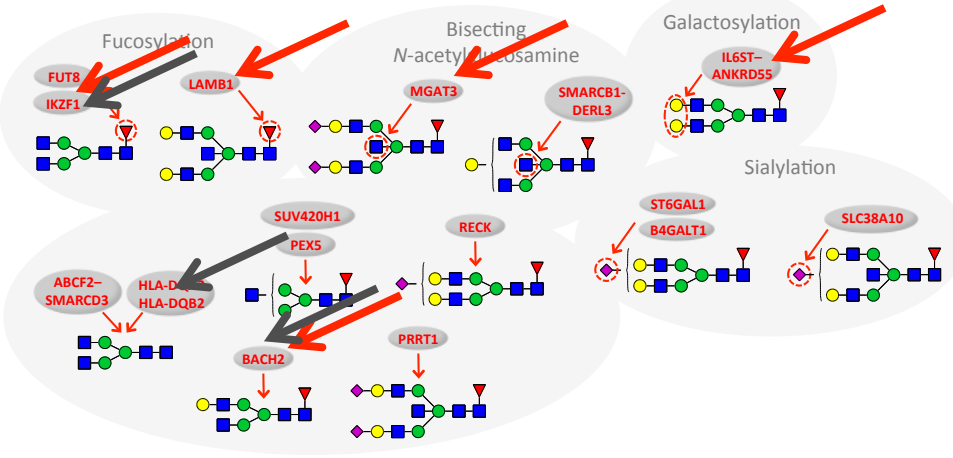
Genes that govern IgG glycosylation show pleiotropy with multiple diseases and traits

94 different phenotypes have at least one SNP in common

Size of letters depends on number of SNPs in common

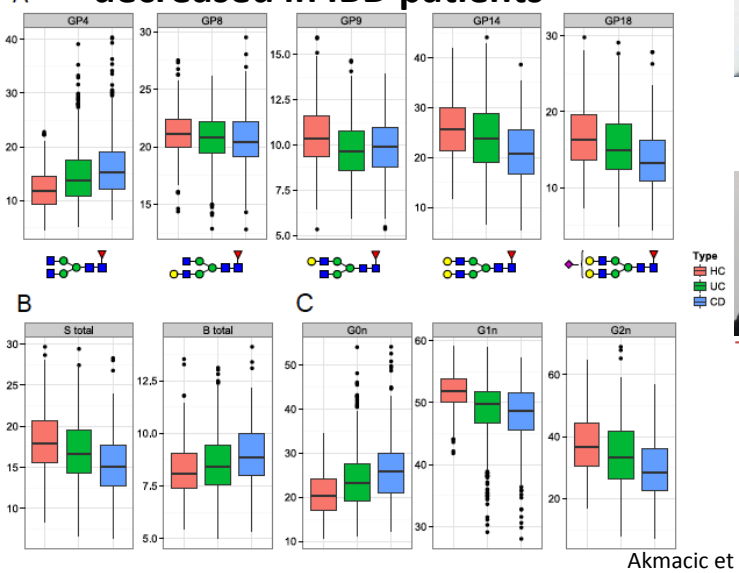


IgG glycosylation shows pleiotropy with Inflammatory Bowel Disease (IBD) and Systemic Lupus Erythematosus (SLE)



