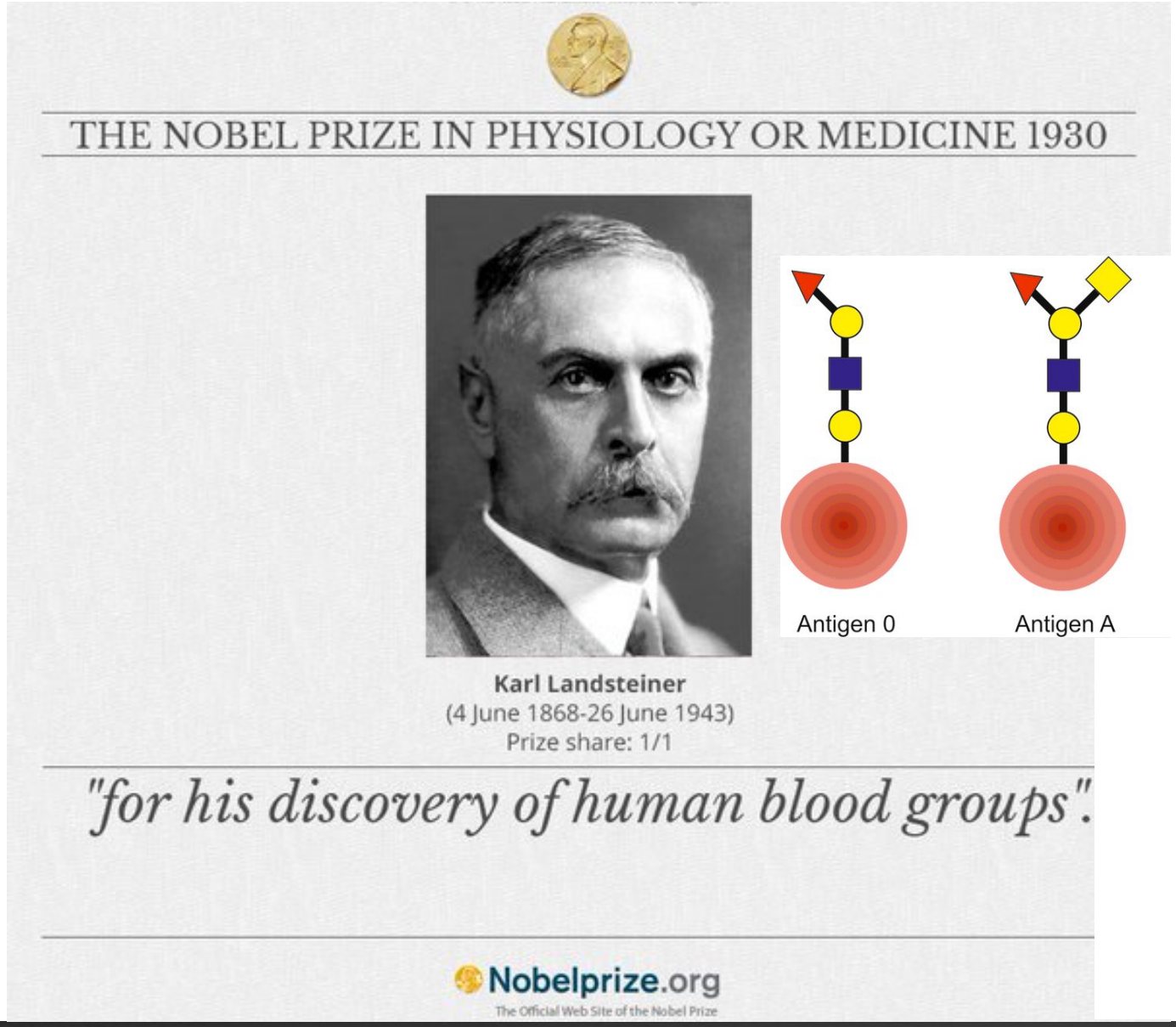
Introduction to glycobiology

ImForFuture

Gordan Lauc

University of Zagreb & Genos

We are all not the same!!!



THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE 1930

Karl Landsteiner
(4 June 1868-26 June 1943)
Prize share: 1/1

"for his discovery of human blood groups".

Nobelprize.org
The Official Web Site of the Nobel Prize

Antigen 0 Antigen A Antigen B

red blood cell

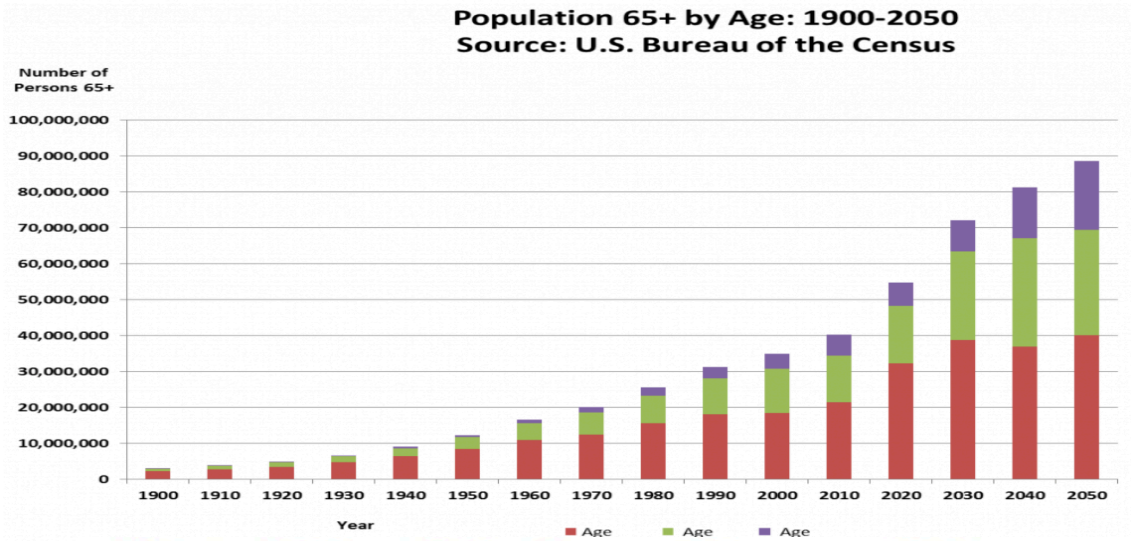
galactose

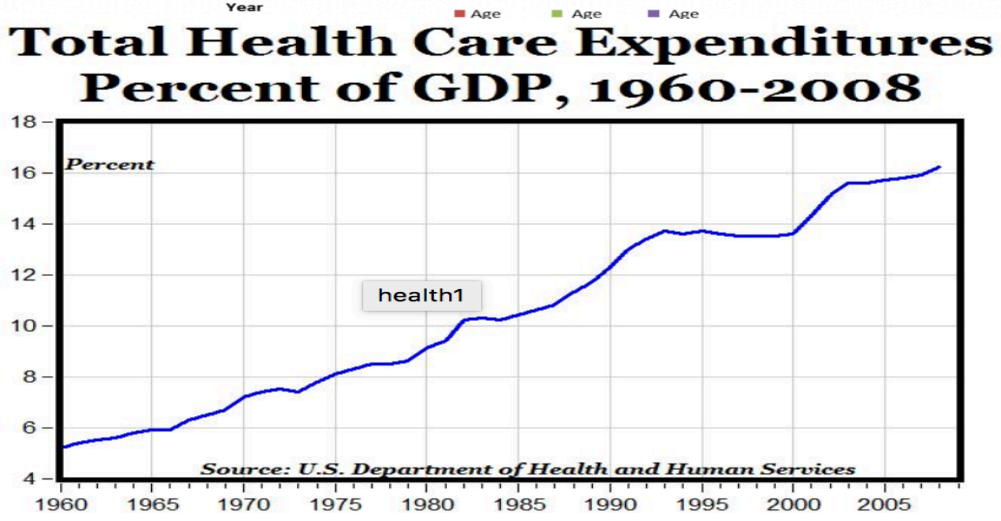
N-acetylglucosamine

fucose

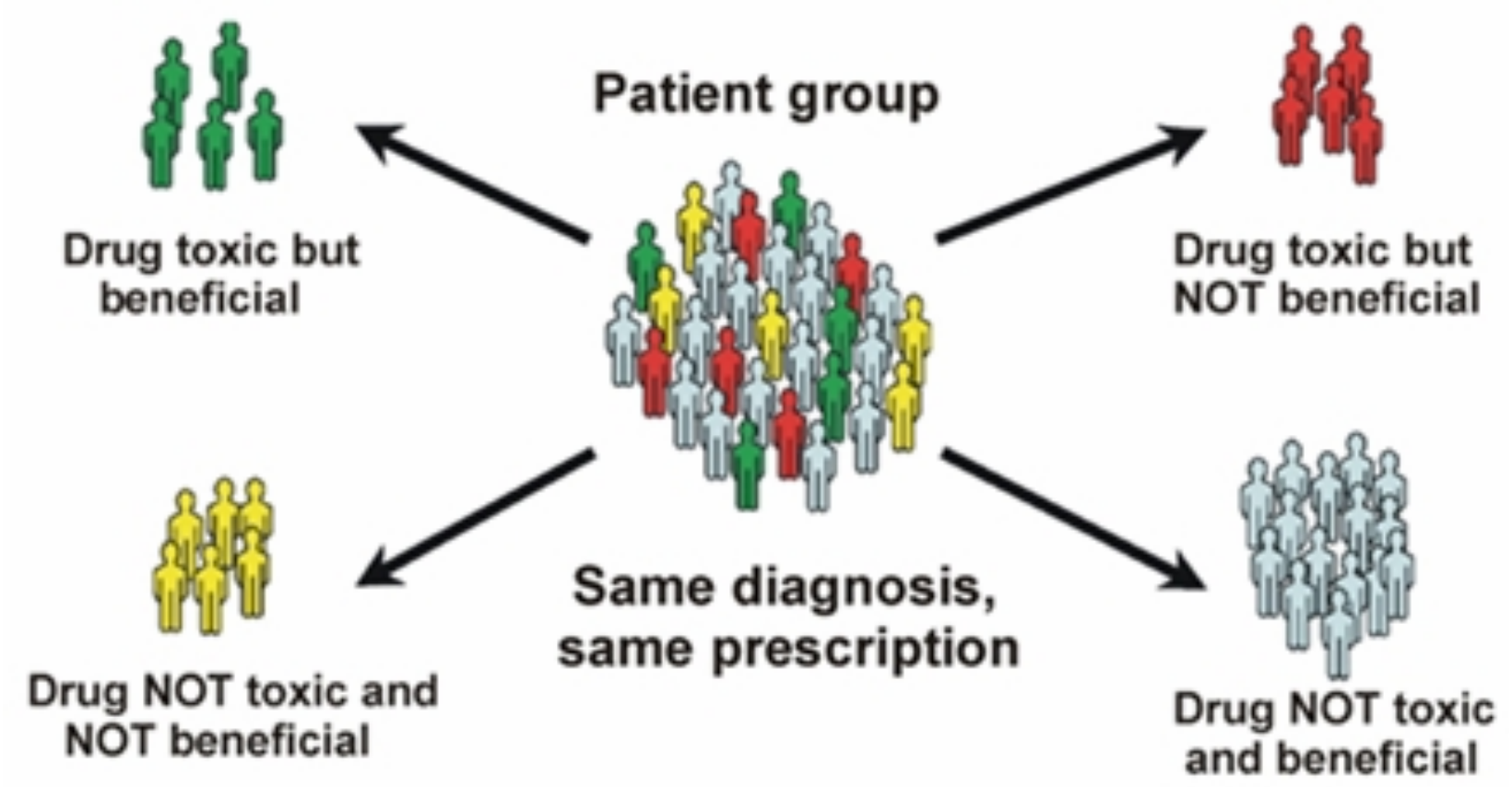
N-acetylgalactosamine

Heatlhy ageing *vs* health deterioration

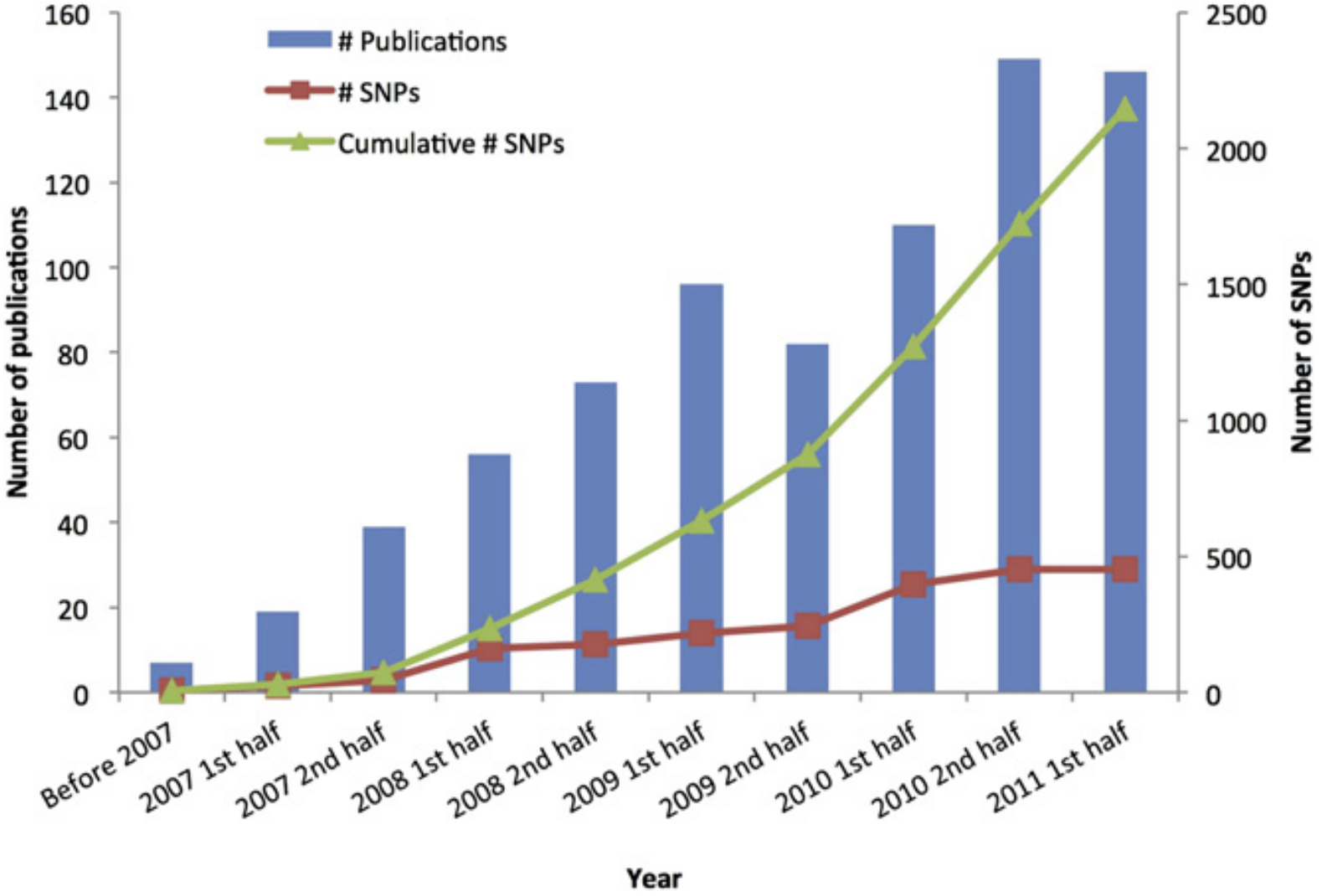


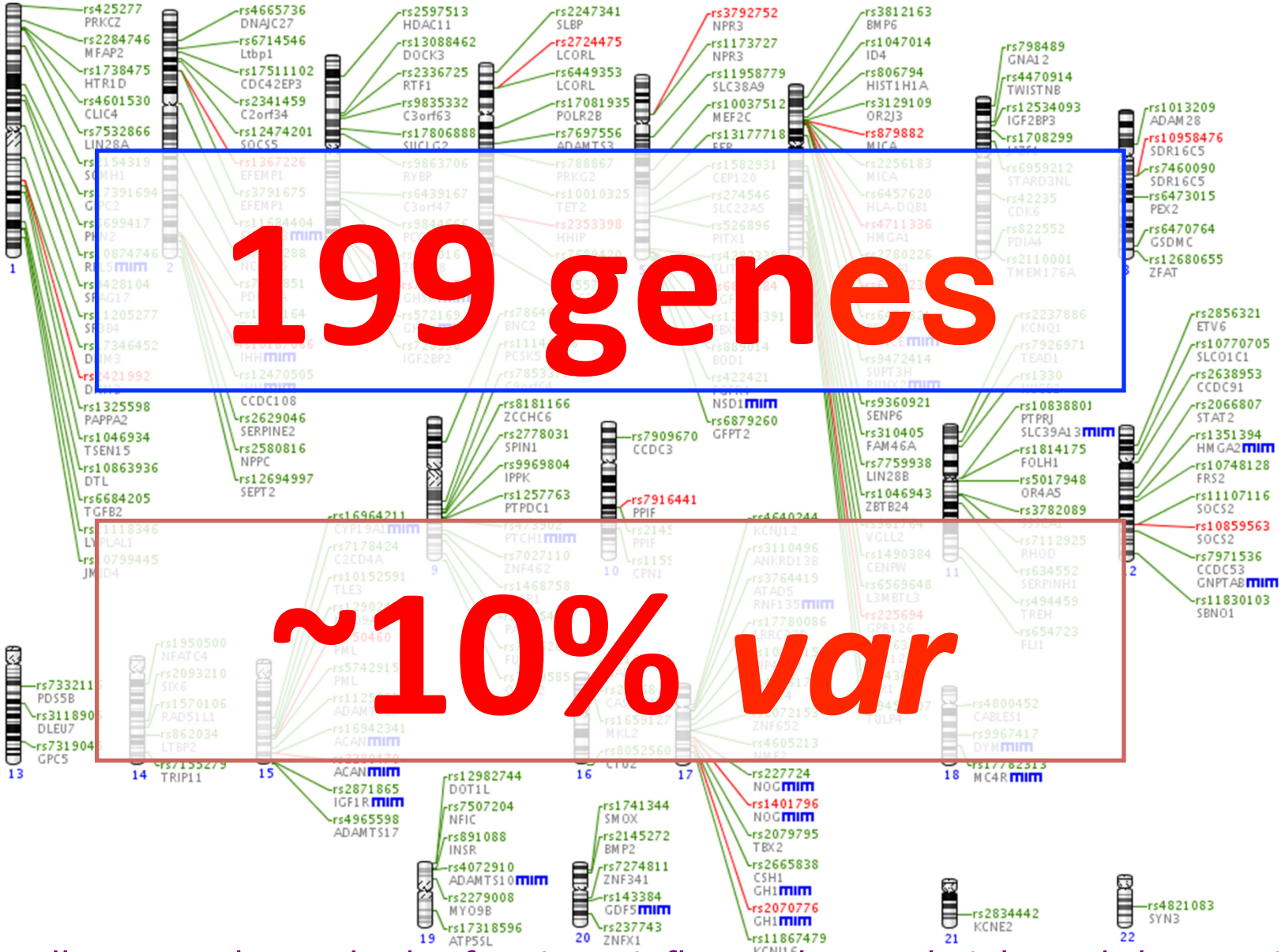


Eficient patient stratification is the holy grail of modern medicine



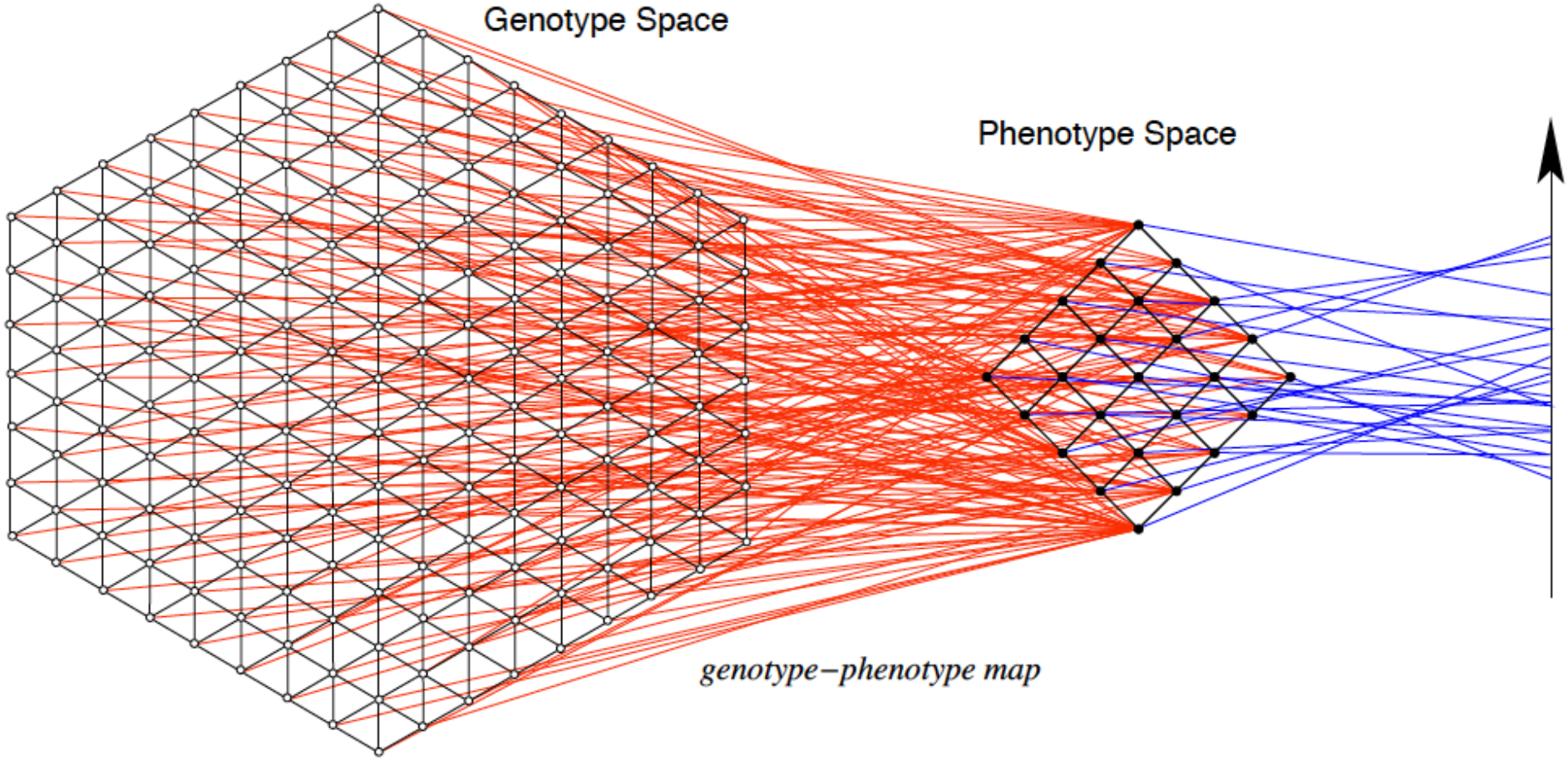
Genome wide association studies (GWAS) initiated revolution in genetics





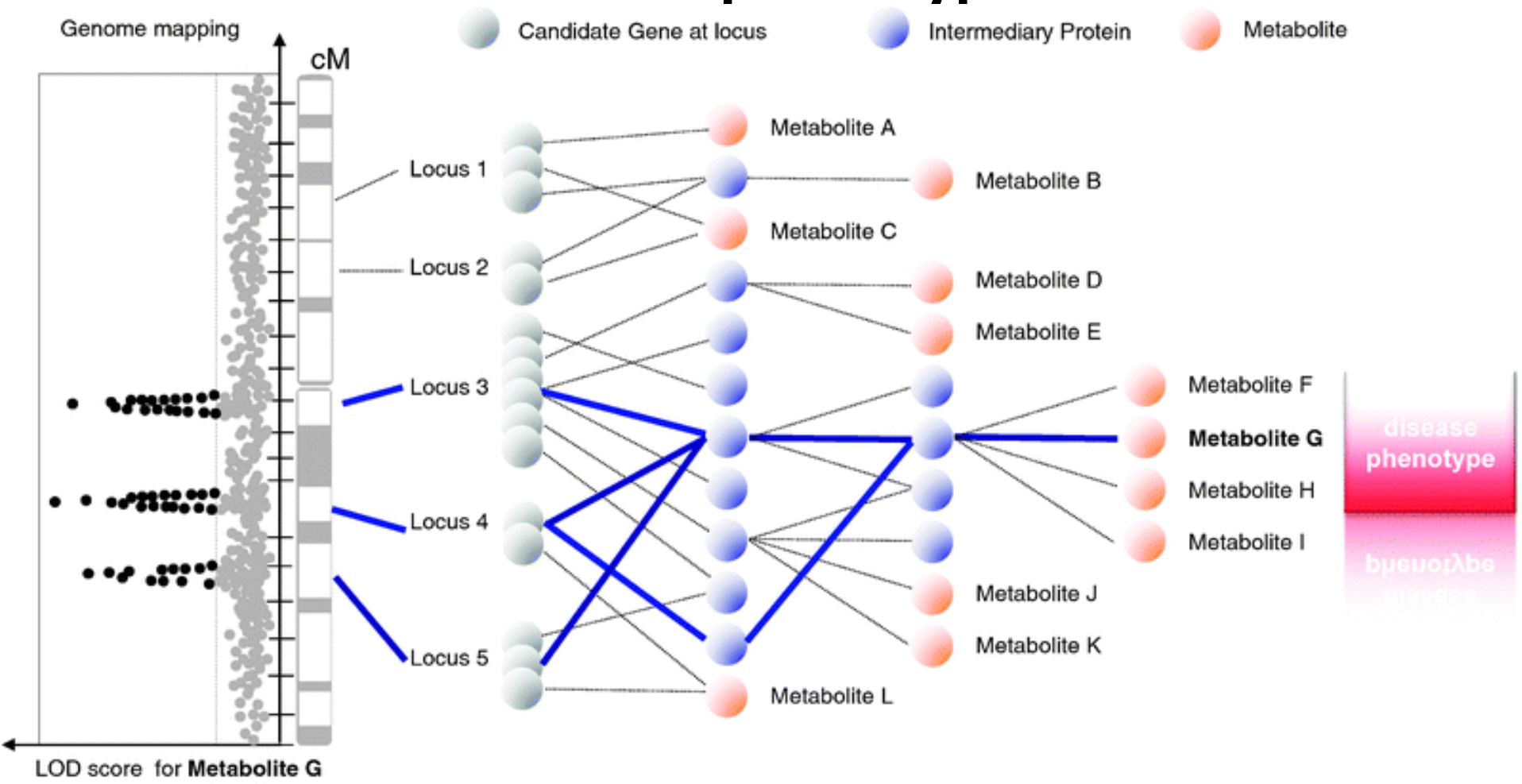
Lango Allen H, et al. *Hundreds of variants influence human height and cluster within genomic loci and biological pathways*. **Nature** 2010;467(7317):832-8.