Lauc et al, *PLoS Genetics*, 2013

Immunosuppresive potential of IgG is decreased in IBD patients

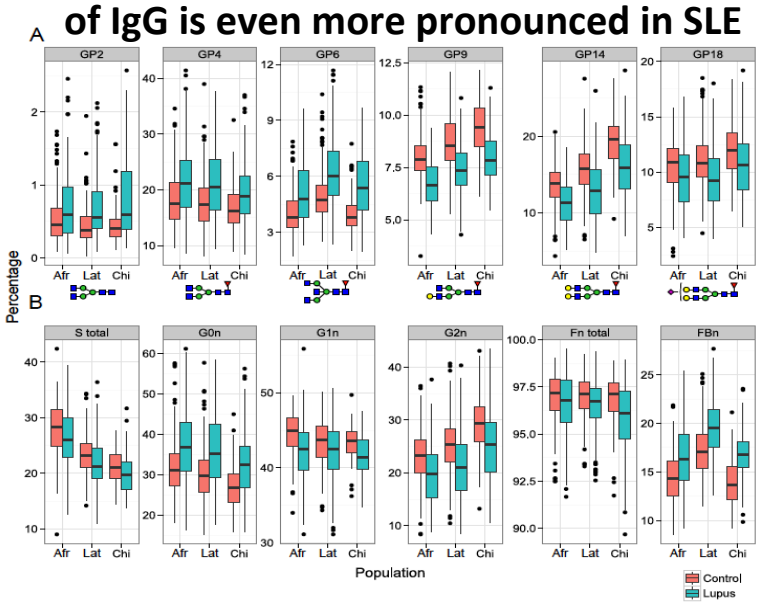


Irena Akmačić Trbojević

Toma Keser

Akmacic et al, *IBD*, 2015

The decrease in immunosuppresive potential of IgG is even more pronounced in SLE



Frano Vučković

Jasminka Krištić

Vučković et al *Arthr Rheum*, 2015

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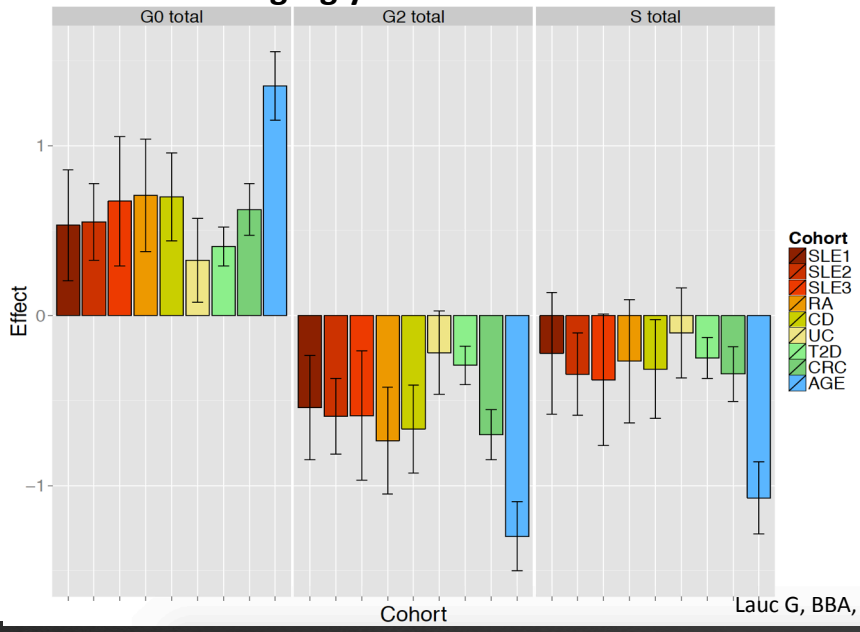
IgG glycome in disease



Lauc G, BBA, 2016

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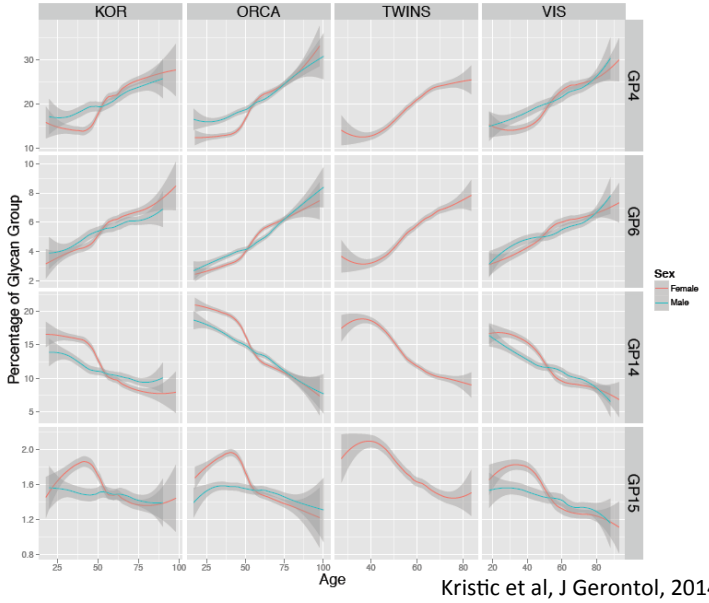
Age is a very strong confounder for IgG glycome



Jasminka Krištić

Toma Keser

Frano Vučković

Kristic et al, J Gerontol, 2014

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IgG glycome composition is an excellent biomarker of chronological and biological age

Ivan Gudeli

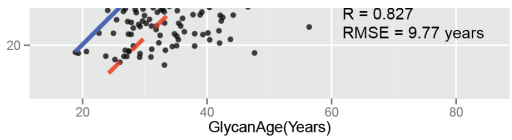
Jasminka

Journals of Gerontology: BIOLOGICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci
doi:10.1093/gerona/glt202

Guest Editorial

Are Glycans the Holy Grail for Biomarkers of Aging? (Comment on: Glycans Are a Novel Biomarker of Chronological and Biological Age by Kristic et al.)