Gene-gene interactions are very complex



Stadler&Stephens, *Comm.Theor.Biol, 2003*

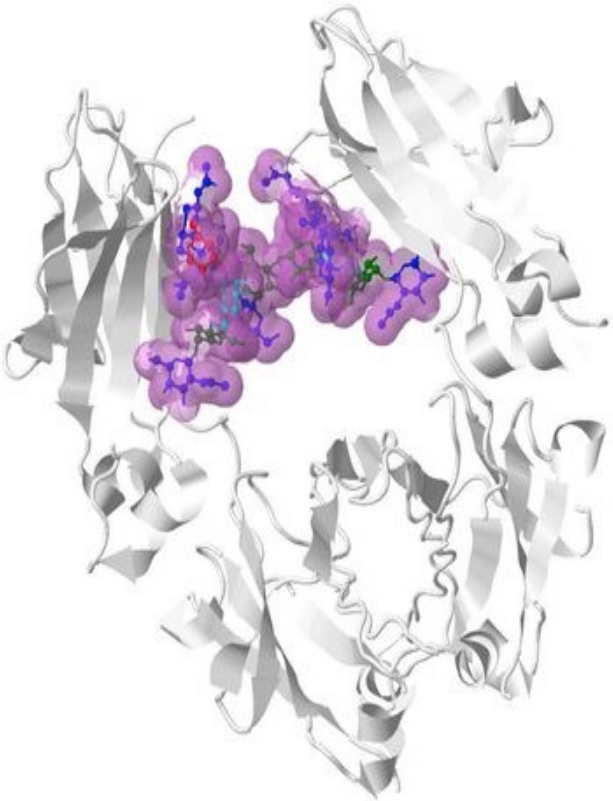
Genetic polymorphisms are very far away from the phenotype

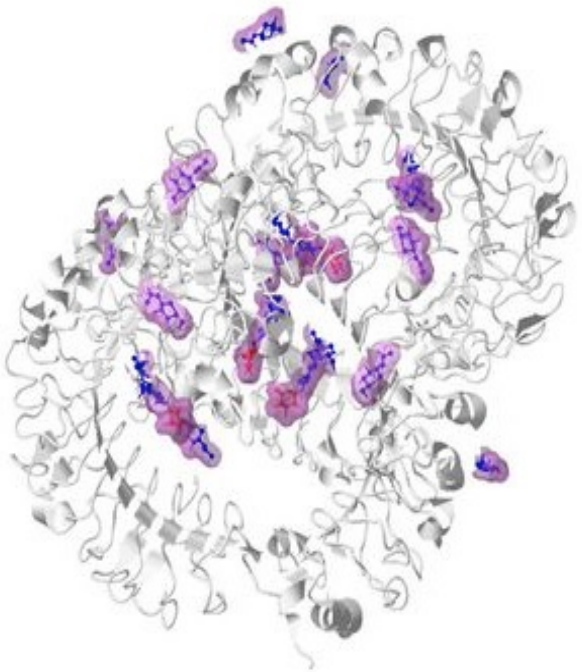


genotype → molecular → networks → phenotype

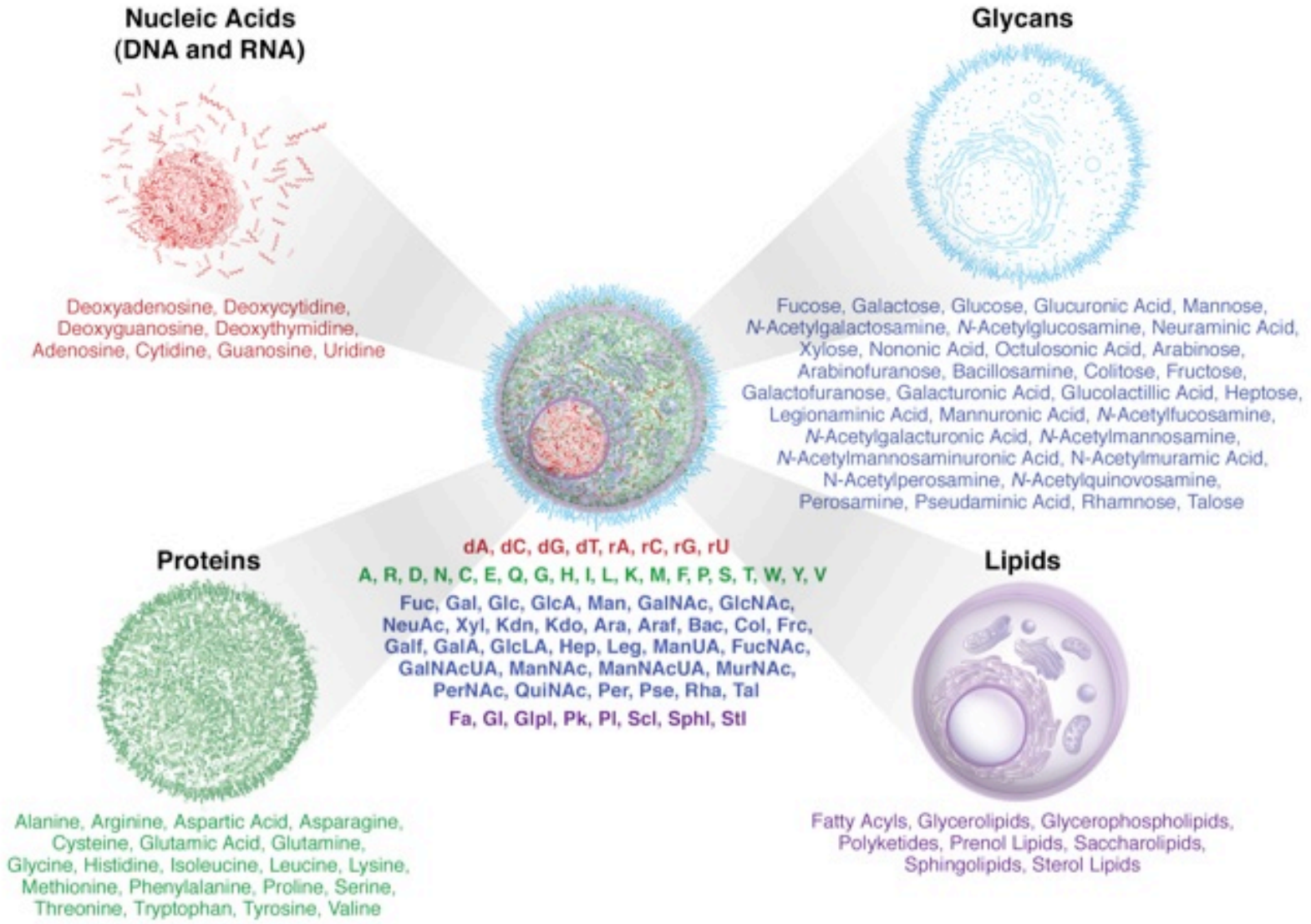
Dumas, Mol Biosystems, 2012

Glycans are important structural component of nearly all proteins



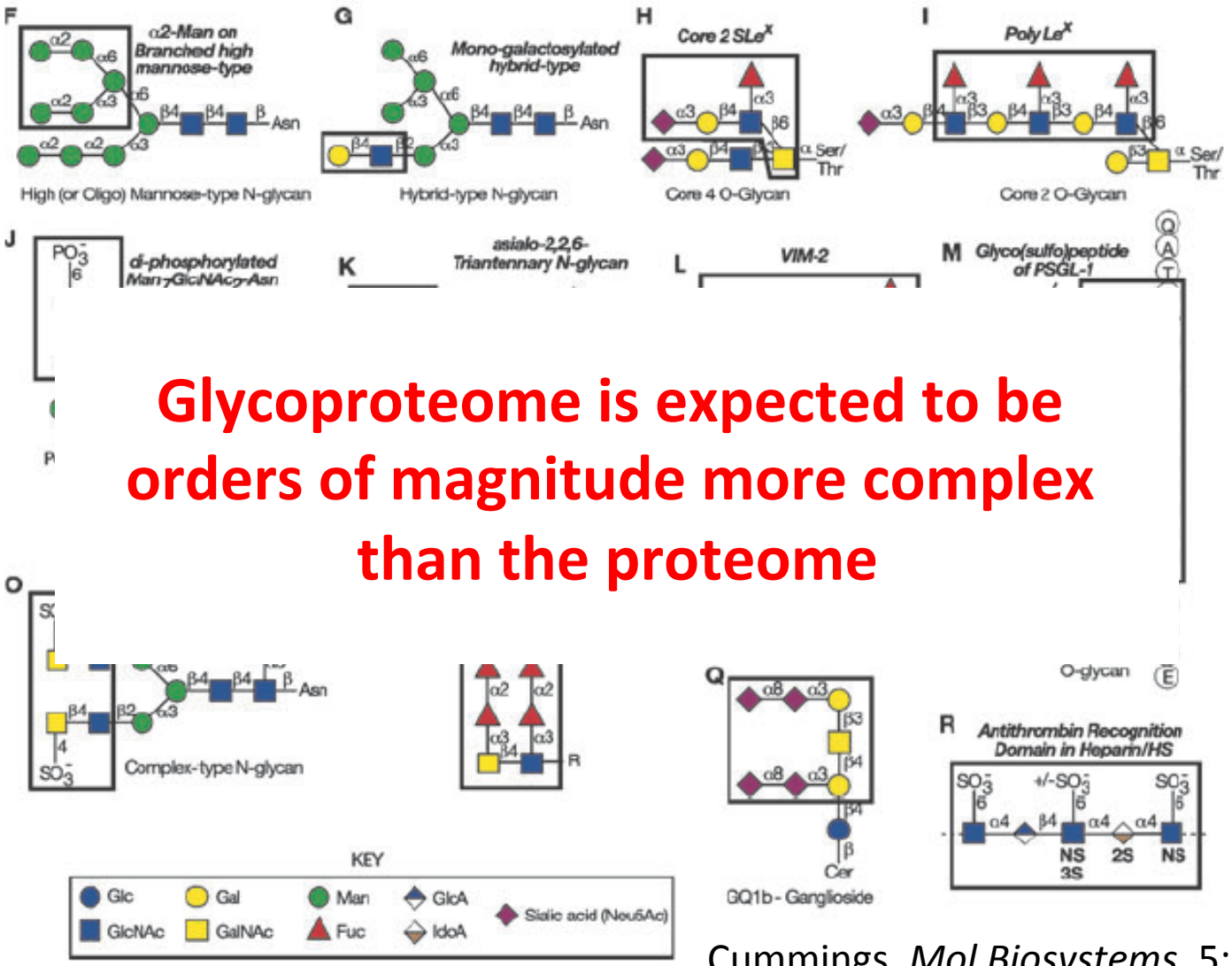


Glycans are one of four principal components of a cell



Marth, Nature Cell Biology, 2008

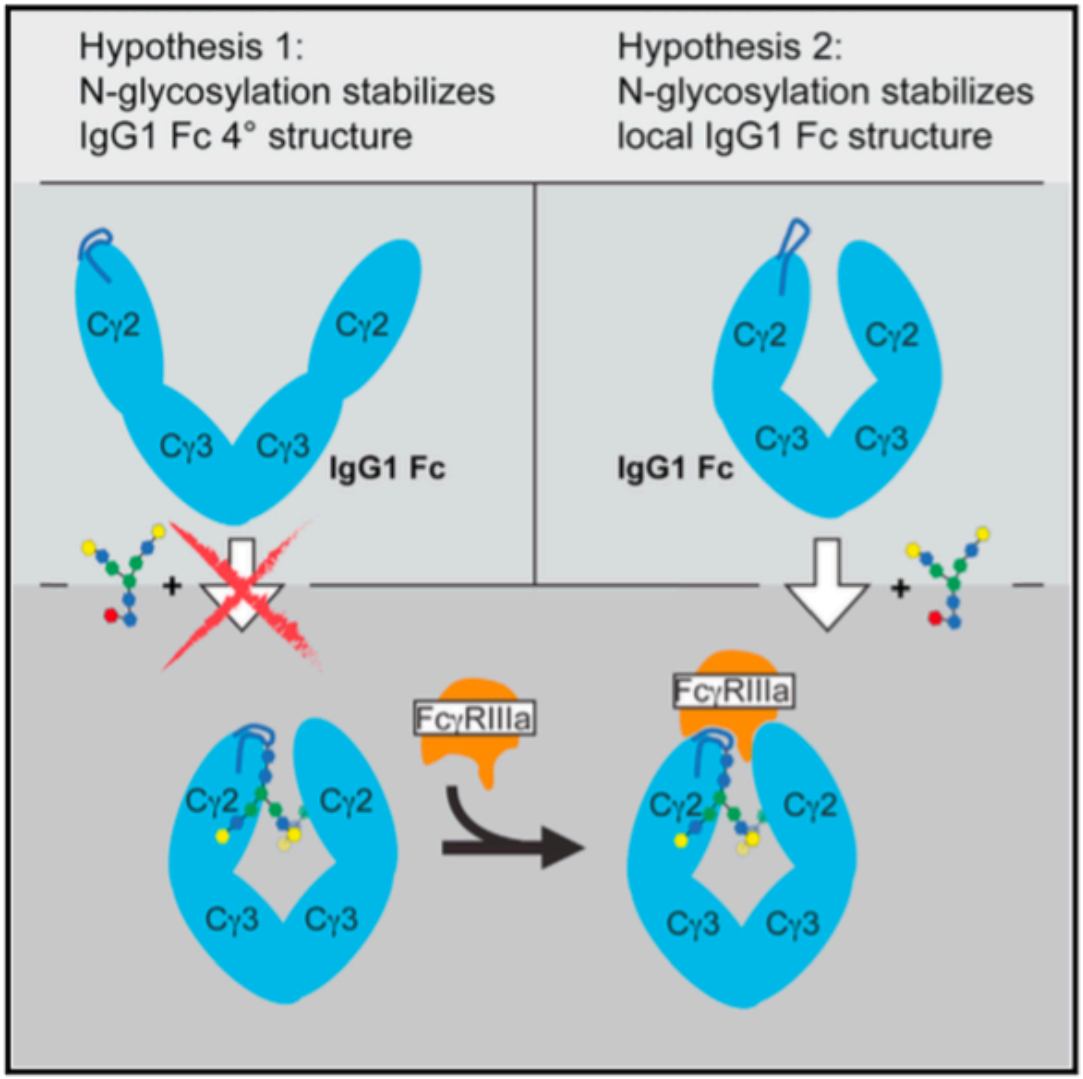
At least 2000 different glycan determinants are being attached to polypeptide backbones

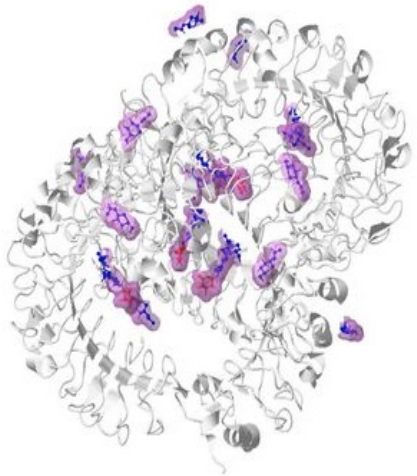


Glycoproteome is expected to be orders of magnitude more complex than the proteome

Cummings, *Mol Biosystems*, 5:1087, 2009

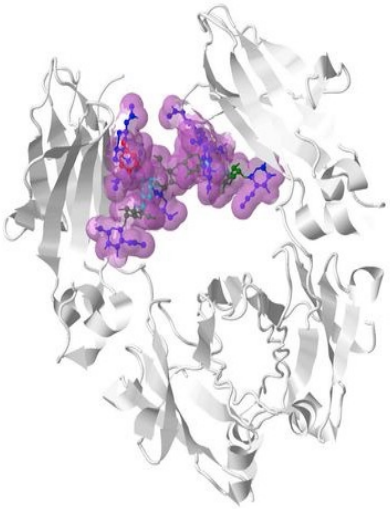
Small local effects of glycans on protein structure can have dramatic physiological efects

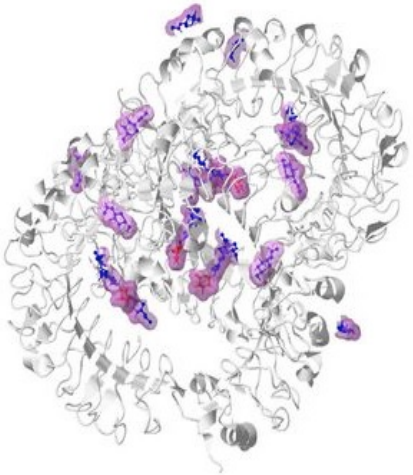


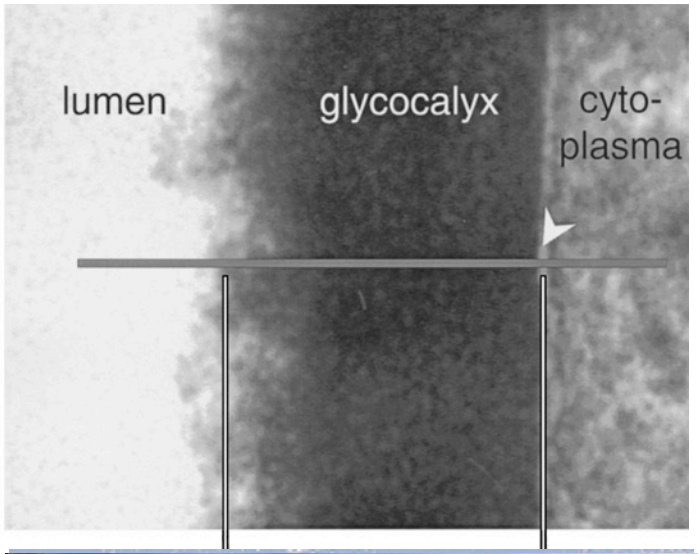


Subedi and Barb, *Structure*, 2015

Contrary to polypeptide part of proteins that is fixed for our lifetime, glycans are dynamic



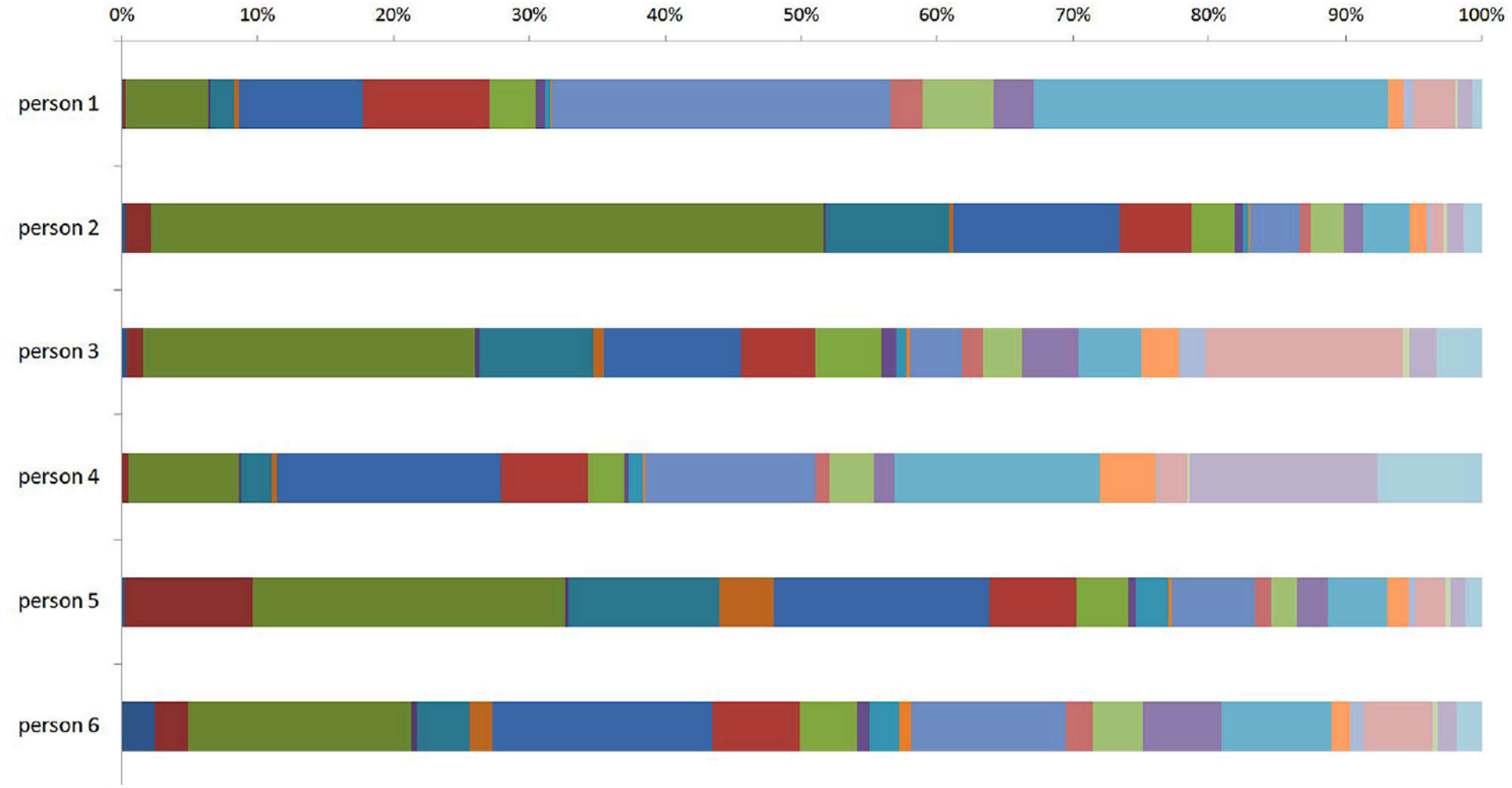




Glycans have four principal modes of action

1. **Glycans are ligands for specific glyco-receptors (lectins)**
   - Selectins, pathogen attachment
2. **Alternative glycosylation alters membrane dynamics of various receptors**
   - Cytokine receptors, GLUTs
3. **Alternative glycosylation modulates structure of a protein and modulates its interaction with specific receptors**
   - IgG, Notch
4. **Glycosylation as a regulatory modification**
   - O-GlcNAc

Glycome composition differs significantly between individuals



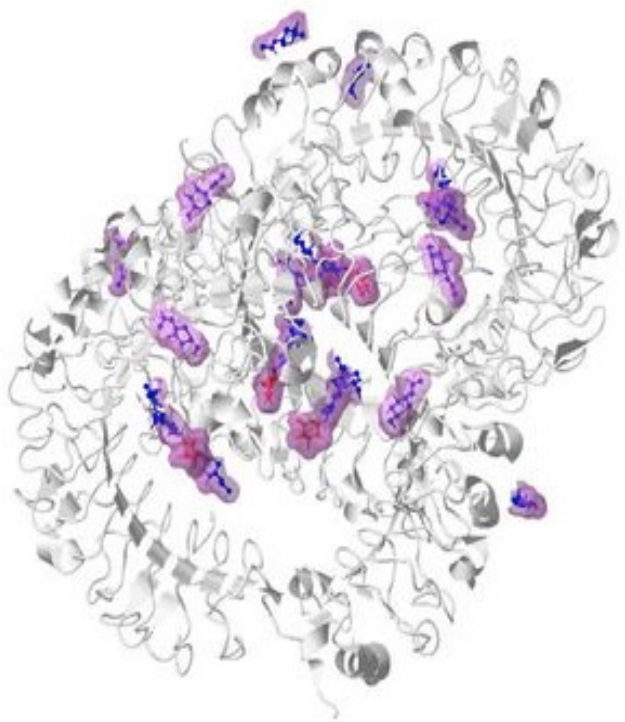
Lauc et al, Front Genet, 2014

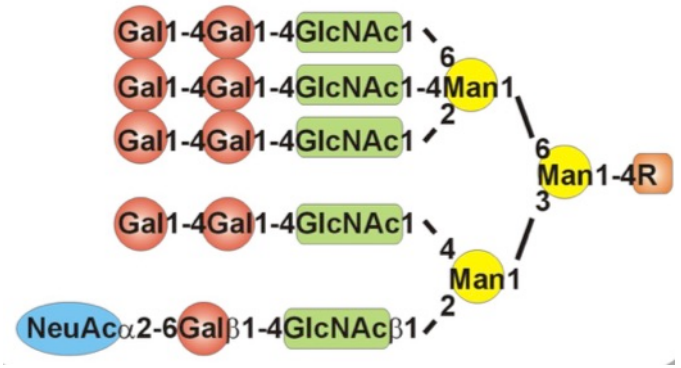
Genome does not contain templates for synthesis of glycan parts of glycoproteins

DNA ⇌ RNA → proteins

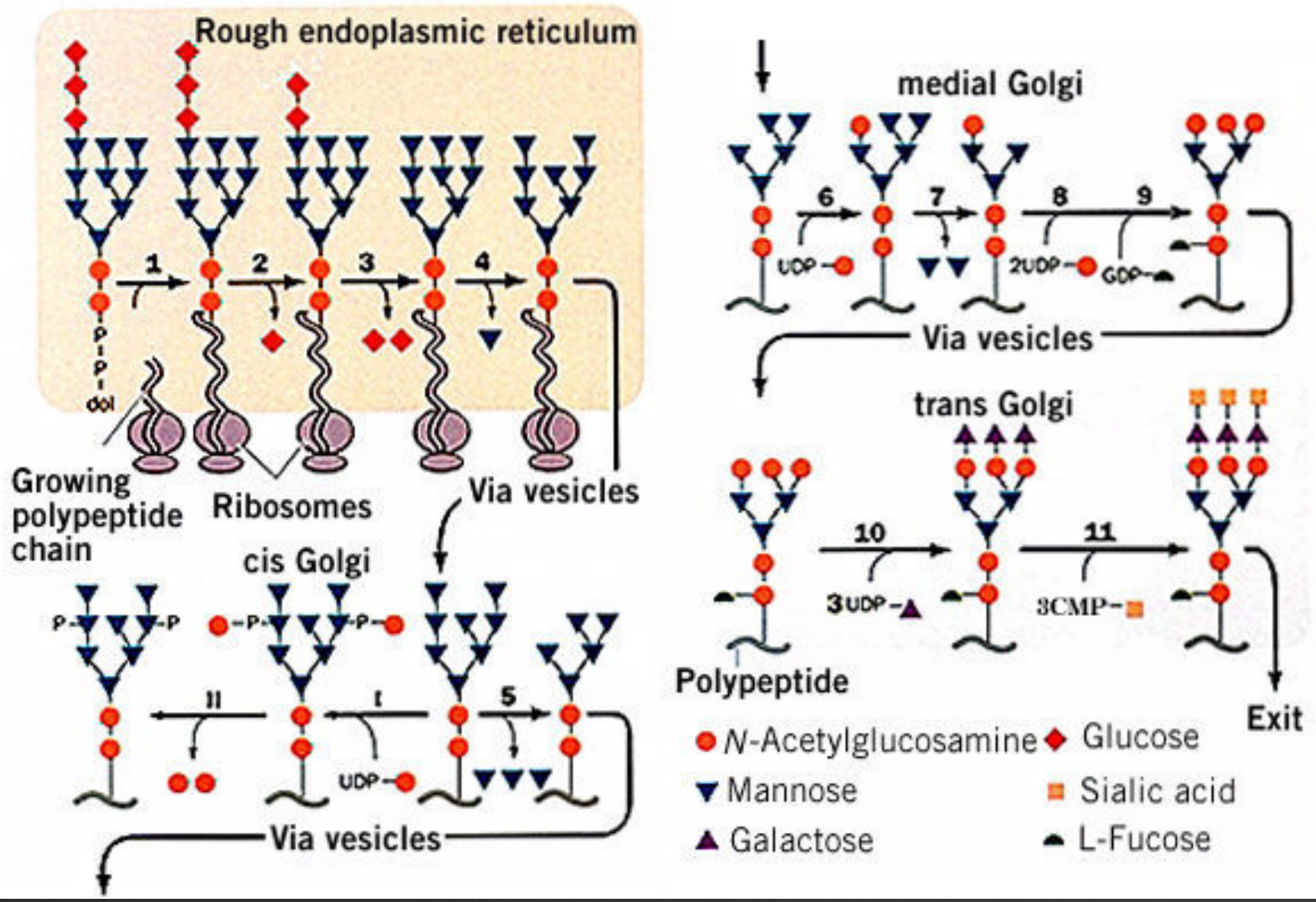
↓ ???

glycoproteins





Glycans are encoded in a complex dynamic network of hundreds of genes



For more than 30 years we know that IgG glycans change in disease

Association of rheumatoid arthritis and primary osteoarthritis with changes in the glycosylation pattern of total serum IgG

R. B. Parekh*, R. A. Dwek*, B. J. Sutton†, D. L. Fernandes*, A. Leung‡, D. Stanworth‡ & T. W. Rademacher*

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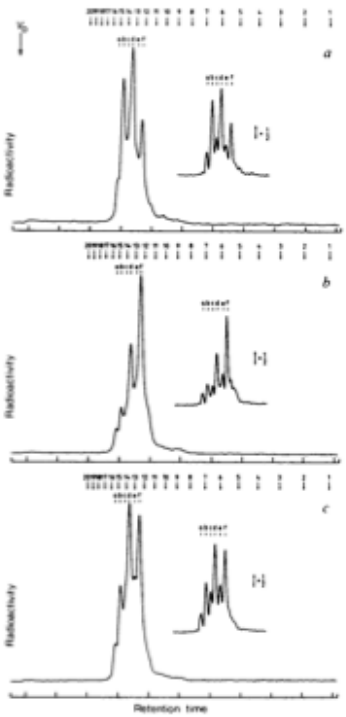
‡ Department of Immunology, Rheumatoid and Allergy Research Unit, University of Birmingham, The Medical School, Vincent Drive, Birmingham B15 2TJ, UK

T. Mizuochi§, T. Taniguchi§, K. Matsuta||, F. Takeuchi||, Y. Nagano||, T. Miyamoto|| & A. Kobata§

§ Department of Biochemistry, Institute of Medical Science, University of Tokyo, Minato-ku, Tokyo 108, Japan
|| Department of Medicine and Physical Therapy, Faculty of Medicine, University of Tokyo, Bunkyo-ku, Tokyo 113, Japan

from 46 IgG samples, indicate that: (1) IgG isolated from normal individuals, patients with RA and patients with OA contains different distributions of asparagine-linked bi-antennary complex-type oligosaccharide structures, (2) in neither disease is the IgG associated with novel oligosaccharide structures, but the observed differences are due to changes in the relative extent of galactosylation compared with normal individuals. This change results in a 'shift' in the population of IgG molecules towards those carrying complex oligosaccharides, one or both of whose arms terminate in *N*-acetylglucosamine. These two arthritides may therefore be glycosylation diseases, reflecting changes in the intracellular processing, or post-secretory degradation of *N*-linked oligosaccharides.

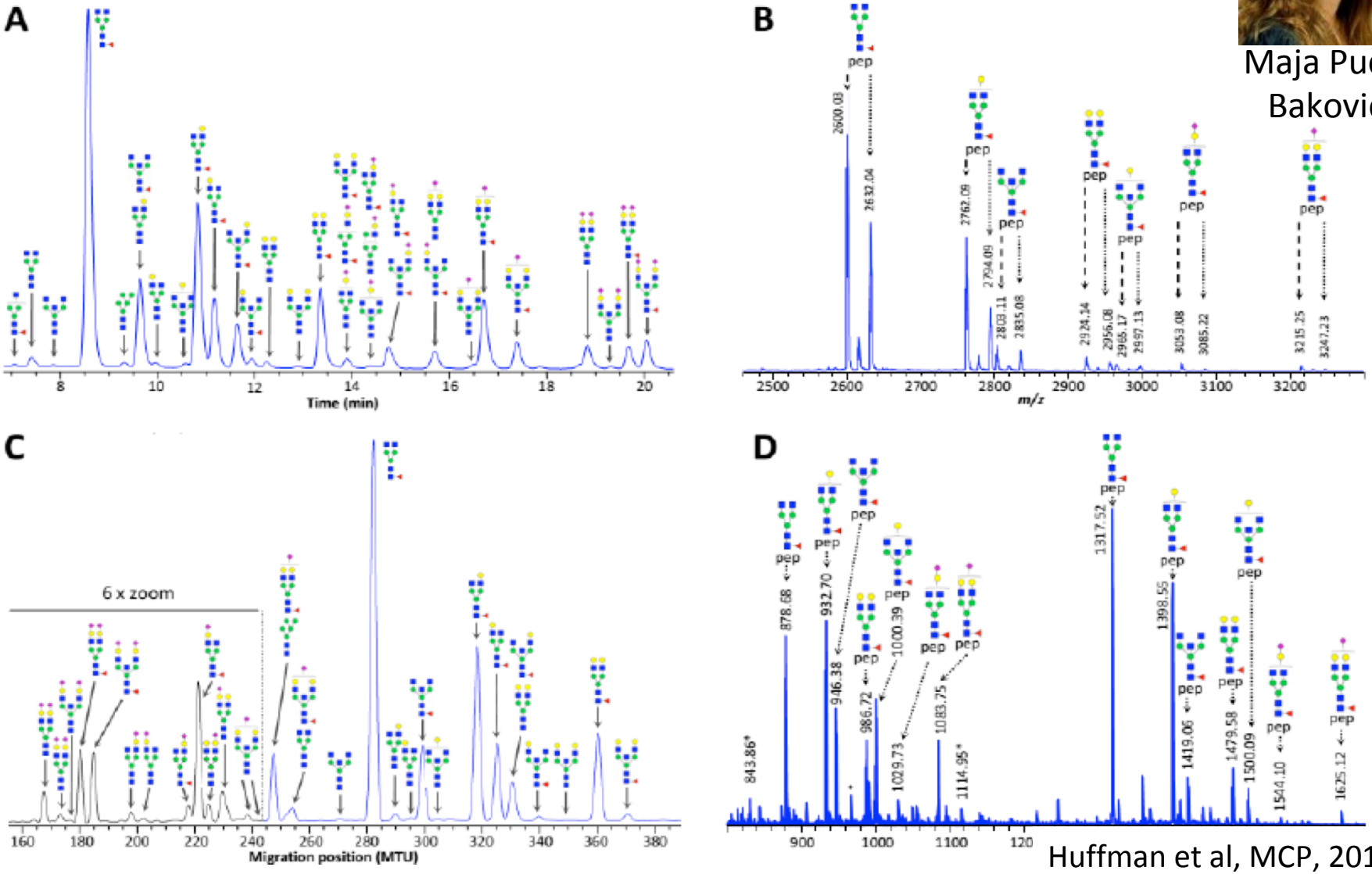
At least 30 different complex-type bi-antennary oligosaccharides are associated with human serum IgG (Fig. 2). To compare the molar proportions of each of these structures, each serum IgG sample was subjected to controlled hydrazinolysis to release intact its associated oligosaccharide moieties[11]. Reduction of the reducing terminal *N*-acetylglucosamine residues using NaB^3H_4 was then performed to label radioactively each carbohydrate chain. Each labelled oligosaccharide mixture was subjected to exhaustive neuraminidase digestion in order to analyse the distribution of neutral structures. The resulting 'asialo' oligosaccharide mixtures were fractionated by Bio-Gel P-4 (~400 mesh) gel filtration chromatography, a technique that separates neutral oligosaccharides on the basis of their effective hydrodynamic volumes[12] (Figs 2, 3).



Parekh et al, *Nature*, 1985

IgG glycome can be reliably quantified in a high-throughput manner

Maja Pučić Baković



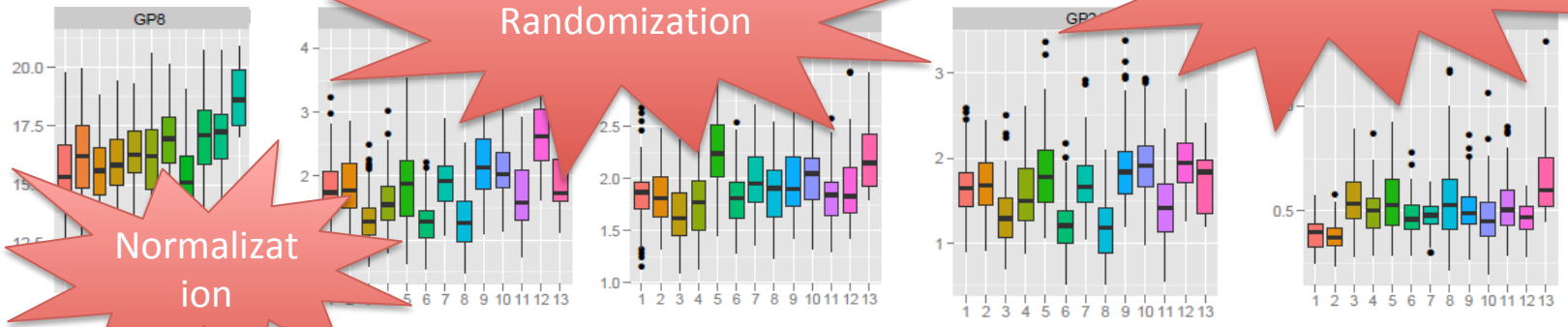
Huffman et al, MCP, 2014

Advancing from low- to high-throughput is not a simple task

F. Vučković

Randomization

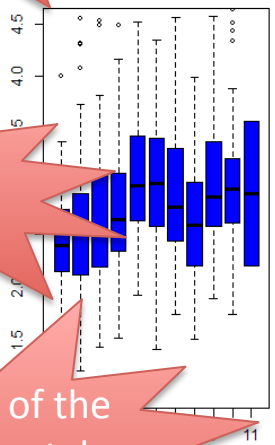
Confounders

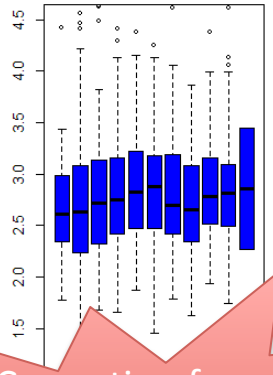


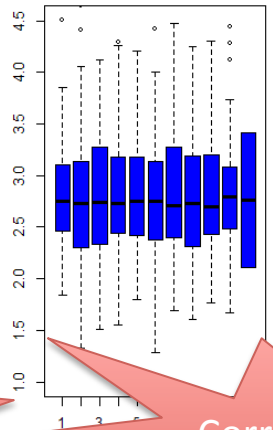
Normalization

Ivo Ugrina

Batch-correction







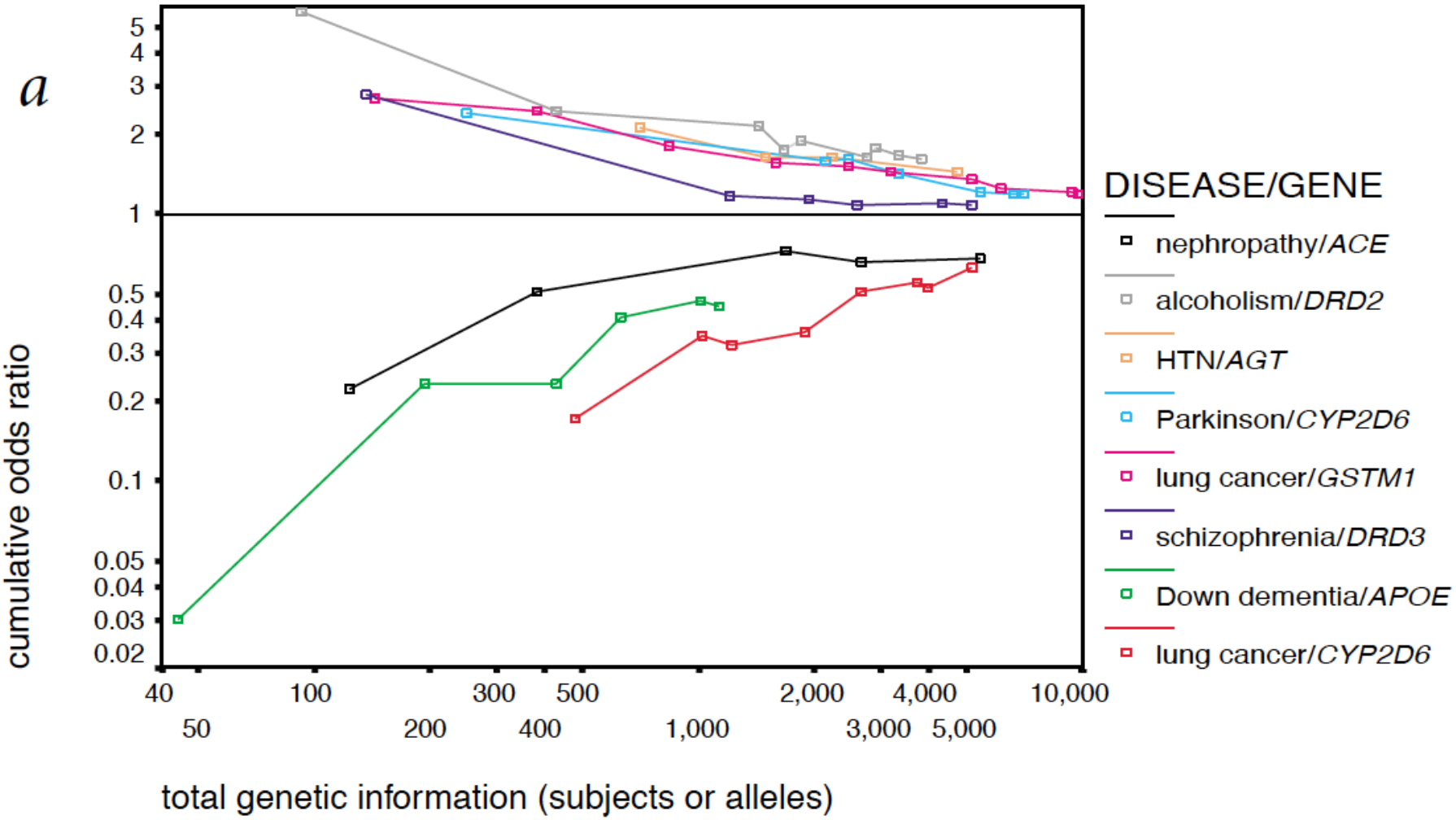
L. Klarić

Structure of the experimental error

Correction for age, gender, relatedness...

Correction for multiple testing

Lesson from genetics: Nearly all published results from small studies are false



Button, *Nat Rev Neurosci*, 14:365, 2013

Ionniadis, *PLOS Medicine*, 2(8): e124, 2005

Distribution of glycans in plasma of ~ 1,000 examinees

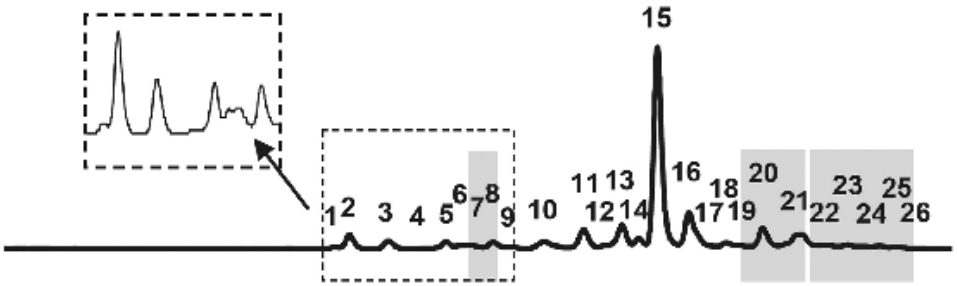
Journal of proteome research

Article

Variability, Heritability and Environmental Determinants of Human Plasma N-Glycome

Ana Knezevic, Ozren Polasek, Olga Gornik, Igor Rudan, Harry Campbell, Caroline Hayward, Alan Wright, Ivana Kolcic, Niaobh O'Donoghue, Jonathan Bones, Pauline M. Rudd, and Gordan Lauc