David G. Le Couteur,[1,2,3] Stephen J. Simpson,[3,4] and Rafael de Cabo[5]



Gudelj et al, Int J leg Med, 2015

Kristić et al, J Gerontol, 2014

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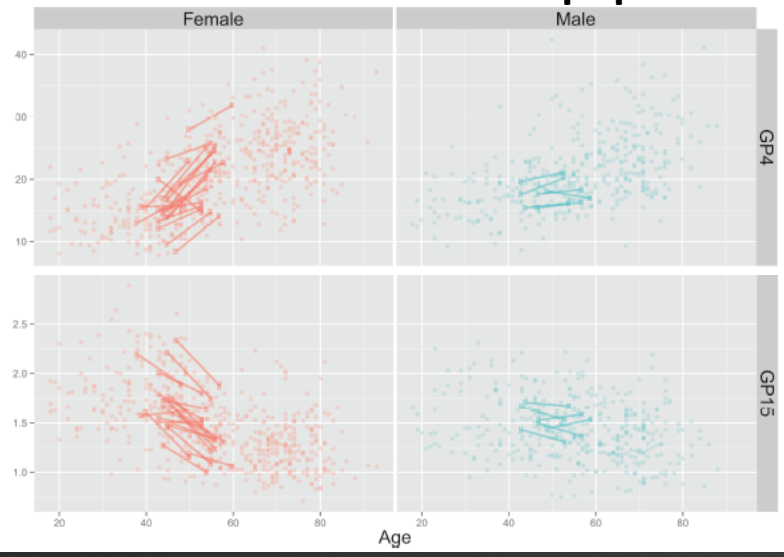
After correcting for chronological age, glycan age index associates with "unhealthy" life

	Orkney		Vis and Korcula	
	Beta	*p*	Beta	*p*
Insulin	0.0755	9.22E-08	0.0402	3.50E-01
Fibrinogen	0.0157	1.98E-06	0.0167	8.83E-05
HbA1c	0.1106	2.63E-06	0.0084	3.16E-03
BMI	0.0585	1.67E-04	0.0344	1.04E-02
Triglycerides	0.0092	1.75E-04	0.0140	1.20E-04
Glucose	0.0113	2.09E-04	0.0091	4.77E-02
Waist circumference	0.1468	2.08E-04		
Calcium	0.0010	2.35E-04	0.0002	7.04E-01
D-dimer	2.9670	8.24E-04		
Cholesterol	0.0036	3.07E-01	0.0201	5.51E-08
LDL	0.0031	3.26E-01	0.0146	6.08E-06
Uric acid	1.0773	4.02E-02	0.7620	9.68E-04

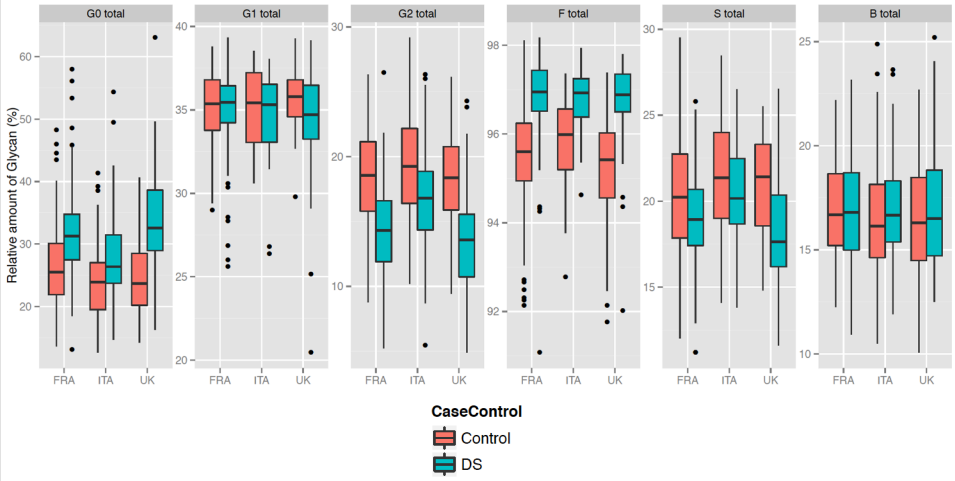
Note: HbA1c = glycosylated hemoglobin; BMI = body mass index; LDL = low-density lipoprotein; *p* = *p* value; beta = regression coefficient.