J. Proteome Res., **2009**, 8 (2), 694-701 • Publication Date (Web): 26 November 2008



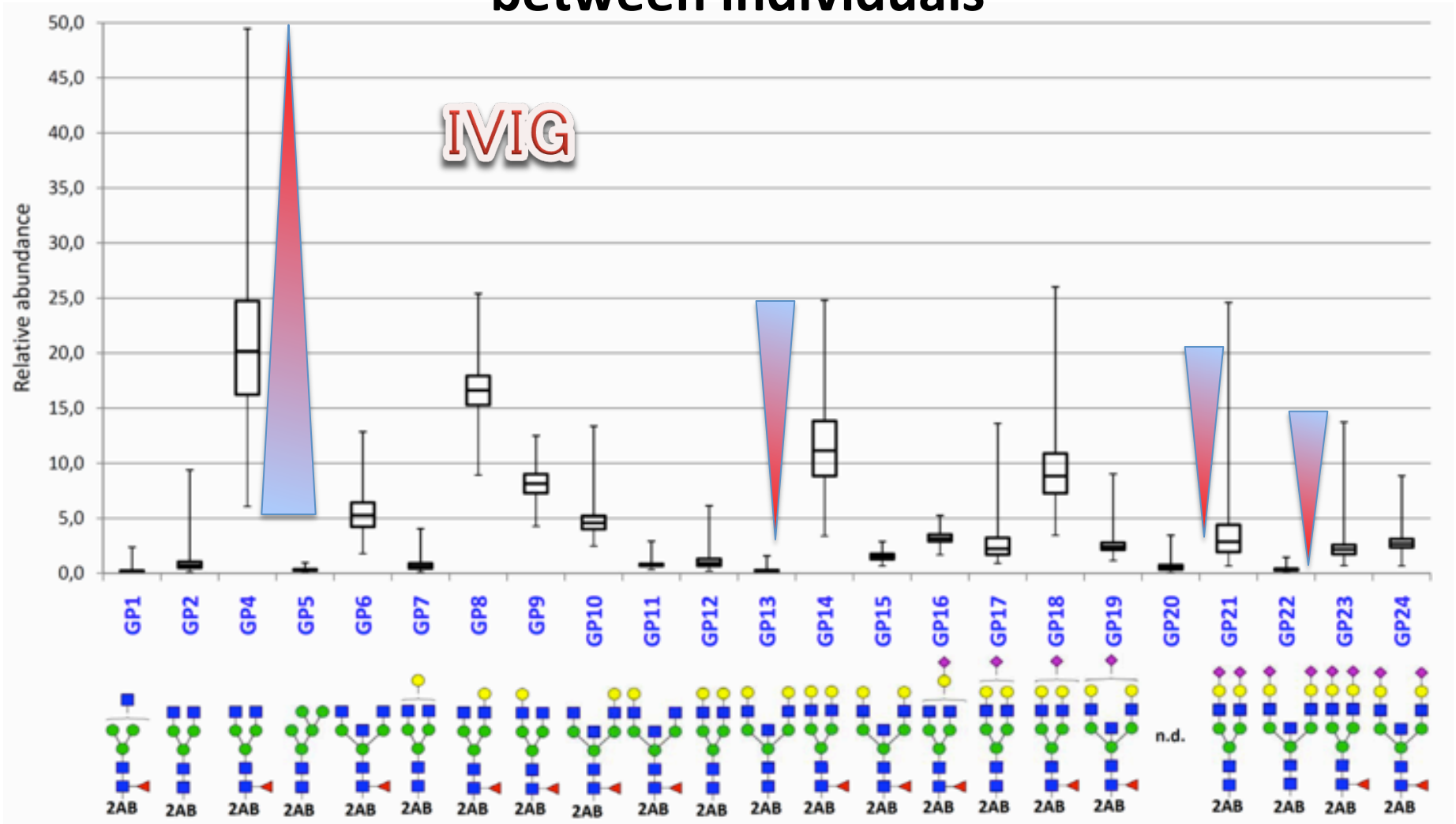
Knežević et al, J. Proteome Res, 2009

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

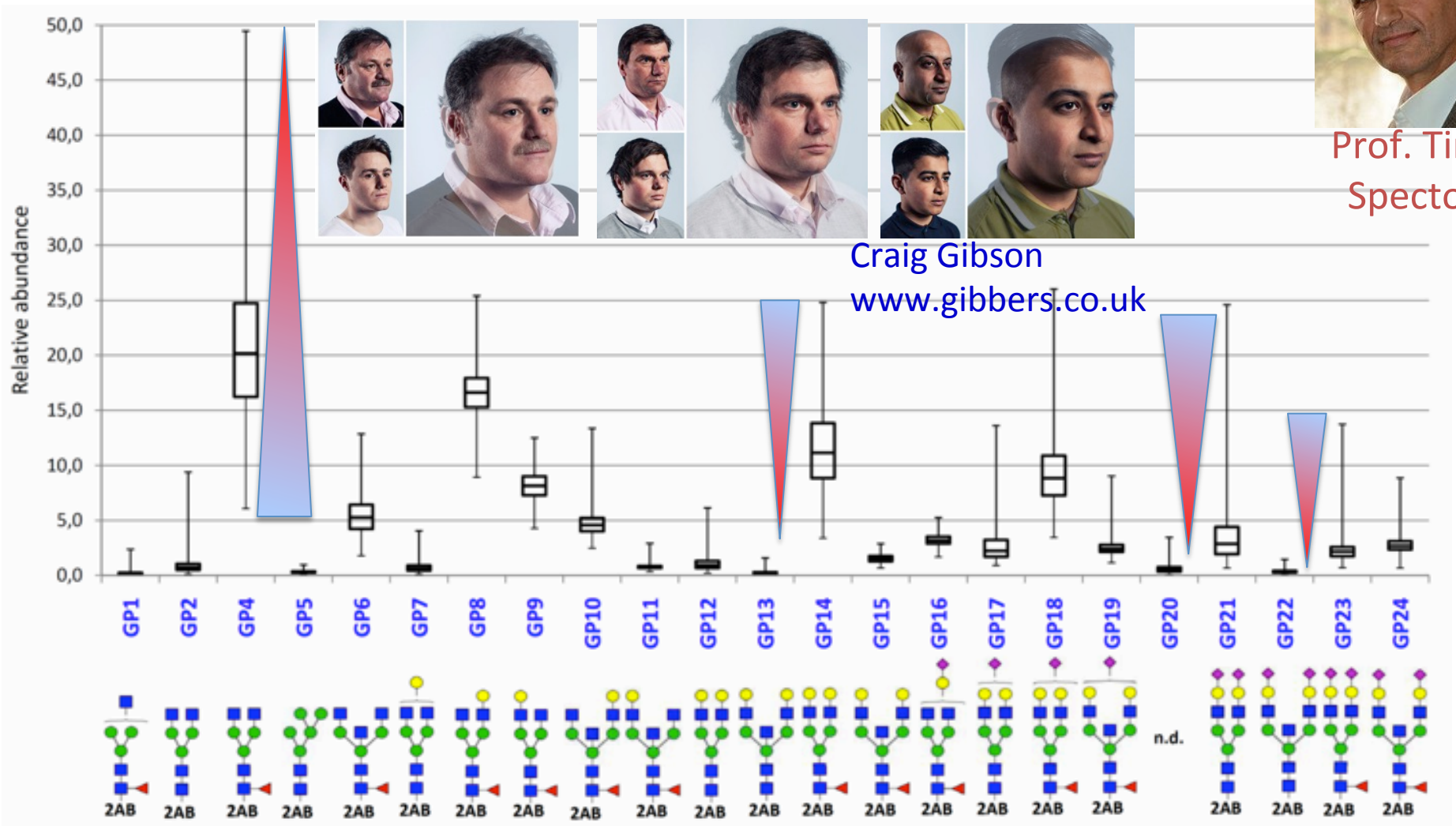
Composition of IgG glycome differs significantly between individuals



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

ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 11, November 2015, pp 2978–2989
DOI 10.1002/art.39273

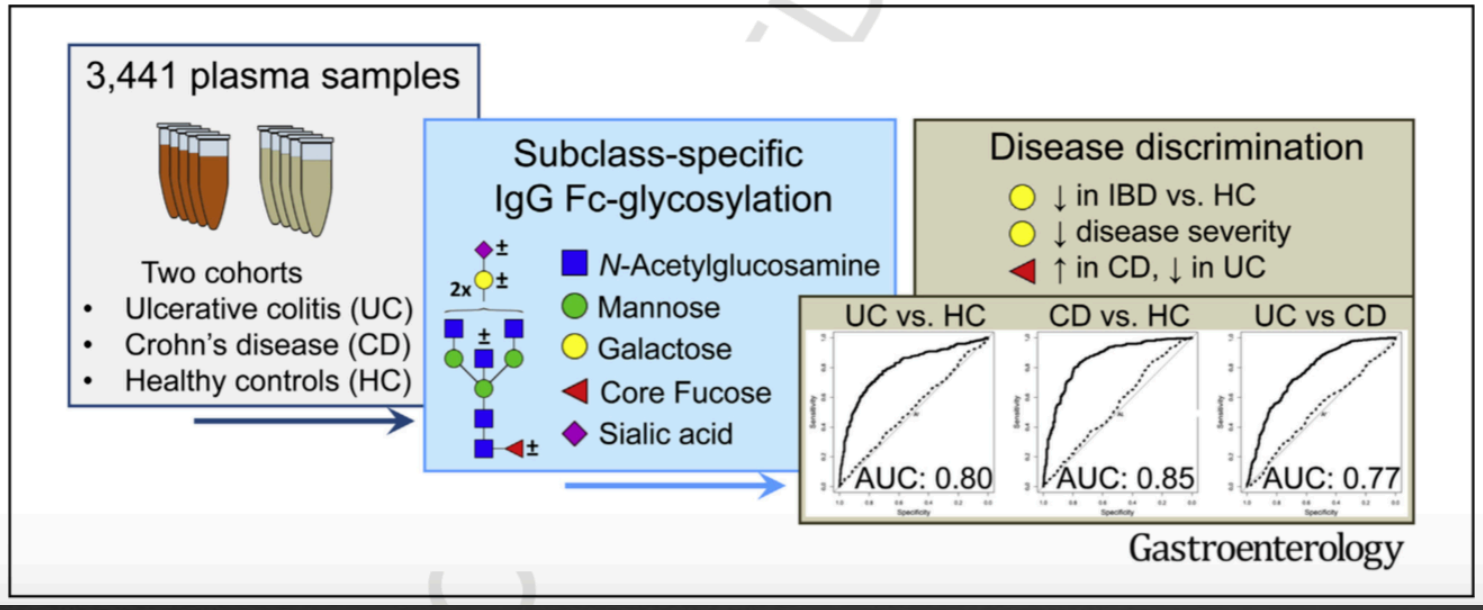
Association of Systemic Lupus Erythematosus With Decreased Immunosuppressive Potential of the IgG Glycome

Frano Vučković,[1] Jasminka Krištić,[1] Ivan Gudelj,[1] Maria Teruel,[2] Toma Keser,[3] Marija Pezer,[1] Maja Pučić-Baković,[1] Jerko Štambuk,[1] Irena Trbojević-Akmačić,[1] Clara Barrios,[4] Tamara Pavić,[3] Cristina Menni,[5] Youxin Wang,[6] Yong Zhou,[7] Liufu Cui,[8] Haicheng Song,[8] Qiang Zeng,[9] Xiuhua Guo,[6] Bernardo A. Pons-Estel,[10] Paul McKeigue,[11] Alan Leslie Patrick,[12] Olga Gornik,[3] Tim D. Spector,[5] Miroslav Harjaček,[13] Marta Alarcon-Riquelme,[14] Mariam Molokhia,[5] Wei Wang,[15] and Gordan Lauc[16]

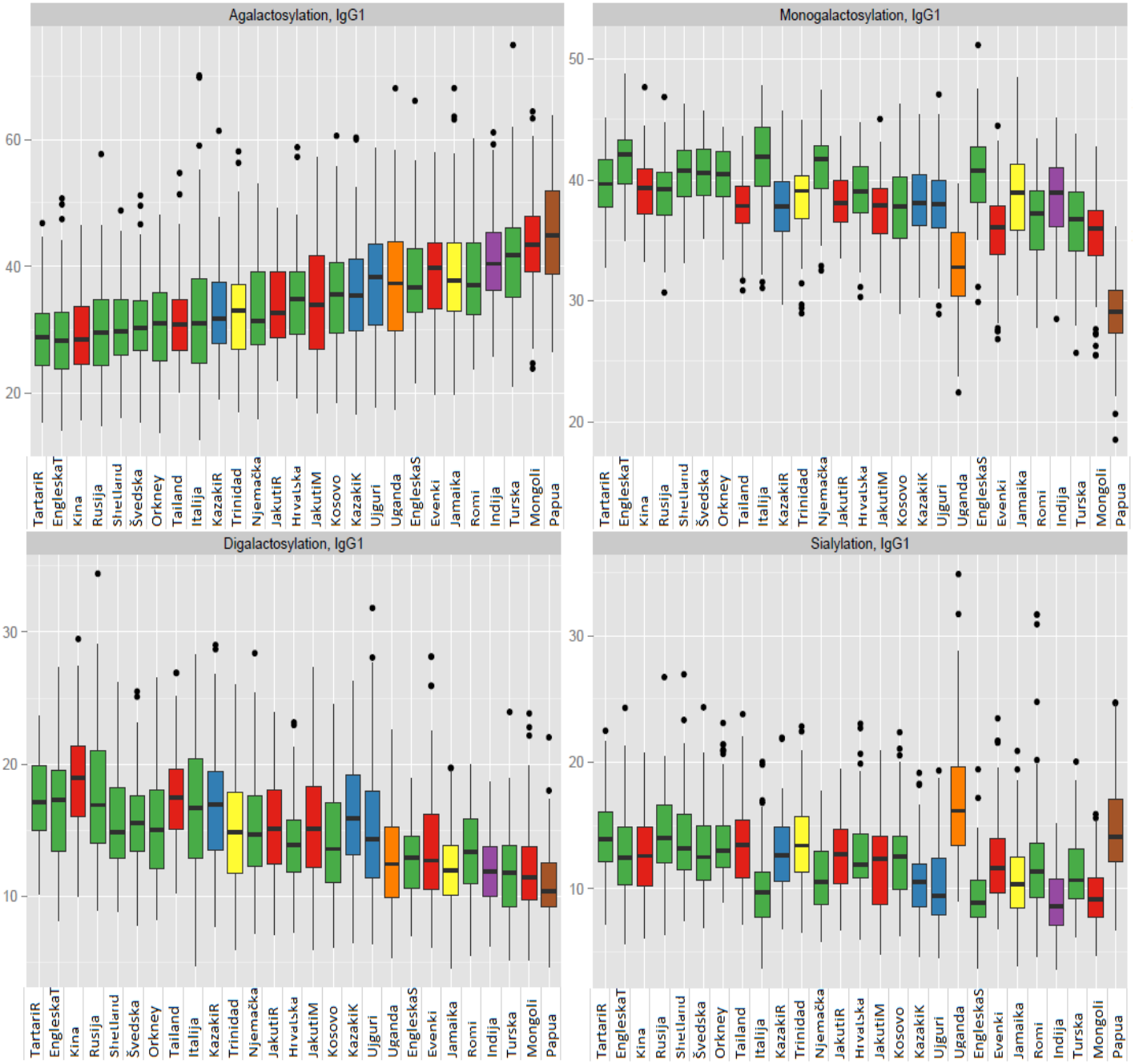
Glycosylation of Immunoglobulin G Associates With Clinical Features of Inflammatory Bowel Diseases

Mirna Šimurina,[1] Noortje de Haan,[2] Frano Vučković,[3] Nicholas A. Kennedy,[4] Jerko Štambuk,[3] David Falck,[2] Irena Trbojević-Akmačić,[3] Florent Clerc,[2] Genadij Razdorov,[3] Anna Khon,[5] Anna Latiano,[6] Renata D'Incà,[7] Silvio Danese,[8] Stephan Targan,[9] Carol Landers,[9] Marla Dubinsky,[9] The Inflammatory Bowel Disease Biomarkers Consortium, Dermot P. B. McGovern,[9] Vito Annese,[10,11] Manfred Wuhrer,[2] and Gordan Lauc[1,3]

[1]Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia; [2]Center for Proteomics and Metabolomics, Leiden University Medical Center, Leiden, The Netherlands; [3]Genos Glycoscience Research Laboratory, BIOCentar, Zagreb, Croatia; [4]University of Exeter, Exeter, UK; [5]Division of Gastroenterology, S. Camillo-Forlanini Hospital, Circonvallazione Gianicolense, Rome, Italy; [6]Division of Gastroenterology, Casa Sollievo della Sofferenza Hospital, Istituto di Ricovero e Cura a Carattere Scientifico, San Giovanni Rotondo, Italy; [7]Division of Gastroenterology, University Hospital, Padua, Italy; [8] Humanitas University, Inflammatory Bowel Disease Center, Department of Gastroenterology, Humanitas Clinical and Research Hospital, Milan, Italy; [9]F. Widjaja Foundation, Inflammatory Bowel and Immunobiology Research Institute, Cedars-Sinai Medical Center, Los Angeles, California; [10]Division of Gastroenterology, University Hospital Azienda Ospedaliero Universitaria Careggi, Florence, Italy; and [11]Valiant Clinic, Dubai, United Arab Emirates



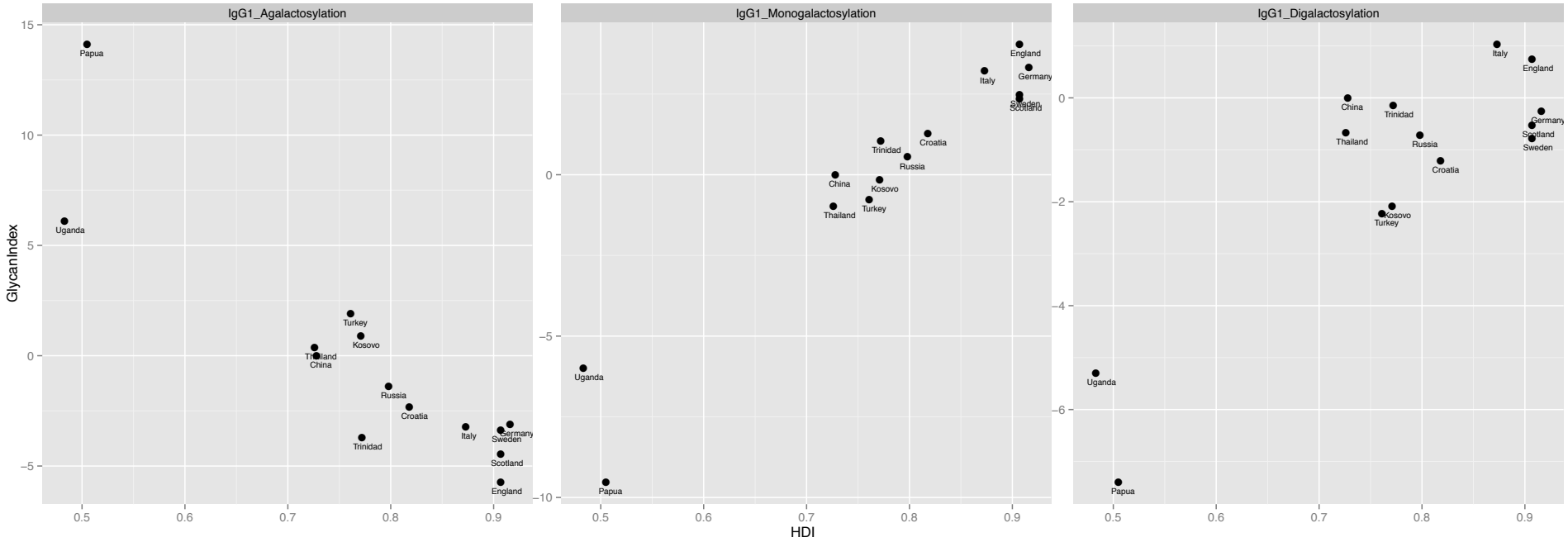
Inter-individual differences dominate over genetic variation in IgG galactosylation



27 populations, 100 individuals from each

- As wide as possible age span
- Fully randomised accross 32 96-well plates
- IgG Fc glycosylation analyses on glycopeptide level by LC-MS
  - Separate data for IgG1, IgG2+3 and IgG4

Galactosylation of IgG strongly associates with the “Human Development Index”



27 populations, 100 individuals from each

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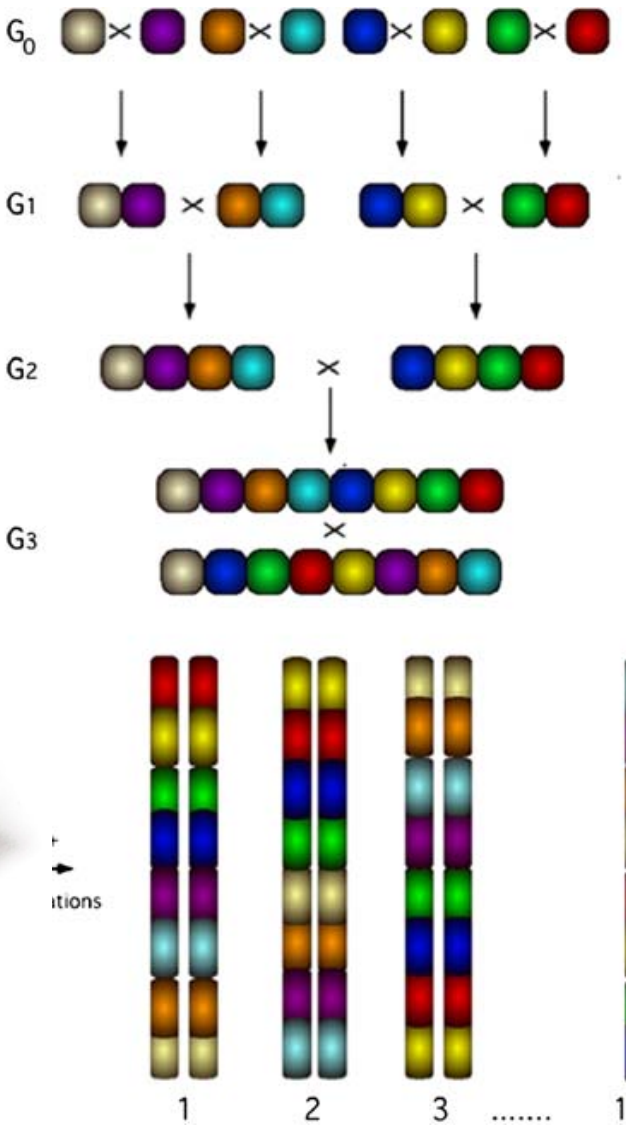
Collaborative Cross cohort of mice strains

Prof Grant Morahan

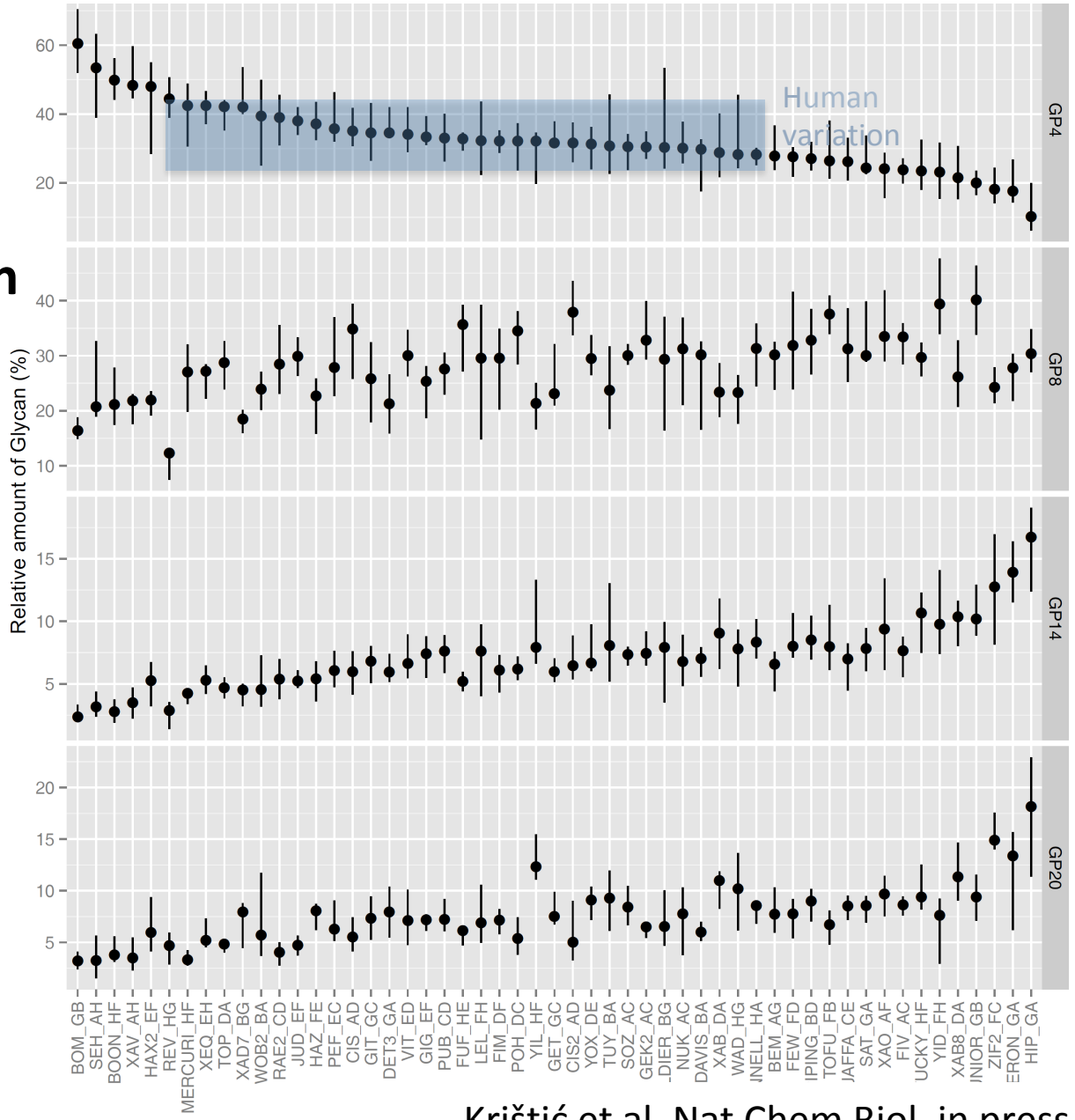
The Collaborative Cross (CC) combines the genomes of eight genetically diverse founder strains:

1. A/J
2. C57BL/6J
3. 129S1/SvImJ
4. NOD/LtJ
5. NZO/HlLtJ
6. CAST/EiJ,
7. PWK/PhJ
8. WSB/EiJ



Morahan et al., Mamm Genome,2008

Variation in galactosylation between mouse strains exceeds variation between human individuals

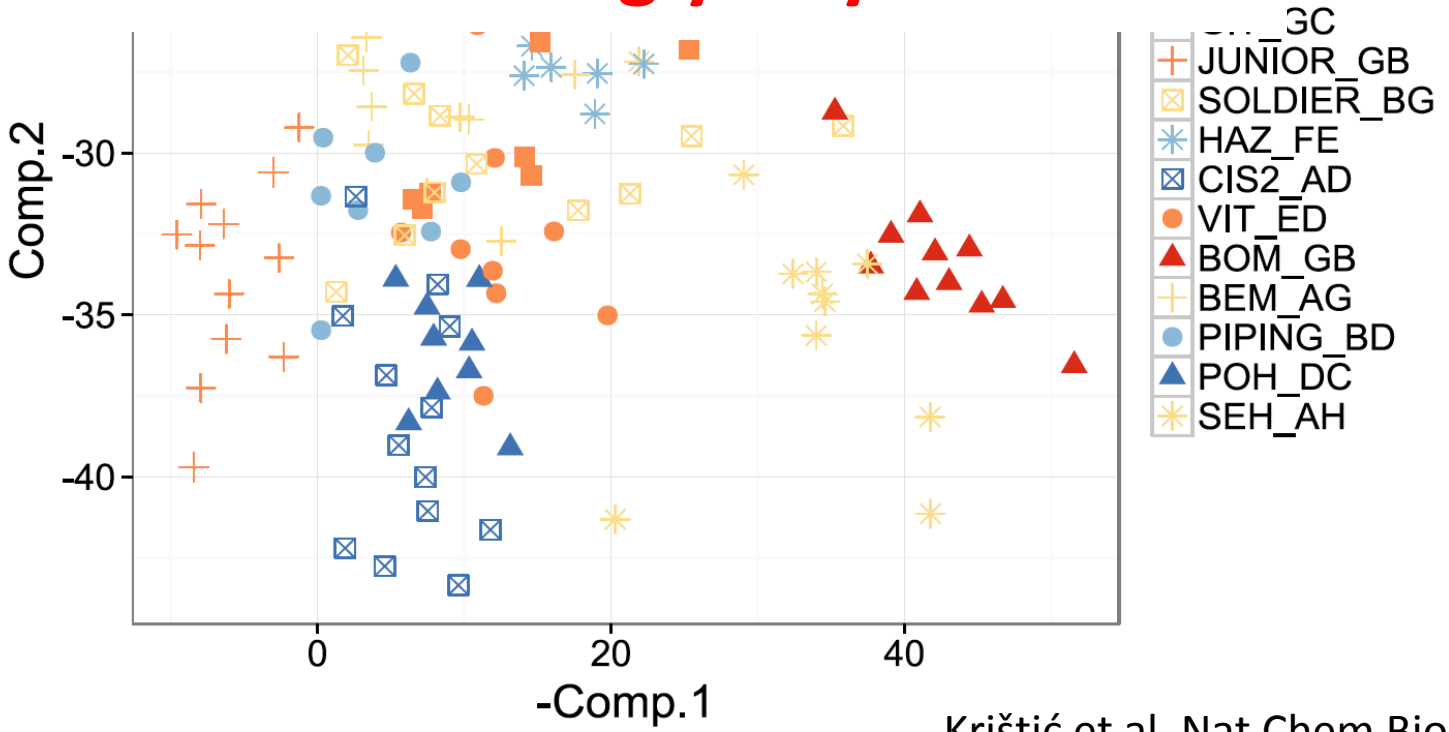


111 mouse strains from the GeneMine Collaborative cross cohort

Krištić et al, Nat Chem Biol, in press

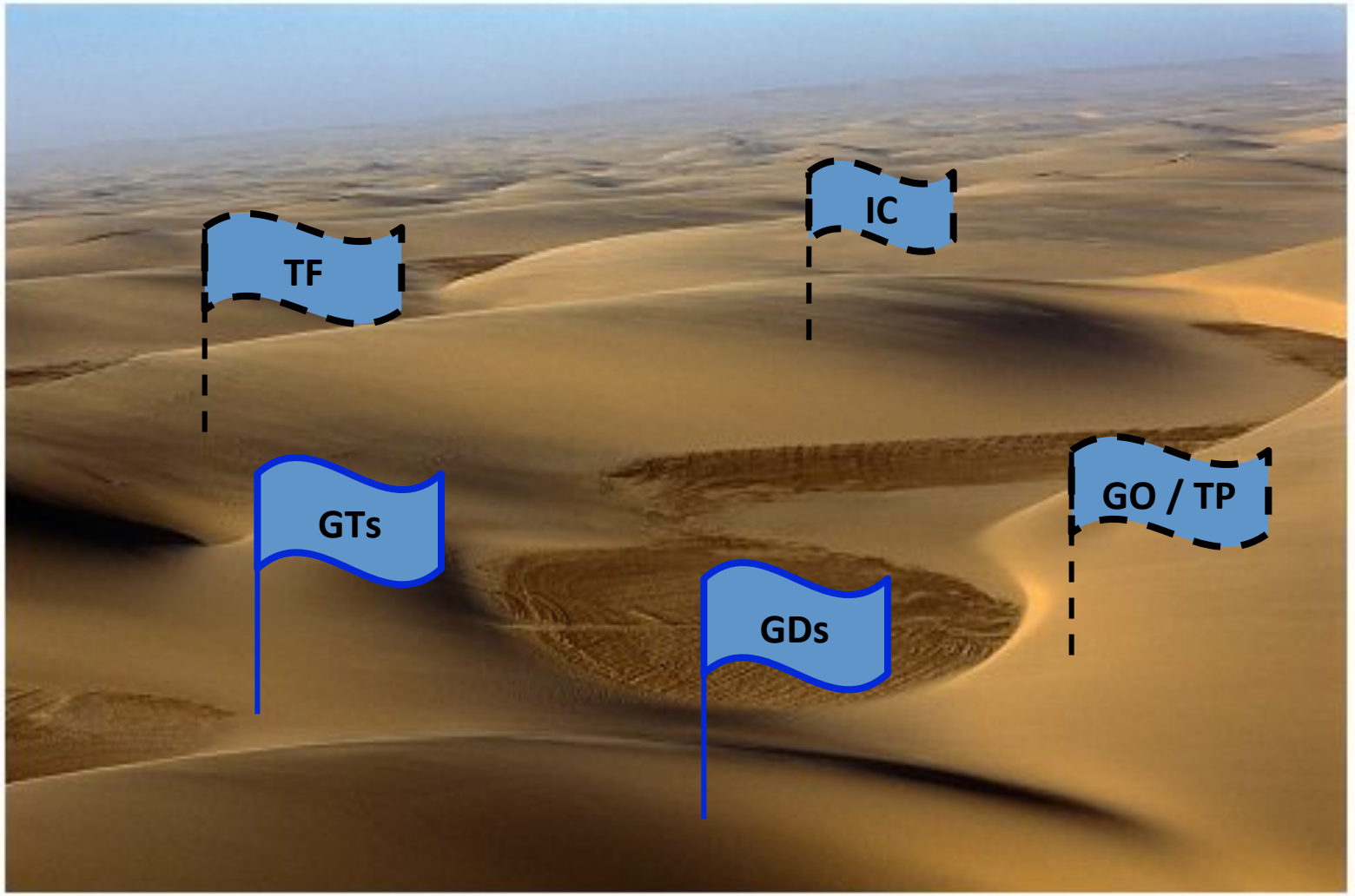
Three generations of inter-breeding generated stable and heritable differences in IgG structure and function between mouse strains

Rapid evolution through alternative glycosylation

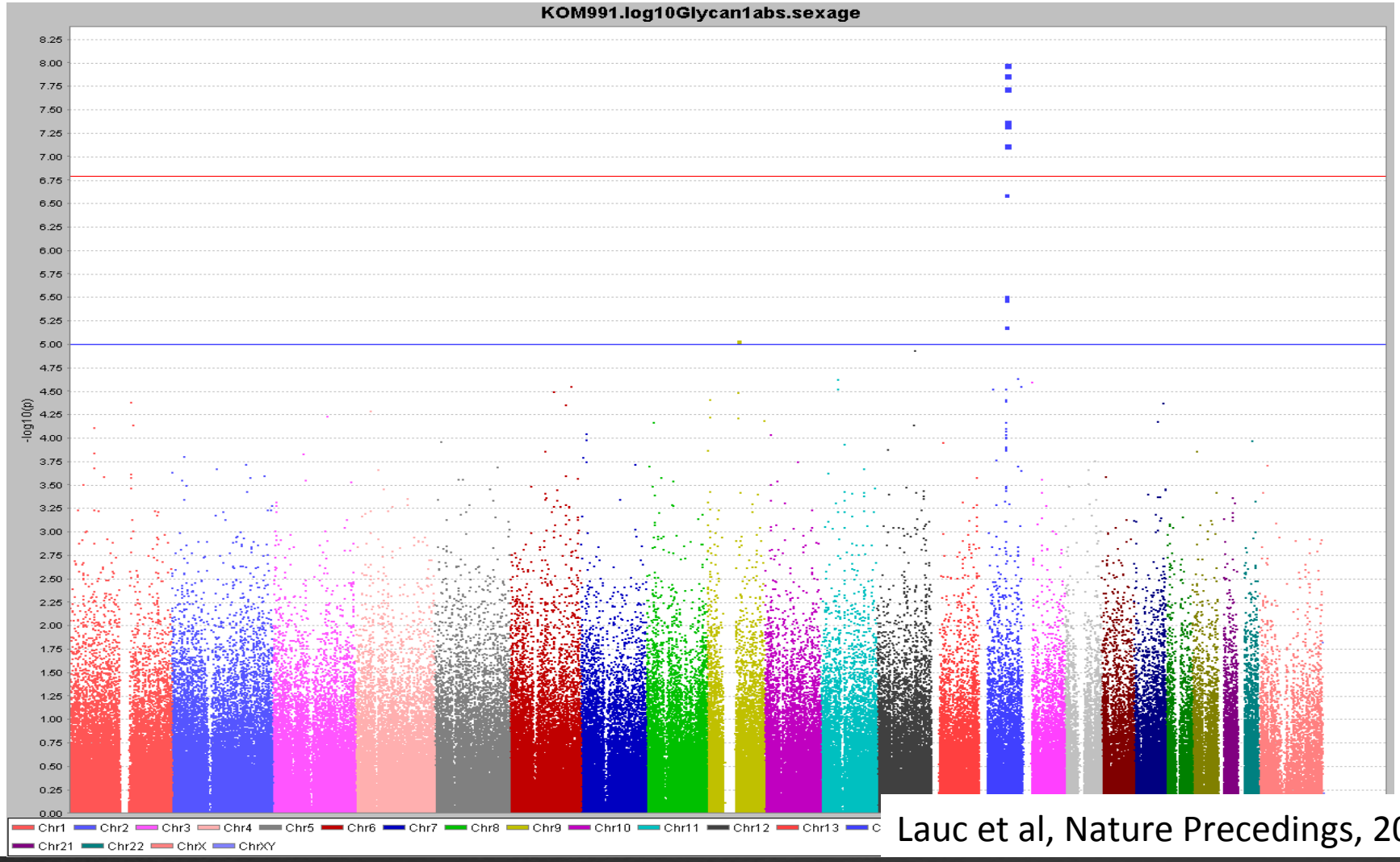


Krištić et al, Nat Chem Biol, in press

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



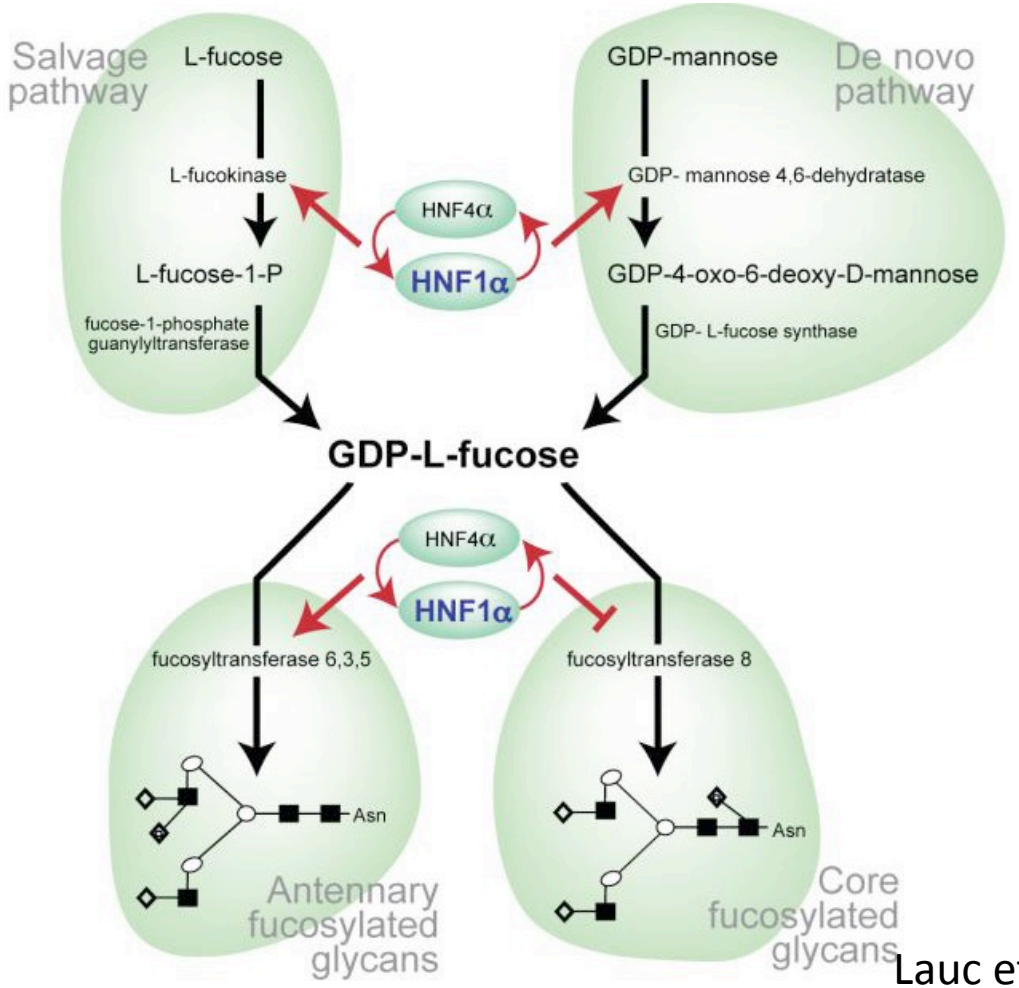
Genome-wide association (GWA) studies can be used to map genes involved in glycosylation



Lauc et al, Nature Precedings, 2009

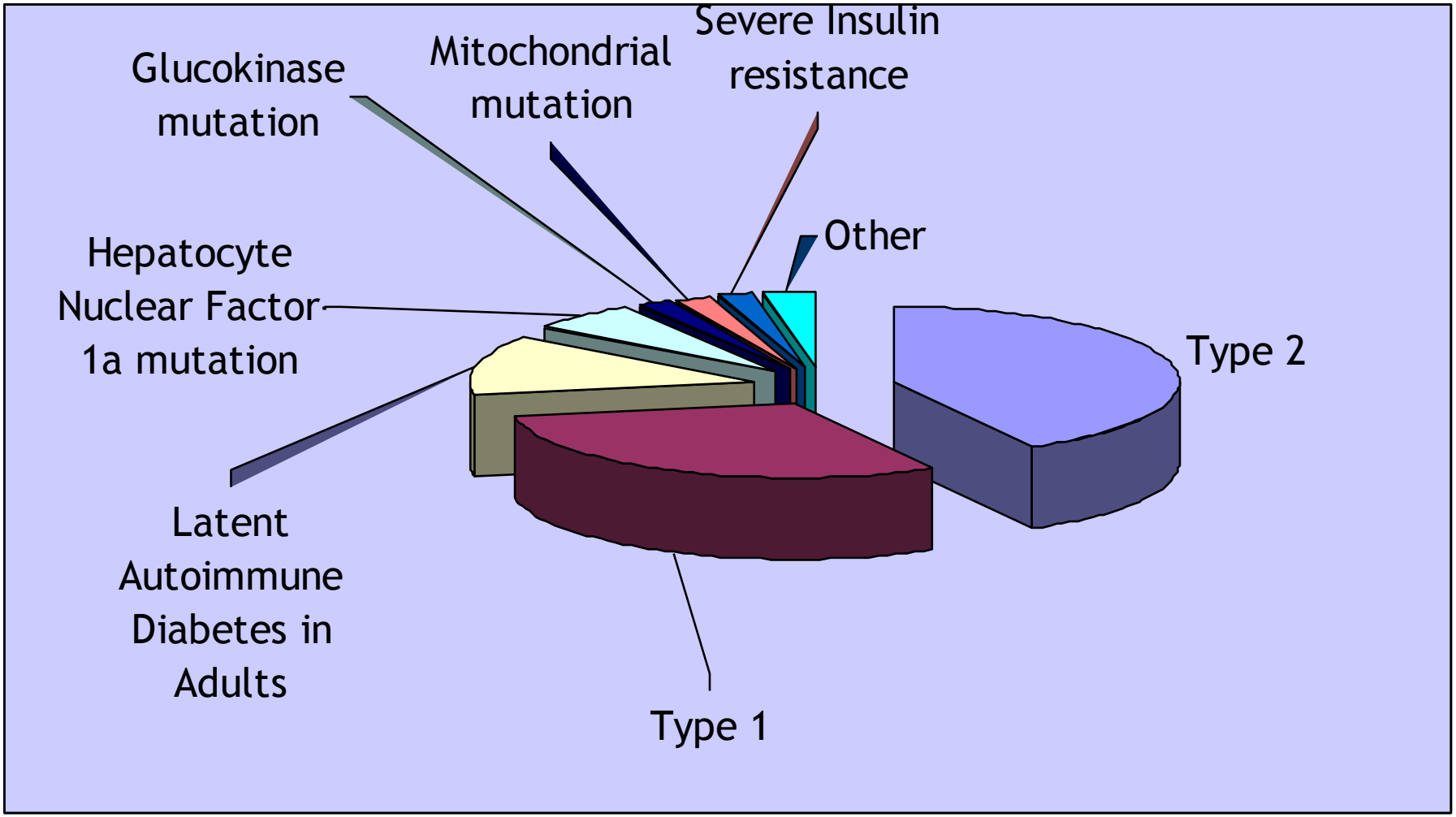
The first GWAS study of human glycome identified HNF1A as a master regulator of plasma protein fucosylation