Kristic et al, J Gerontol, 2014

Changes within an individual generally follow trends observed in a population



IgG glycome in Down syndrome reflects accellerated ageing



Lifestyle interventions can change IgG glycome composition even in older adults

Prof. Eline Slagboom

www.impactaging.com AGING, January 2016, Vol. 8 No 1

Research Paper

Metabolic effects of a 13-weeks lifestyle intervention in older adults: The Growing Old Together Study

Ondine van de Rest[1,#], Bianca A.M. Schutte[2,#], Joris Deelen[2,#], Stephanie A.M. Stassen[3], Erik B. van den Akker[2,4], Diana van Heemst[3], Petra Dibbets-Schneider[5], Regina. A. van Dipten-van der Veen[1], Milou Kelderman[1], Thomas Hankemeier[6], Simon P. Mooijaart[3], Jeroen van der Grond[5], Jeanine J. Houwing-Duistermaat[7], Marian Beekman[2], Edith J.M. Feskens[1], and P. Eline Slagboom[2]

Intensive excersize makes IgG glycome more pro-inflammatory, but only transiently

Prof. Markus Perola

frontiers in Physiology

ORIGINAL RESEARCH
published: 10 January 2017
doi: 10.3389/fphys.2016.00689

The Effects of Intensive Weight Reduction on Body Composition and Serum Hormones in Female Fitness Competitors

Juha J. Hulmi[1,2], Ville Isola[1], Marianna Suonpää[3], Neea J. Järvinen[1], Marja Kokkonen[4], Annika Wennerström[5,6], Kai Nyman[7], Markus Perola[5,6,8], Juha P. Ahtiainen[1] and Keijo Häkkinen[1]*

GENOS www.genos-glyco.com UNI-ZG

IgG glycome is better predictor of mortality, than NMR biomarkers or methylation

Prof. Ian Deary

Marioni *et al. Genome Biology* (2015) 16:25
DOI 10.1186/s13059-015-0584-6

Genome Biology

RESEARCH Open Access

DNA methylation age of blood predicts all-cause mortality in later life

Riccardo E Marioni[1,2,3†], Sonia Shah[3,4†], Allan F McRae[3,4†], Brian H Chen[5,6†], Elena Colicino[7†], Sarah E Harris[1,2], Jude Gibson[8], Anjali K Henders[9], Paul Redmond[10], Simon R Cox[1,10], Alison Pattie[10], Janie Corley[10], Lee Murphy[8], Nicholas G Martin[9], Grant W Montgomery[9], Andrew P Feinberg[11,12], M Daniele Fallin[11,13], Michael L Multhaup[11], Andrew E Jaffe[13,14], Roby Joehanes[5,15,16], Joel Schwartz[7,17], Allan C Just[7], Kathryn L Lunetta[5,18], Joanne M Murabito[5,19], John M Starr[1,20], Steve Horvath[21,22†], Andrea A Baccarelli[7,17†], Daniel Levy[5,6†], Peter M Visscher[3,4†], Naomi R Wray[3*†] and Ian J Deary[1,10*†]

Dr. Krista Fisher

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PLOS | MEDICINE

Biomarker Profiling by Nuclear Magnetic Resonance Spectroscopy for the Prediction of All-Cause Mortality: An Observational Study of 17,345 Persons

Krista Fischer[1☯*], Johannes Kettunen[2,3,4☯], Peter Würtz[2,4☯*], Toomas Haller[1], Aki S. Havulinna[3], Antti J. Kangas[4], Pasi Soininen[4,5], Tõnu Esko[1,6,7,8,9,10], Mari-Liis Tammesoo[1], Reedik Mägi[1], Steven Smit[1], Aarno Palotie[2,6,11], Samuli Ripatti[2,11], Veikko Salomaa[3], Mika Ala-Korpela[4,5,12¶], Markus Perola[1,2¶], Andres Metspalu[1,13¶]