Ana Mužinić

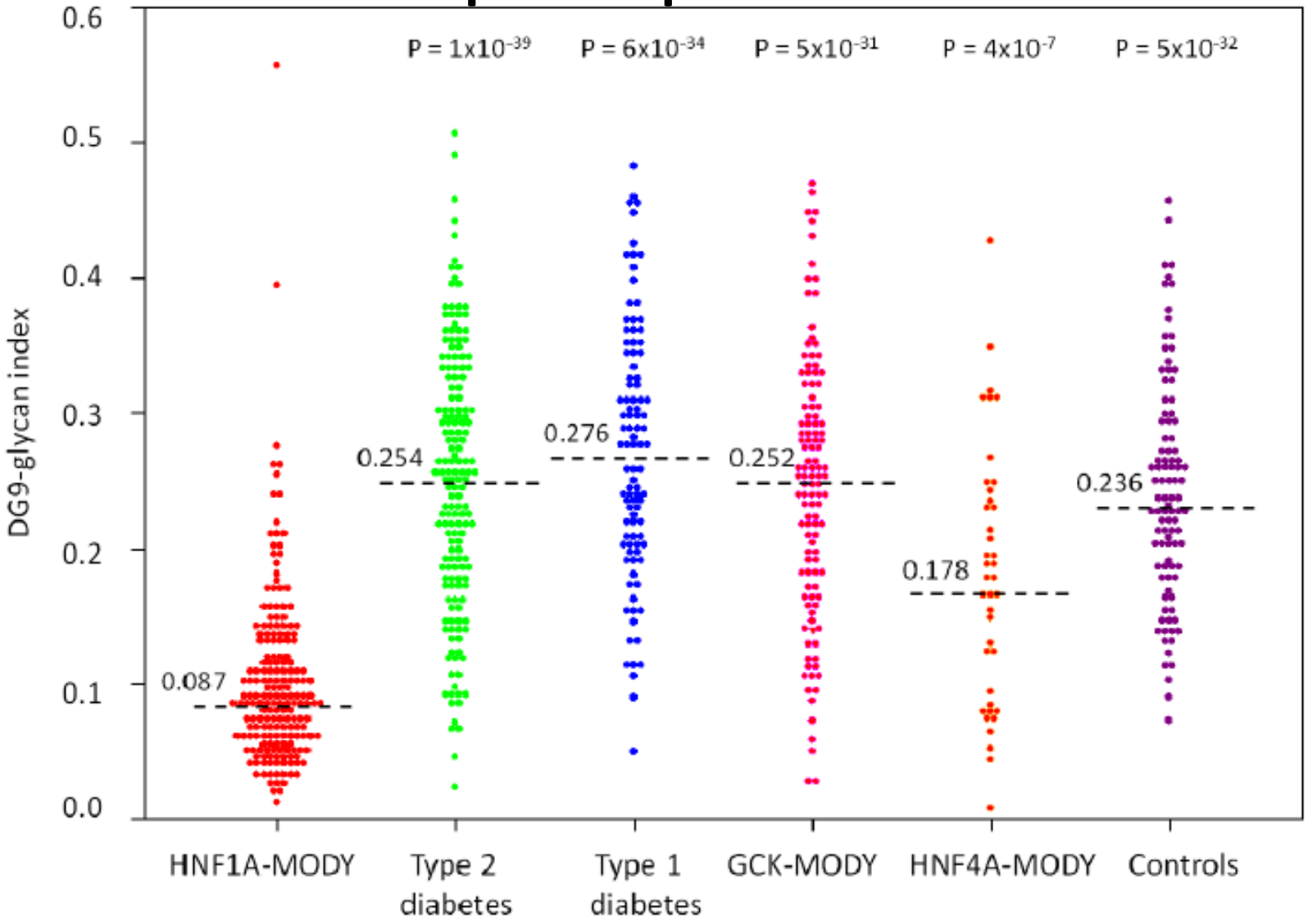


Lauc et al, *PLoS Genetics*, 2010

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

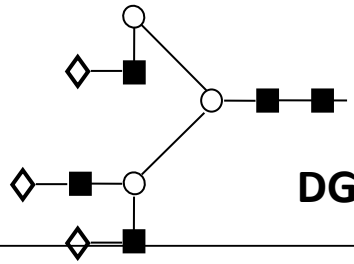


Mutations in HNF1A result in decreased fucosylation of plasma proteins

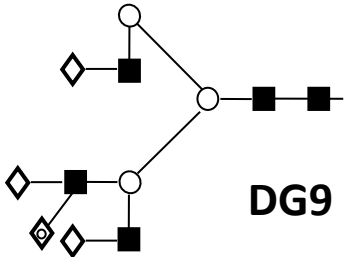


Glycan ratio (DG9 - index) is a robust biomarker for HNF1A-MODY

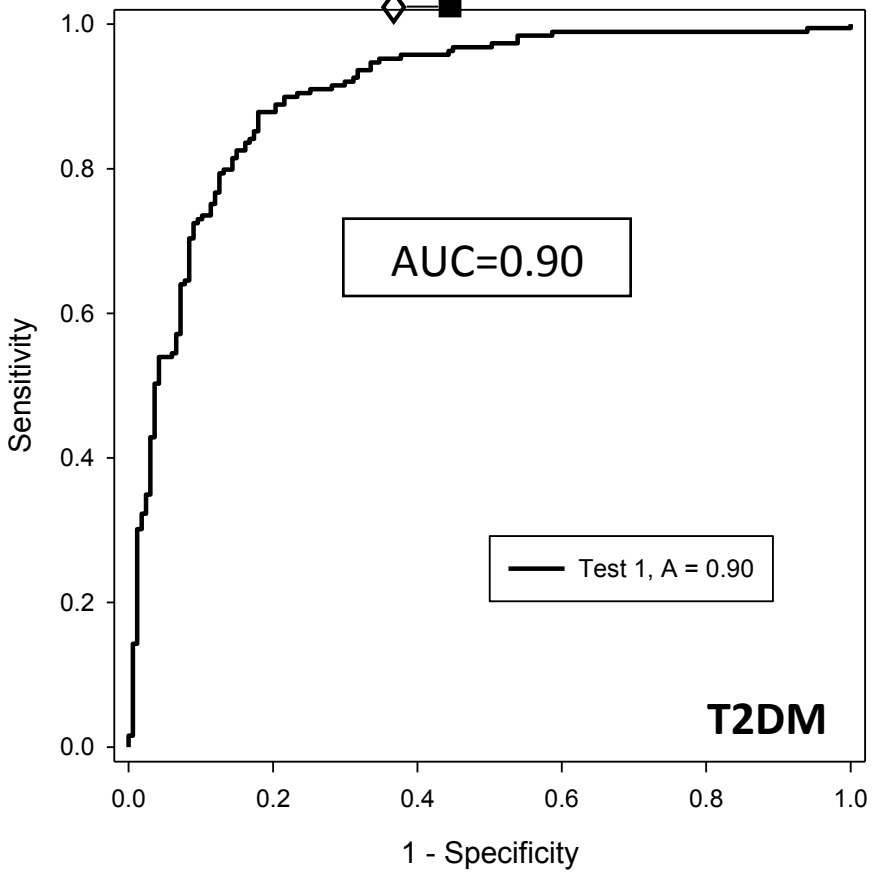
Mislav Novokmet

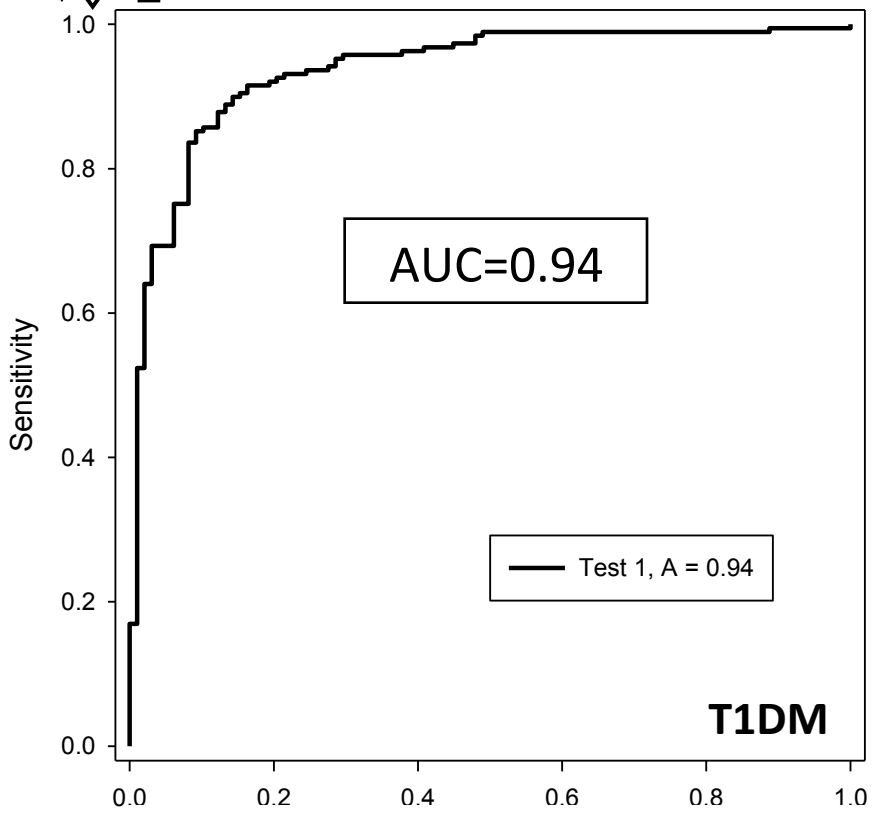


DG8



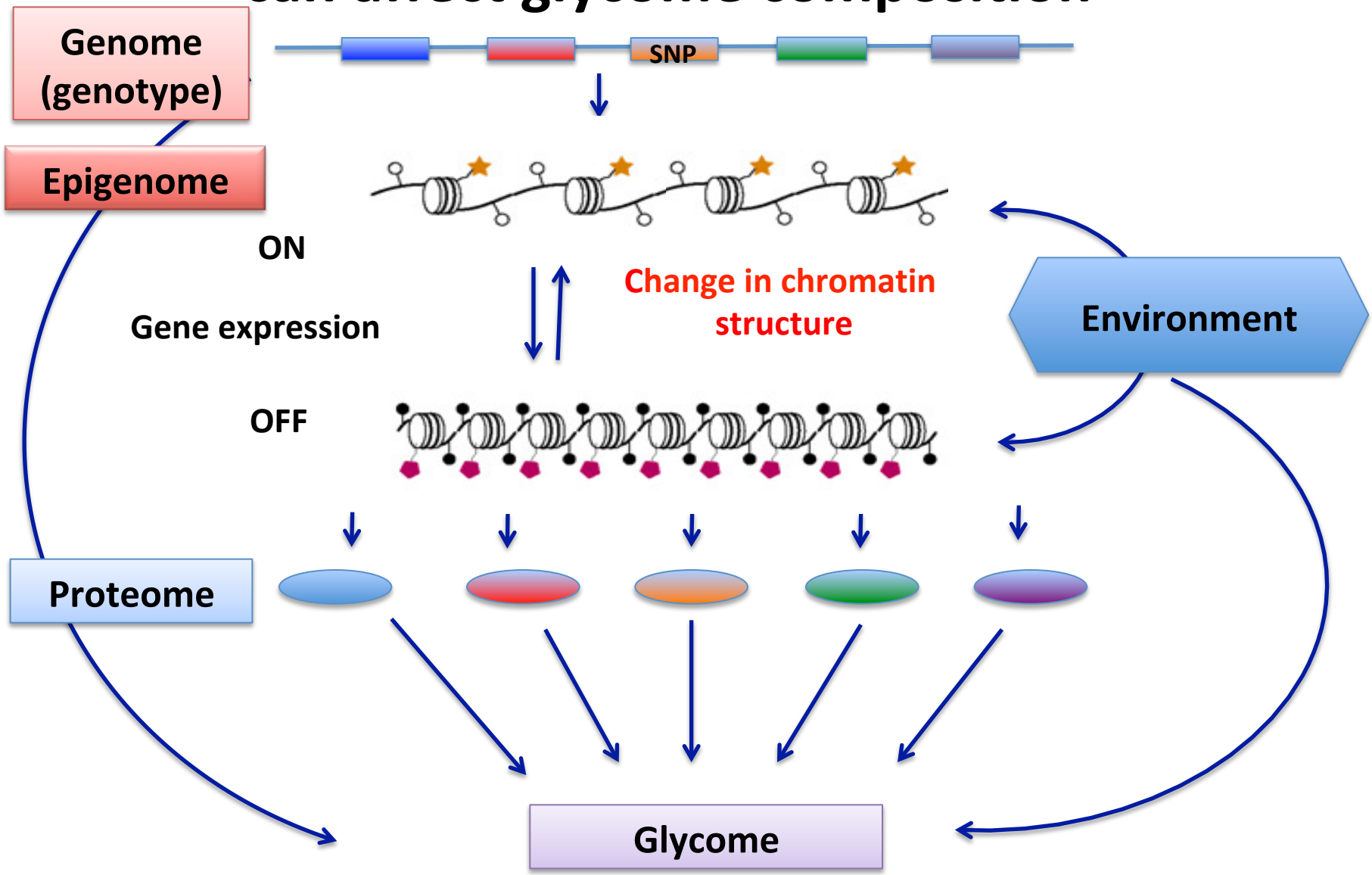
DG9





Thanabalasingham et al, *Diabetes, 2013*

Epigenetic memory of past environmental events can affect glycome composition



Epigenetic silencing of *HNF1A* associates with changes in plasma *N*-glycome

Prof V. Zoldoš

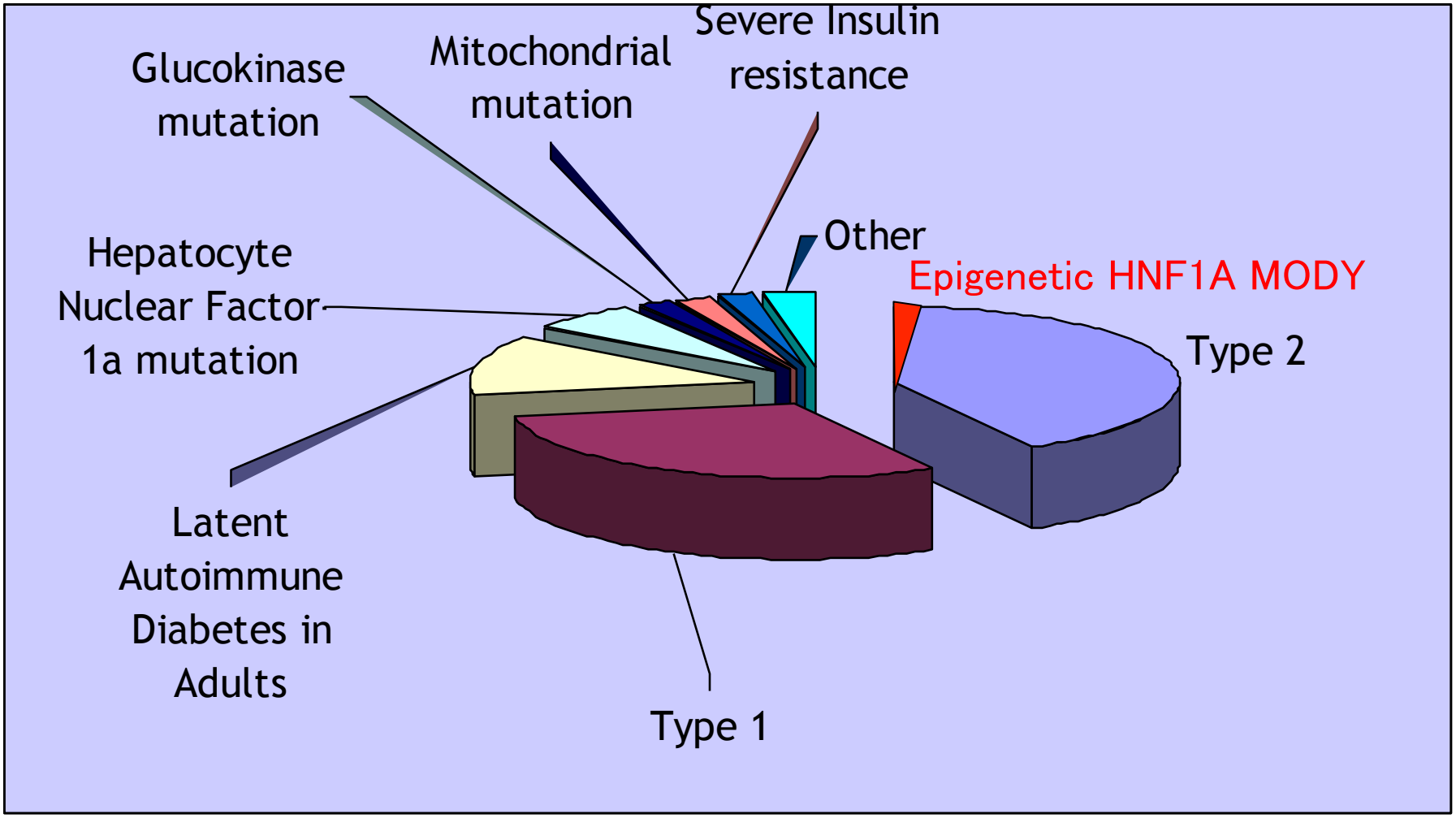
Epigenetics 7:2, 164-172; February 2012; © 2012 Landes Bioscience

Epigenetic silencing of *HNF1A* associates with changes in the composition of the human plasma *N*-glycome

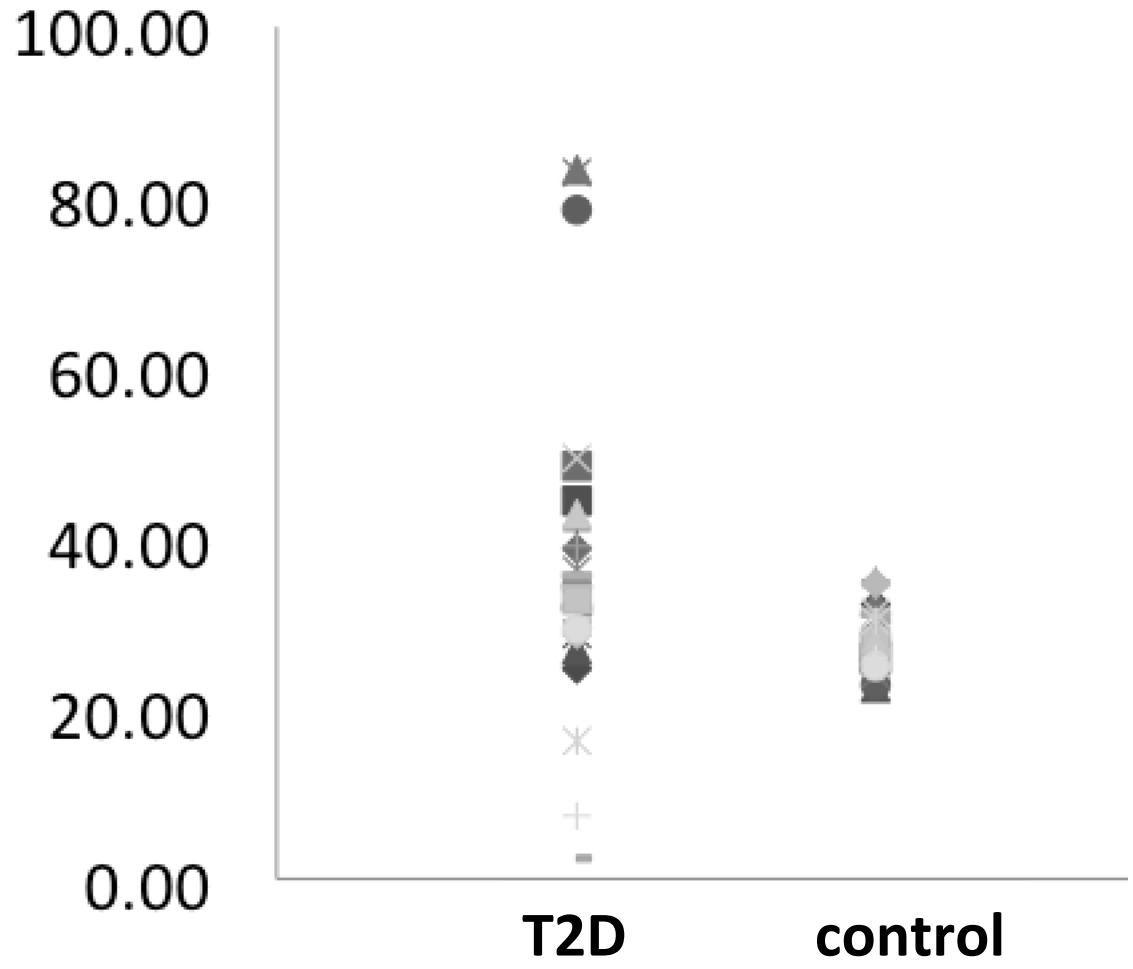
Vlatka Zoldoš,[1,†] Tomislav Horvat,[1,†] Mislav Novokmet,[2] Cyrille Cuenin,[3] Ana Mužinić,[2] Maja Pučić,[2] Jennifer E. Huffman,[4] Olga Gornik,[5] Ozren Polašek,[6] Harry Campbell,[7] Caroline Hayward,[8] Alan F. Wright,[8] Igor Rudan,[6,7] Katharine Owen,[8,9] Mark I. McCarthy,[8-10] Zdenko Herceg[3,*] and Gordan Lauc[2,5,*]

[1]University of Zagreb Faculty of Science; University of Zagreb; Zagreb, Croatia; [2]Genos Ltd.; Glycobiology Laboratory; Zagreb, Croatia; [3]International Agency for Research on Cancer; Lyon, France; [4]MRC Human Genetics Unit; Institute of Genetics and Molecular Medicine; Western General Hospital; Edinburgh, UK; [5]University of Zagreb; Faculty of Pharmacy and Biochemistry; University of Zagreb; Zagreb, Croatia; [6]University of Split Medical School; Split, Croatia; [7]Centre for Population Health Sciences; The University of Edinburgh Medical School; Edinburgh, UK; [8]Oxford Centre for Diabetes; Endocrinology and Metabolism; University of Oxford; Churchill Hospital; Oxford, UK; [9]Oxford NIHR Biomedical Research Centre; Churchill Hospital; Oxford, UK; [10]Wellcome Trust Centre for Human Genetics; University of Oxford; Oxford, UK

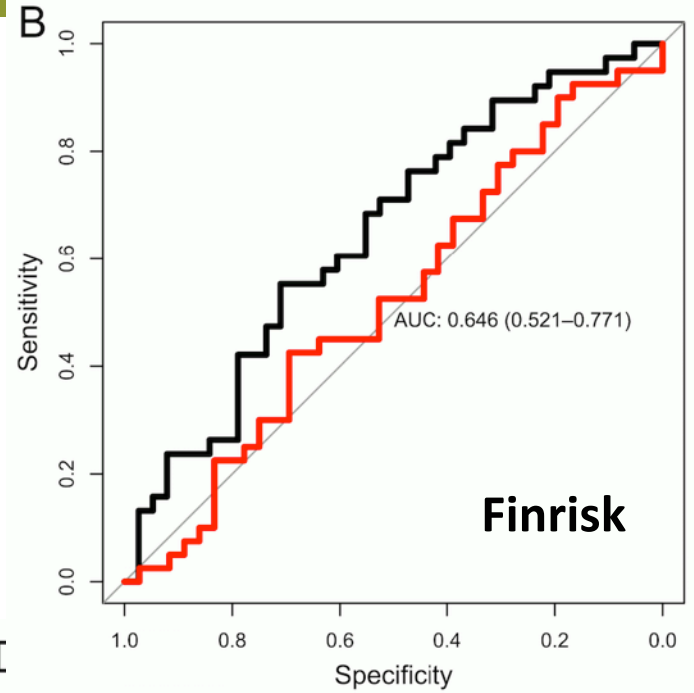
“Epigenetic HNF1A-MODY” might be a new subtype of diabetes

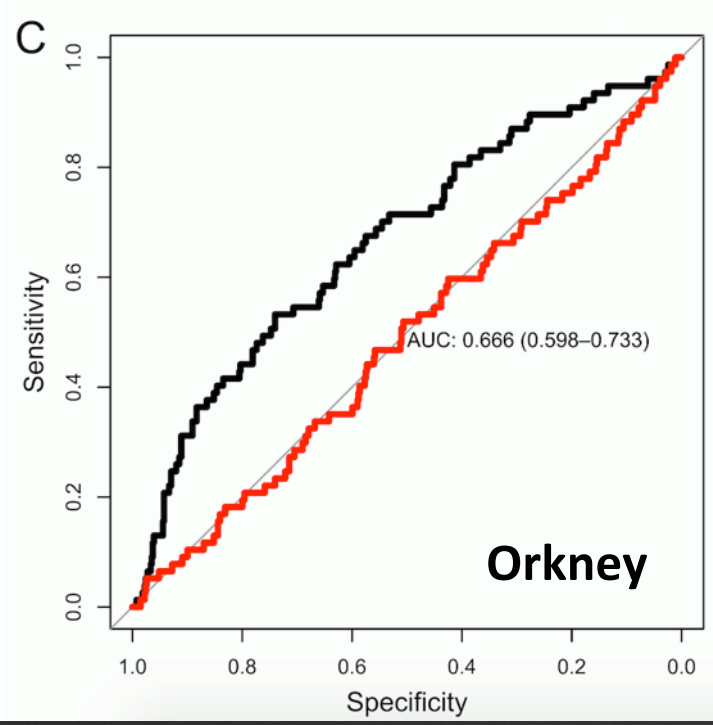


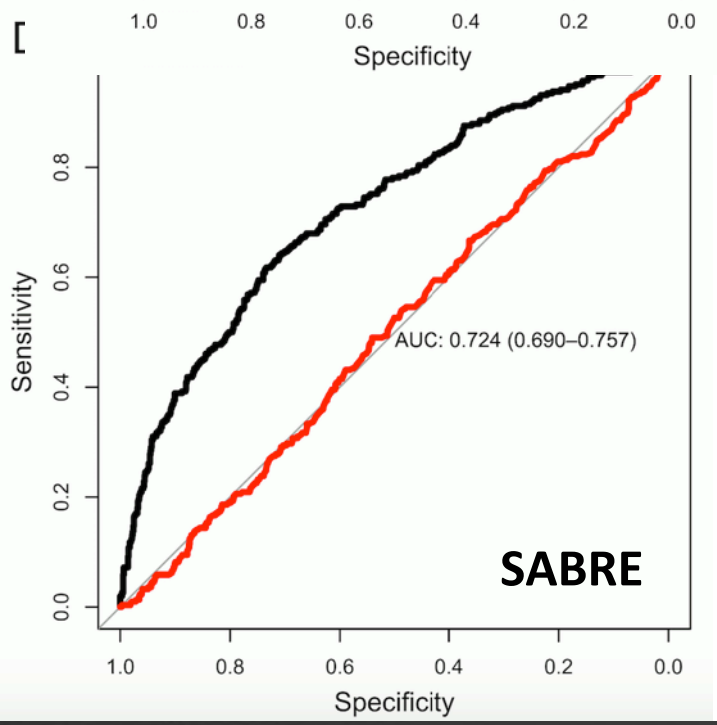
Methylation of HNF1A is significantly increased in a subgroup of T2D patients



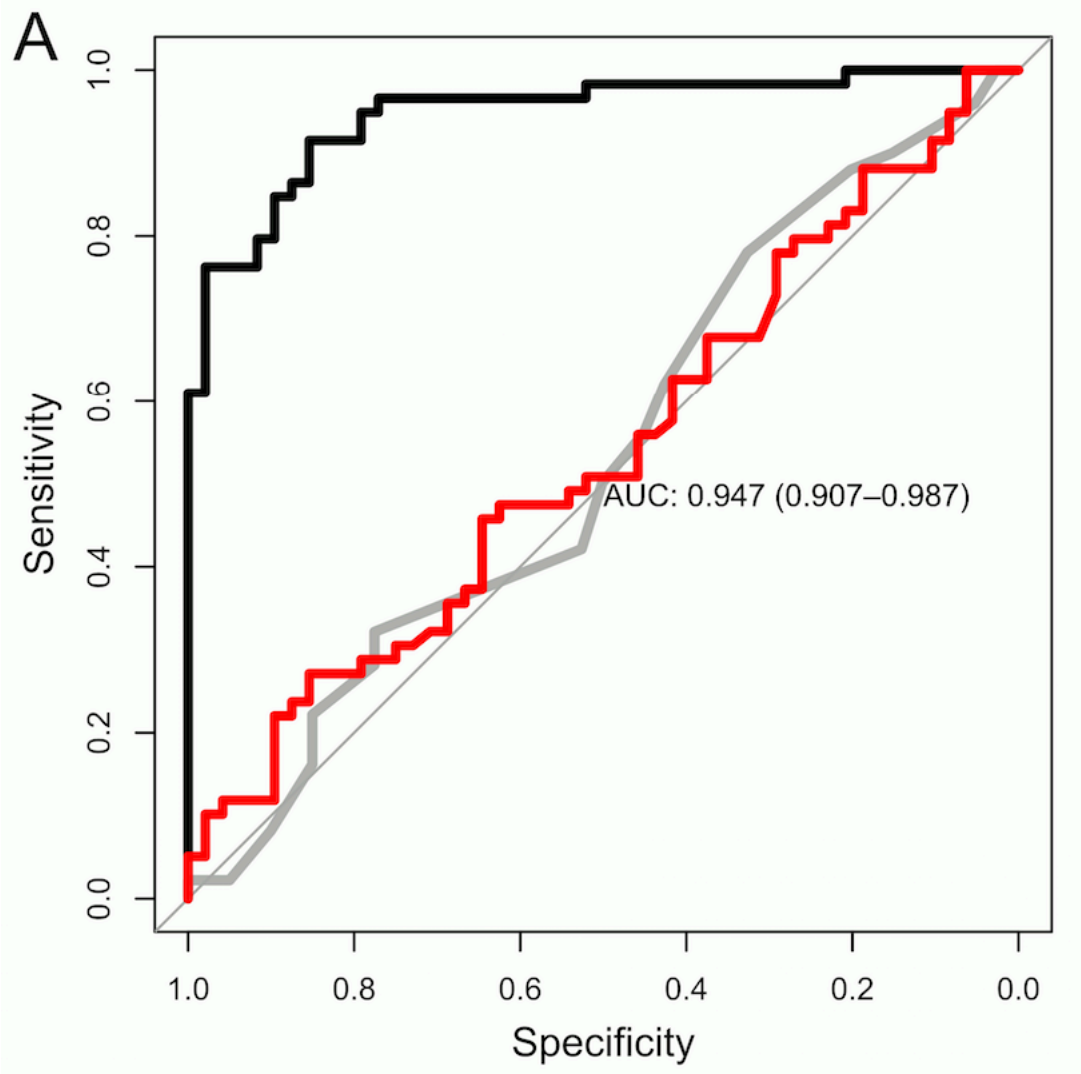
Plasma glycome can predict development of type 2 diabetes in some individuals



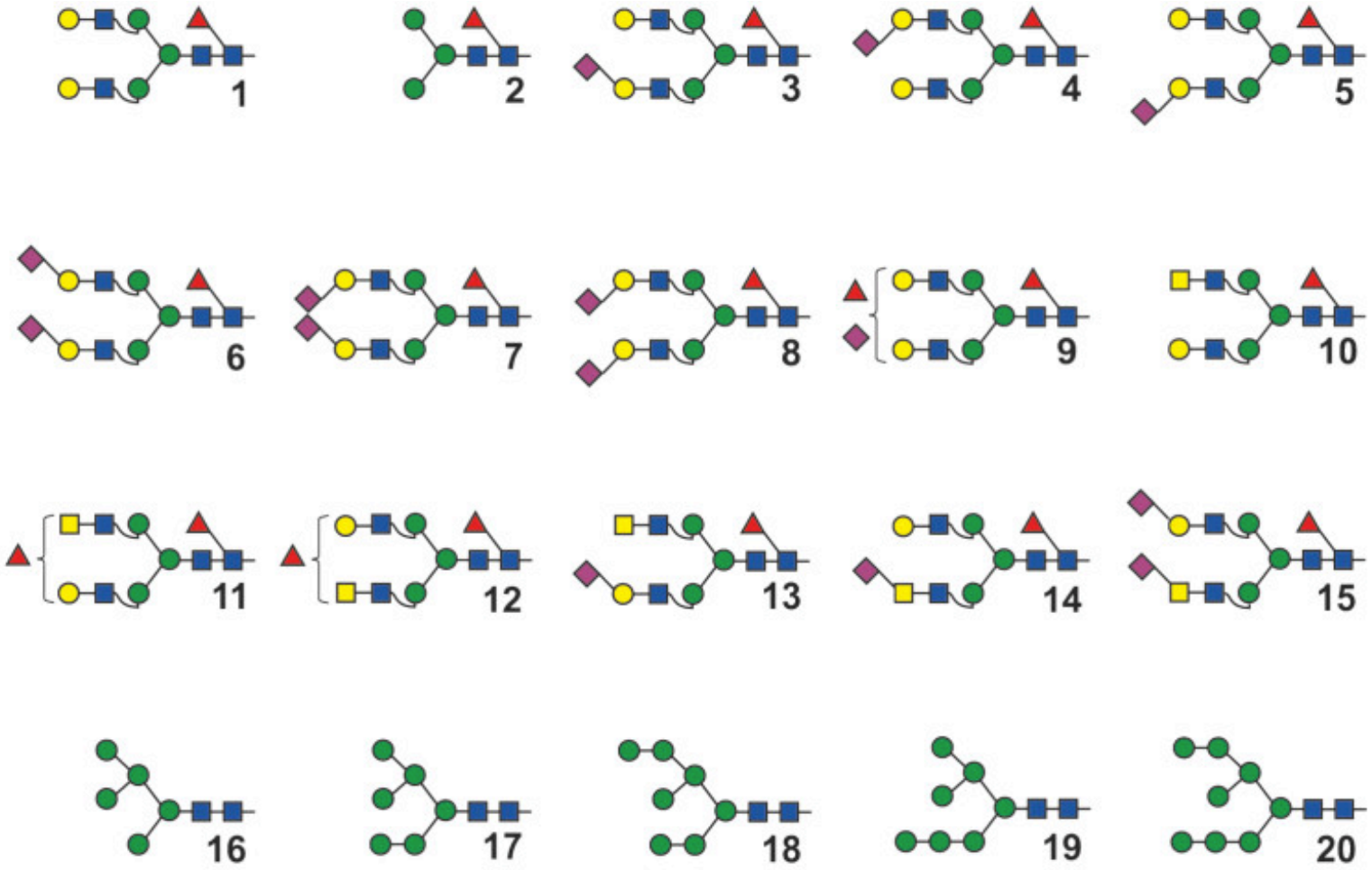




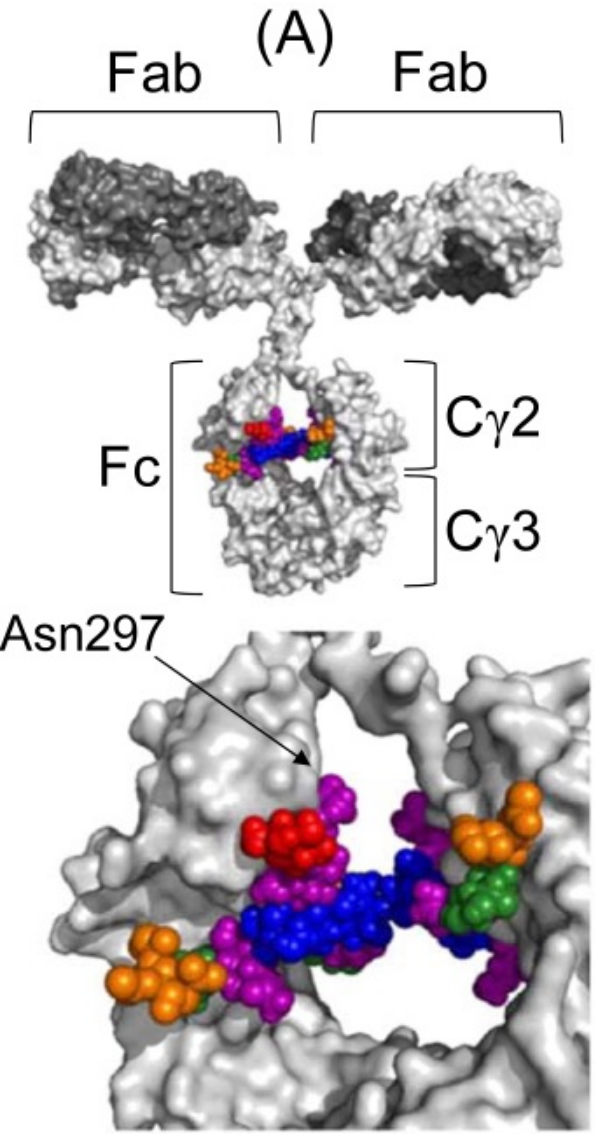
Plasma glycome is a very good predictor for hyperglycemia in acute disease



The analysis of plasma glycome (glycomics) blurs protein-specific effects



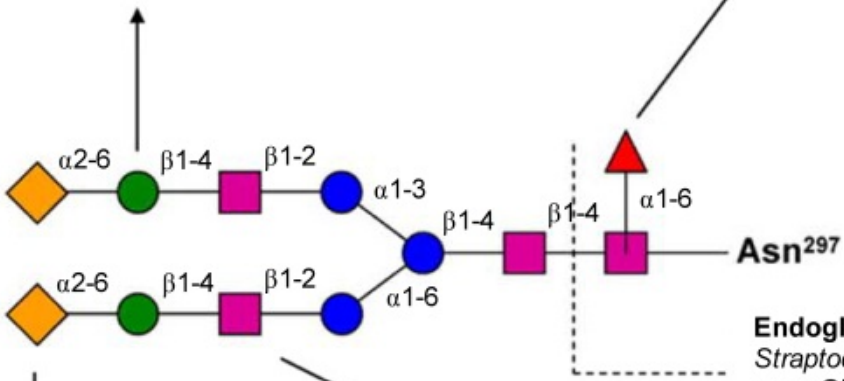
IgG glycosylation is functionally important



(B)

Galactose is required for high affinity C1q binding [21]. Removal of galactose either increases or decreases affinity for FcγR, depending on specific FCγR and IgG subtype pairig [22].

"Removal of fucose enhances IgG affinity for FCγRIIIA [24].



Endoglycosidase-S isolated from *Straptococcus pyogenes* cleaves the core GlcNAc residues, leaving all but the reducing GlcNAc (and fucose if present).

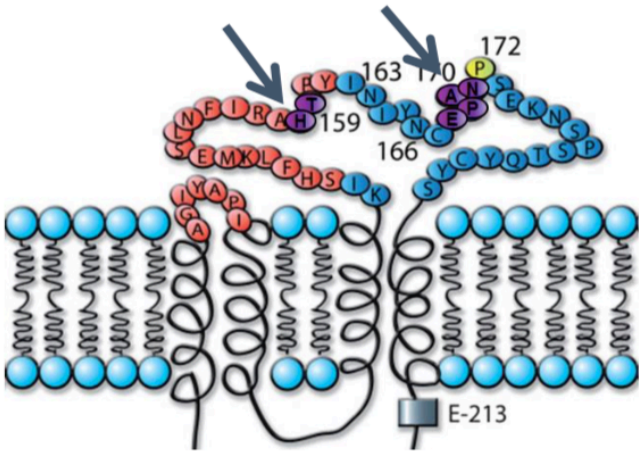
"Anti-inflammatory" properties (presence of sialic acid decreases binding to FcγRIII/IV, but maintains functional FcγRIII B interaction) [20].

"Exposed GlcNAc residues ("*G0*") glycoform is seen in rhematoid arthritis) [23].

Sialic acid Galactose GlcNAc Mannose Fucose

Ublituximab, glyco-engineered anti CD20 mAb is much more effective than Rituximab

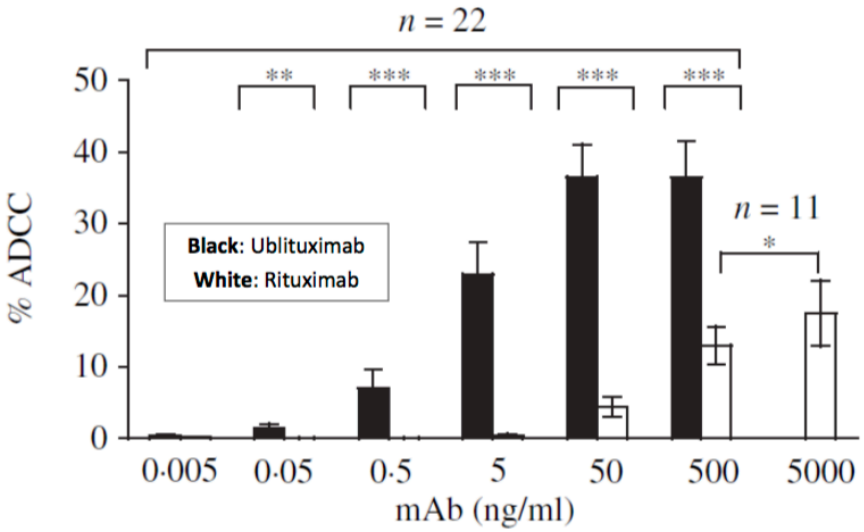
Figure 1: CD20 Antigen Binding Epitope of Ubliutimxab



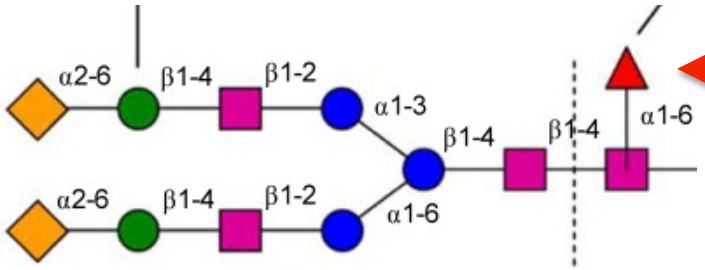
Red: Key ofatumumab epitope amino acids
Purple: Core amino acids of ublituximab epitope

Figure adapted from Ruuls et al, 2008

Figure 2: ADCC Comparison of Rituximab and Ublituximab in CLL Patient Cells



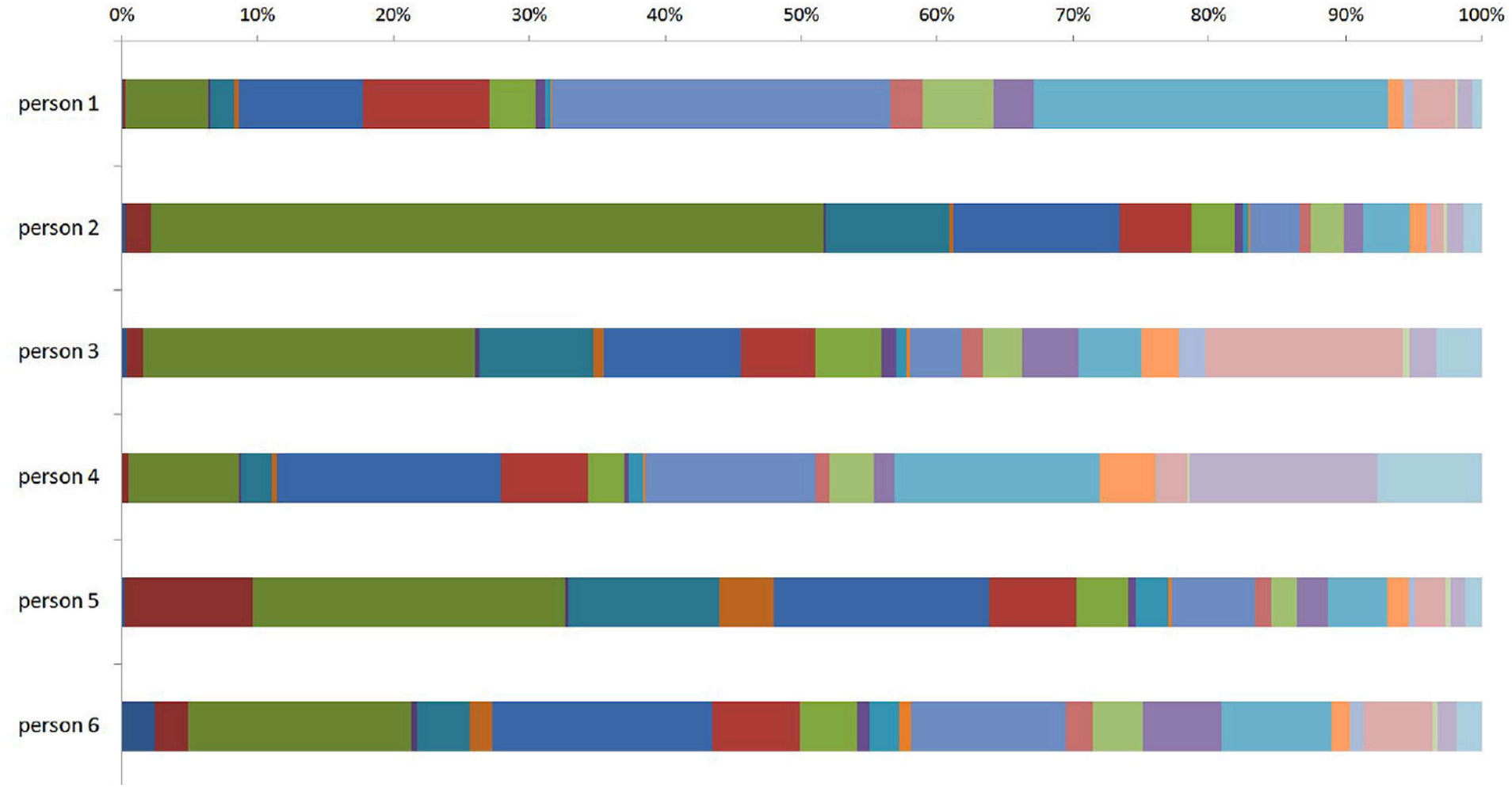
De Romeuf et al, 2008



Core fucose

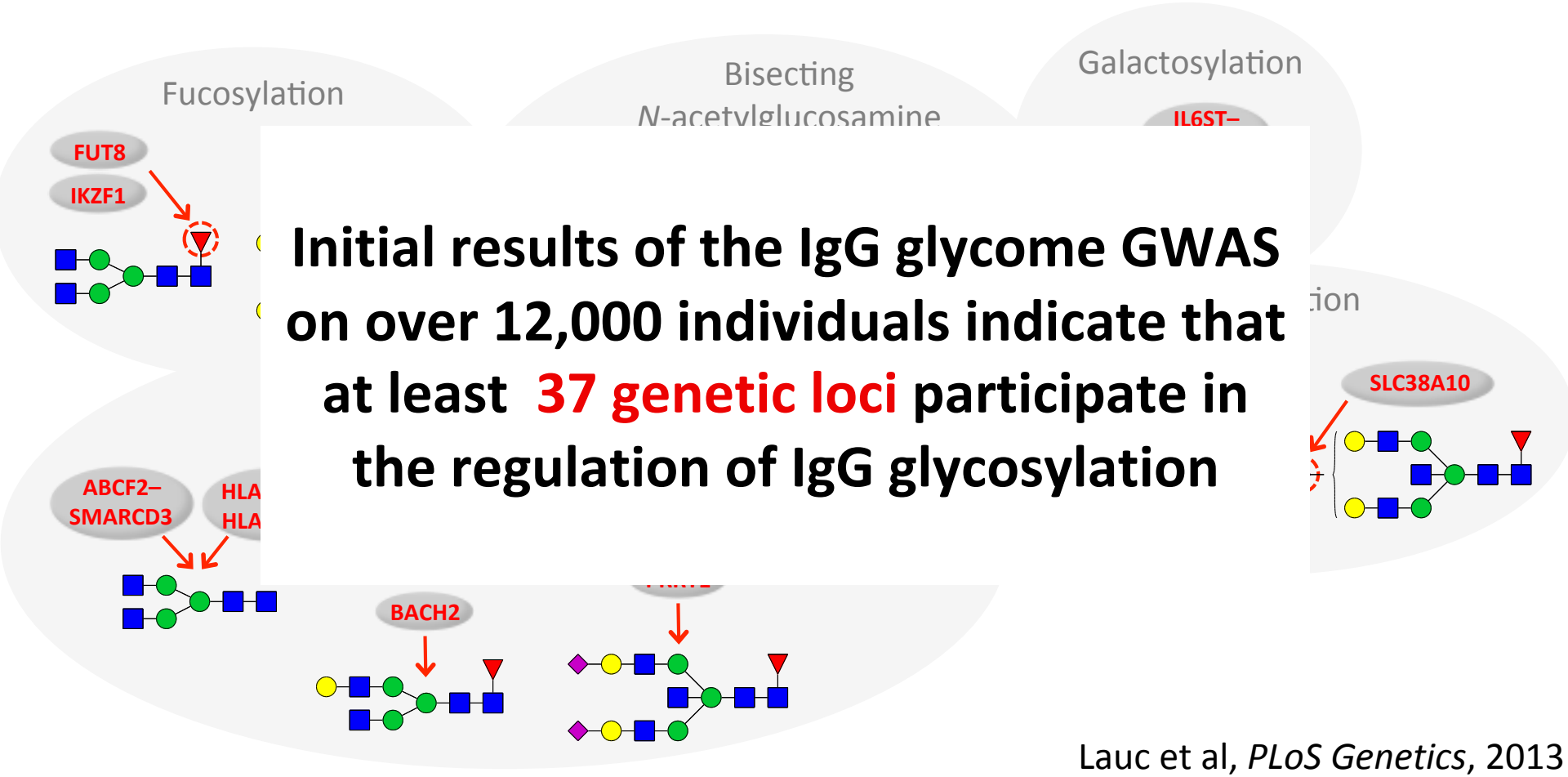
de Romeuf et al, Br J Haematol 2008
Sharman et al, Blood 2014

Antibody drugs act in the context of high concentrations of host immunoglobulins



Lauc et al, Front Genet, 2014

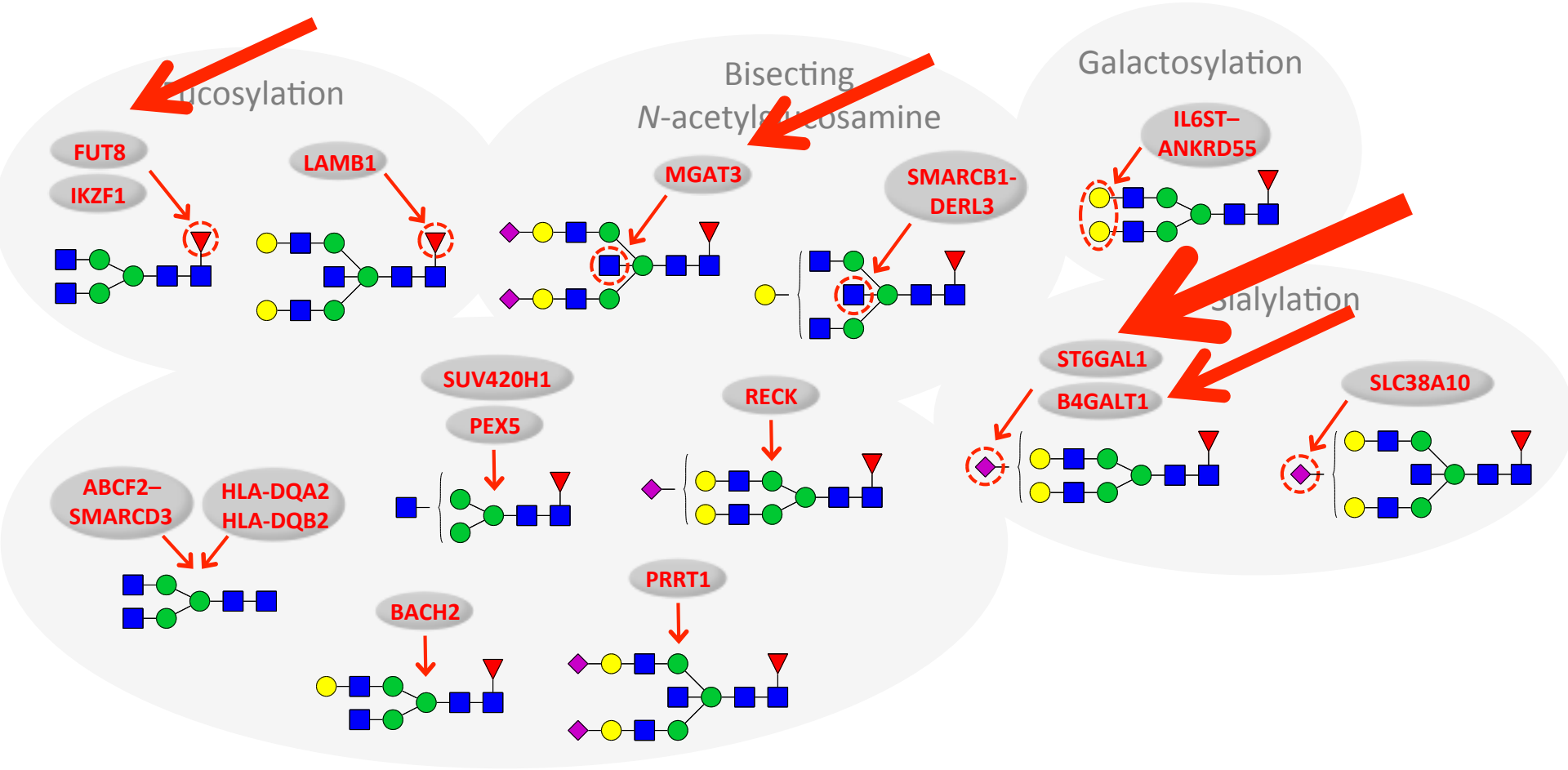
GWAS of IgG glycome performed on 2247 individuals identified 16 genome wide significant associations



Initial results of the IgG glycome GWAS on over 12,000 individuals indicate that at least 37 genetic loci participate in the regulation of IgG glycosylation

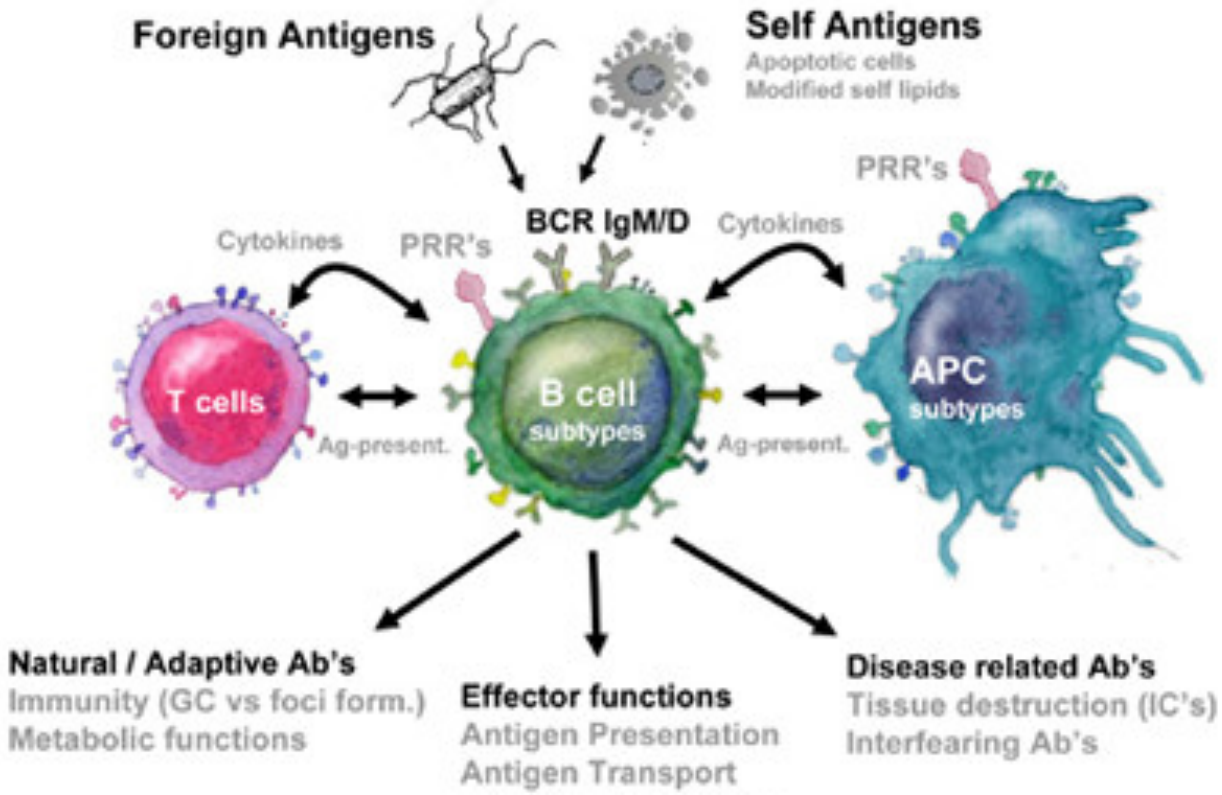
Lauc et al, *PLoS Genetics*, 2013
Wahl et al, Front Immunol, 2018