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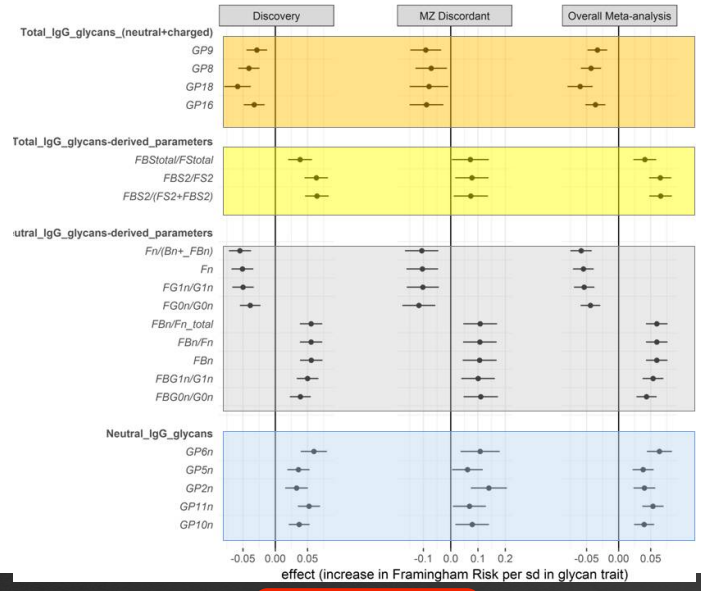
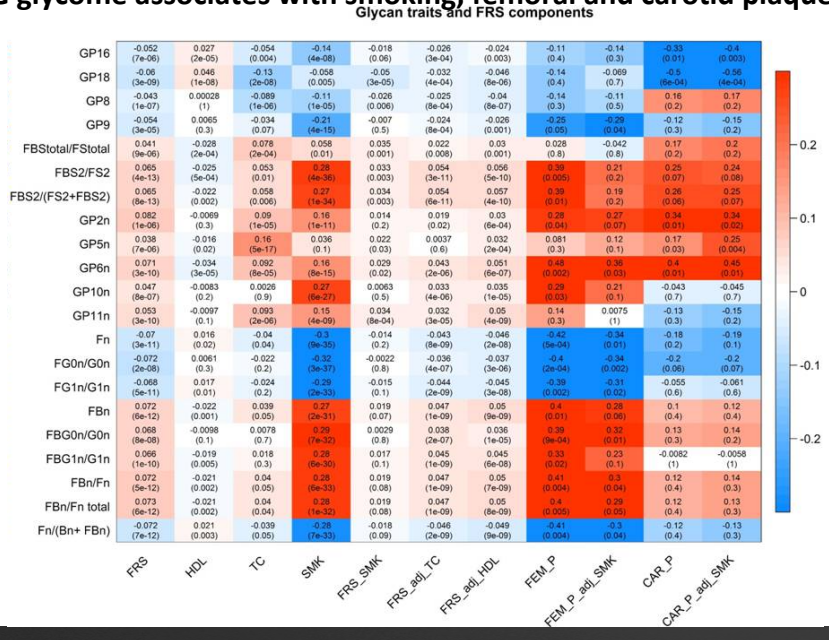
IgG glycome strongly associates with Framingham cardiovascular risk score

Prof. Tim Spector



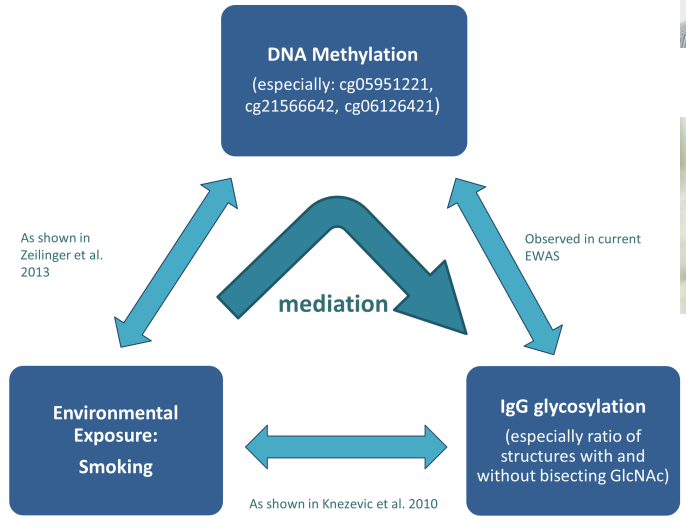
IgG glycome associates with smoking, femoral and carotid plaques



Effects of smoking on IgG glycome is mediated by DNA methylation

Dr. Christian Gieger

Annika Wahl



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Grant Morahan

Manfred Wuhrer
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Falk Nimmerjahn

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Nenad Šestan

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Christian Gieger, Jan Krumsiek

Dermot McGovern

Karsten Suchre

Gastone Castelani
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Wei Wang

Wei Wang

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GlycoBioM
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znanstveni centri izvrsnosti
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INTEGRA-LIFE
Ministarstvo poduzetništva i obrta
MINPO
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