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

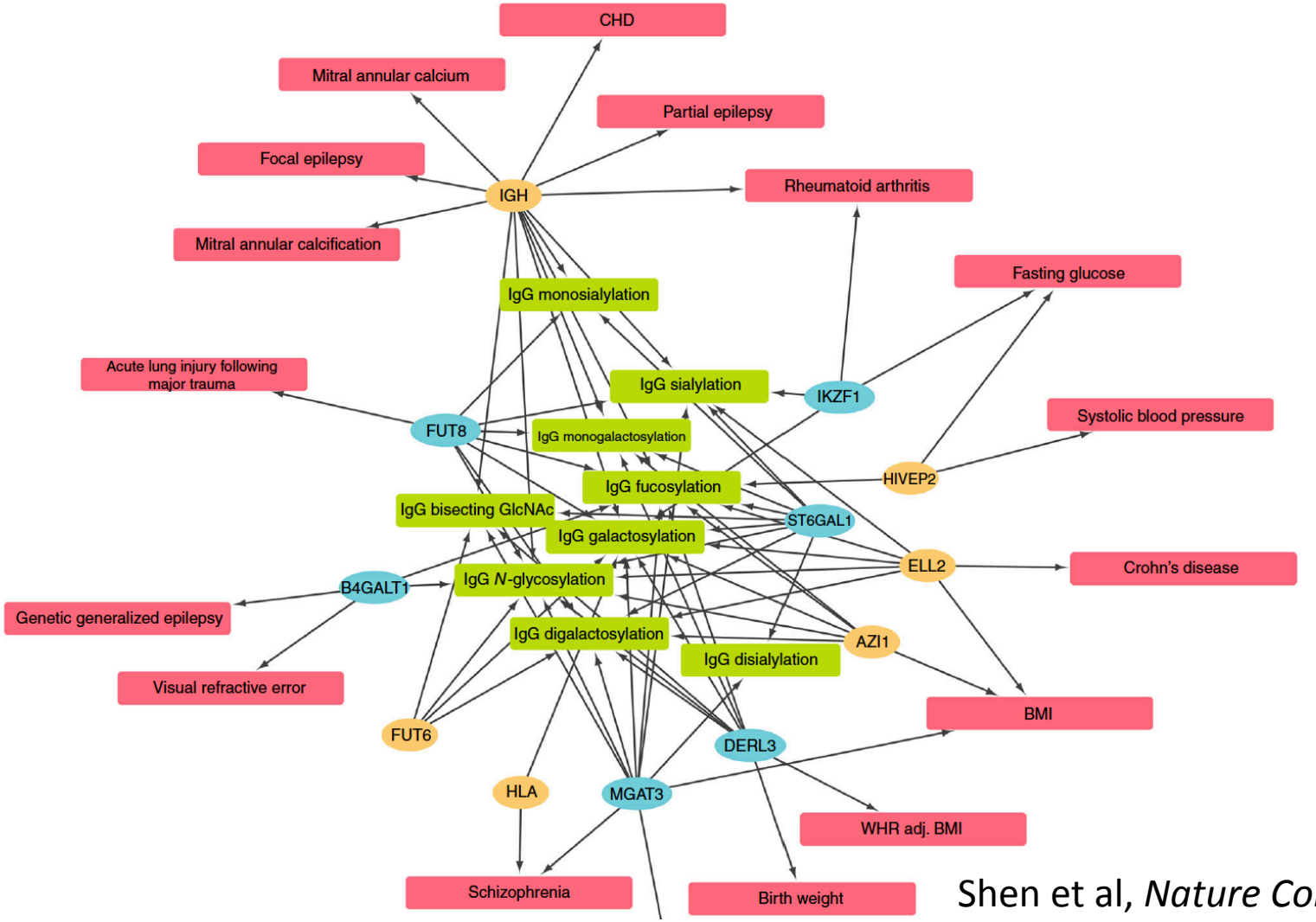


Lauc et al, *PLoS Genetics*, 2013

Many factors participate in the “decision” about optimal IgG glycosylation

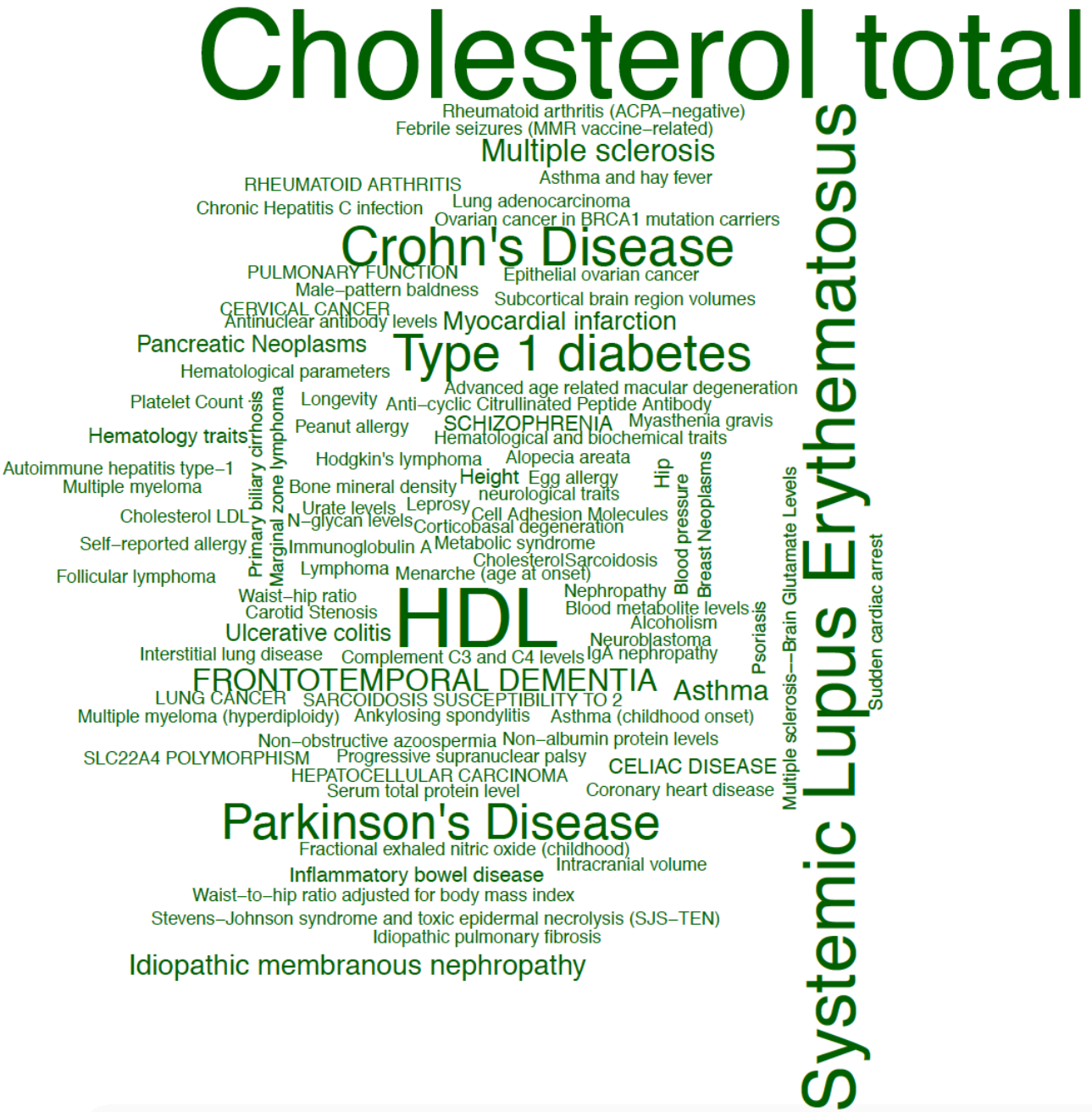


Genes that govern IgG glycosylation show pleiotropy with multiple diseases and traits



Shen et al, *Nature Comm*, 2017

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

Changes in IgG glycosylation associate with numerous diseases

ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 00, Month 2015, pp 00–00
DOI 10.1002/art.39273

Systemic Lupus Erythematosus Is Associated With Decreased
unosuppressive Potential of the IgG Glycome

ić,[1] Jasminka Krištić,[1] Ivan Gudelj,[1] Maria Teruel Artacho,[2] Toma Keser,[3]
aja Pučić-Baković,[1] Jerko Štambuk,[1] Irena Trbojević-Akmačić,[1] Clara Barrios,[4]
Cristina Menni,[5] Youxin Wang,[6] Yong Zhou,[7] Liufu Cui,[8] Haicheng Song,[8]

CLINICAL RESEARCH www.jasn.org

Glycosylation Profile of IgG in Moderate Kidney Dysfunction

Clara Barrios,*† Jonas Zierer,*‡ Ivan Gudelj,§ Jerko Štambuk,§ Ivo Ugrina,§ Ev
María José Soler,† Tamara Pavić,‖ Mirna Šimurina,‖ Toma Keser,‖ Maja Pučić-B
Massimo Mangino,* Julio Pascual,† Tim D Spector,* Gordan Lauc,§‖ and Crist

ORIGINAL ARTICLE

Mutations in *HNF1A* R
Plasma Glycan Profile

Gaya Thanabalasingham,[1,2] Jennifer E. Hu
Igor Rudan,[6,7] Anna L. Gloyn,[1,2] Caroline
Ana Muzinic,[5] Neelam Hassanali,[1] Maja Pucic,[5] Amanda J. Bennett,[1] Abdelkader Essafi,[3]
Ozren Polasek,[7] Saima A. Mughal,[1,2] Irma Redzic,[9] Dragan Primorac,[7,10] Lina Zgaga,[6] Ivana Kolcic,[7]
Torben Hansen,[11,12,13] Daniela Gasperikova,[14] Erling Tjora,[15,16] Mark W.J. Strachan,[17]

REVIEWS

The role of glycosylation in IBD

Evropi Theodoratou, Harry Campbell, Nicholas T. Ventham, Daniel Kolarich, Maja Pučić-Baković, Vlatka Zoldoš, Daryl Fernandes, Iain K. Pemberton, Igor Rudan, Nicholas A. Kennedy, Manfred Wuhrer, Elaine Nimmo, Vito Annese, Dermot P. B. McGovern, Jack Satsangi and Gordan Lauc

Abstract | A number of genetic and immunological studies give impetus for investigating the role of glycosylation in IBD. Experimental mouse models have helped to delineate the role of glycosylation in intestinal mucins and to explore the putative pathogenic role of glycosylation in colitis. These experiments have been

Glycomics should be integrated in the “big data” science

ARTICLE

DOI: 10.1038/s41467-017-00453-3 OPEN

Multivariate discovery and replication of fiv novel loci associated with Immunoglobulin *N*-glycosylation

Xia Shen[1,2,3], Lucija Klarić[1,3,4], Sodbo Sharapov[5,6], Massimo Mangino[7,8], Zheng Ning[2],

ARTICLE

Received 10 Aug 2016 | Accepted 16 Dec 2016 | Published 27 Feb 2017 DOI: 10.1038/ncomms14357 OPEN

Connecting genetic risk to disease end points through the human blood plasma proteome

Karsten Suh
Johannes Ra
Marija Pezer
Yasmin A. M
Gabi Kasten

ARTICLE

DOI: 10.1038/s41467-017-01525-0 OPEN

Network inference from glycoproteomics dat reveals new reactions in the IgG glycosylatic pathway

Elisa Benedetti[1], Maja Pučić-Baković[2], Toma Keser[3], Annika Wahl[4,5], Antti Hassinen[6], Jeong-Y
Lin Liu[7], Irena Trbojević-Akmačić[2], Genadij Razdorov[2], Jerko Štambuk[2], Lucija Klarić[2,8,9], Ivo U
Maurice H.J. Selman[12], Manfred Wuhrer[12], Igor Rudan[8], Ozren Polasek[13,14], Caroline Haywa
Harald Grallert[4,5,15], Konstantin Strauch[16,17], Annette Peters[5], Thomas Meitinger[18], Christian Gieg
Marija Vilaj[2], Geert-Jan Boons[7,19], Kelley W. Moremen[7], Tatiana Ovchinnikova[20], Nicolai Bovin[20]
Sakari Kellokumpu[6], Fabian J. Theis[1,21], Gordan Lauc[2,3] & Jan Krumsiek[1,14]

Diabetes Care 1

Check for updates

N-Glycan Profile and Kidney Disease in Type 1 Diabetes

https://doi.org/10.2337/dc17-1042

Mairead L. Bermingham,[1] Marco Colombo,[2]
Stuart J. McGurnaghan,[1]
Luke A.K. Blackbourn,[1] Frano Vučković,[3]
Maja Pučić Baković,[3]
Irena Trbojević-Akmačić,[3] Gordan Lauc,[3]
Felix Agakov,[4] Anna S. Agakova,[4]

Contents lists available at ScienceDirect

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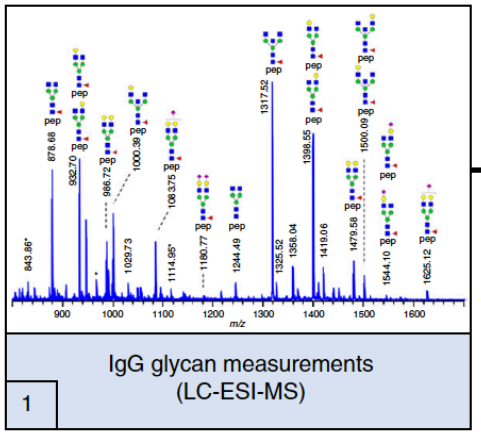
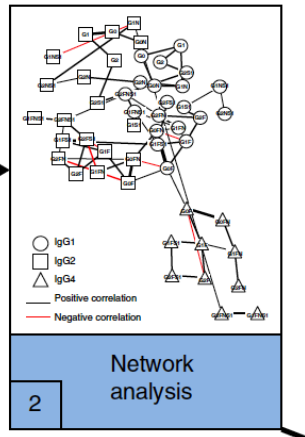
journal homepage: www.elsevier.com/locate/bbagen

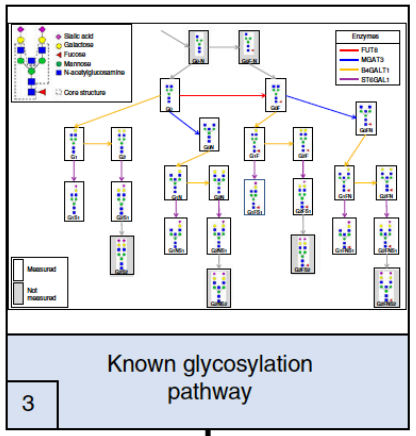
IgG glycan patterns are associated with type 2 diabetes in independent European populations

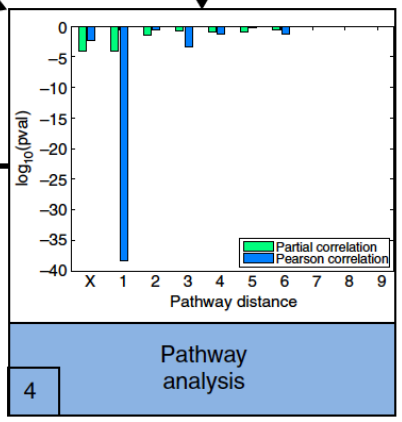
Roosmarijn F.H. Lemmers[a,b], Marija Vilaj[c,1], Daniel Urda[d,1], Felix Agakov[d], Mirna Šimurina[e], Lucija Klaric[c,e,f], Igor Rudan[g], Harry Campbell[g], Caroline Hayward[f], Jim F. Wilson[f,g], Aloysius G. Lieverse[b], Olga Gornik[e], Eric J.G. Sijbrands[a], Gordan Lauc[c,e], Mandy van Hoek[a,*]

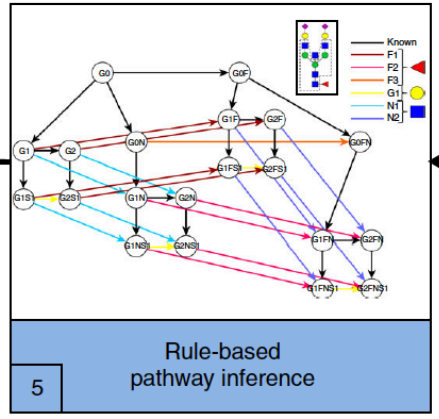
Network analysis can be used to modify prior knowledge

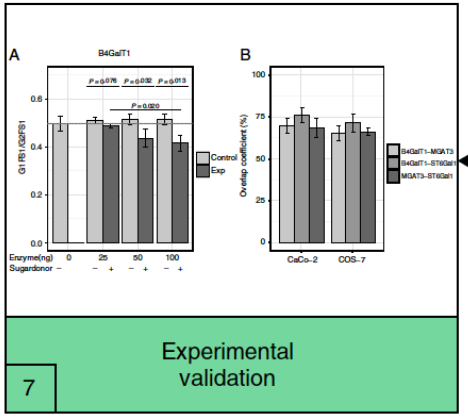


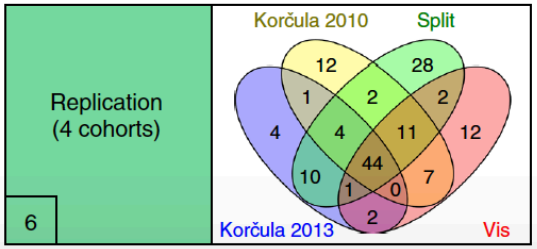












Elisa Benedetti

Jan Krumsiek

Benedetti et al
Nat Comm,
2018

HelmholtzZentrum münchen
German Research Center for Environmental Health

Are glycosylation changes in a disease a cause or a consequence?

ARTHRITIS & RHEUMATISM
Vol. 62, No. 8, August 2010, pp 2239–2248
DOI 10.1002/art.27533
© 2010, American College of Rheumatology

Aberrant IgG Galactosylation Precedes Disease Onset, Correlates With Disease Activity, and Is Prevalent in Autoantibodies in Rheumatoid Arthritis

Altan Ercan,[1] Jing Cui,[1] Dereck E. W. Chatterton,[2] Kevin D. Deane,[3] Melissa M. Hazen,[4] William Brintnell,[5] Colin I. O'Donnell,[3] Lezlie A. Derber,[3] Michael E. Weinblatt,[1] Nancy A. Shadick,[1] David A. Bell,[6] Ewa Cairns,[5] Daniel H. Solomon,[1] V. Michael Holers,[3] Pauline M. Rudd,[2] and David M. Lee[1]

Objective. **To examine the association between aberrant IgG galactosylation and disease parameters in rheumatoid arthritis (RA).**

Methods. **Analysis of *N*-glycan in serum samples from multiple cohorts was performed. The IgG *N*-glycan content and the timing of *N*-glycan aberrancy relative to disease onset were compared in healthy subjects and in patients with RA. Correlations between aberrant galactosylation and disease activity were assessed in the RA**

Basic and translational research

EXTENDED REPORT

Anti-citrullinated protein antibodies acquire a pro-inflammatory Fc glycosylation phenotype prior to the onset of rheumatoid arthritis

Yoann Rombouts,[1] Ewoud Ewing,[2] Lotte A van de Stadt,[3] Maurice H J Selman,[2] Leendert A Trouw,[1] André M Deelder,[2] Tom W J Huizinga,[1] Manfred Wuhrer,[2] Dirkjan van Schaardenburg,[3,4] René E M Toes,[1] Hans U Scherer[1]

ABSTRACT

Objective To determine whether anticitrullinated protein antibodies (ACPA) exhibit specific changes in Fc glycosylation prior to the onset of arthritis.

Methods Serum samples of patients with ACPA-positive

pathogenicity are incompletely understood, it is intriguing that ACPA can be present in asymptomatic individuals and in patients with joint pain (arthralgia) years before the onset of arthritis.[6–9] In this early period, ACPA do not cause apparent path-

n moment predis-
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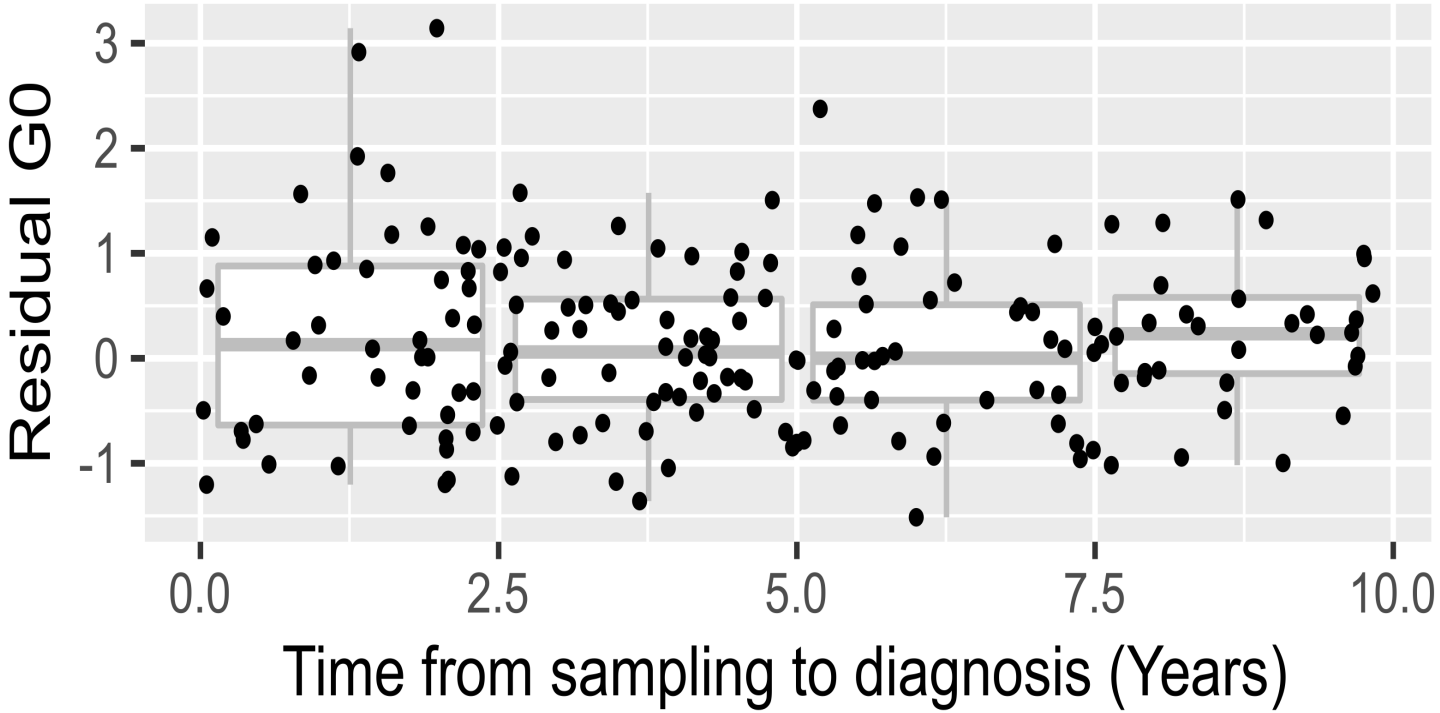
Research Paper

Galactosylation and Sialylation Levels of IgG Predict Relapse in Patients With PR3-ANCA Associated Vasculitis

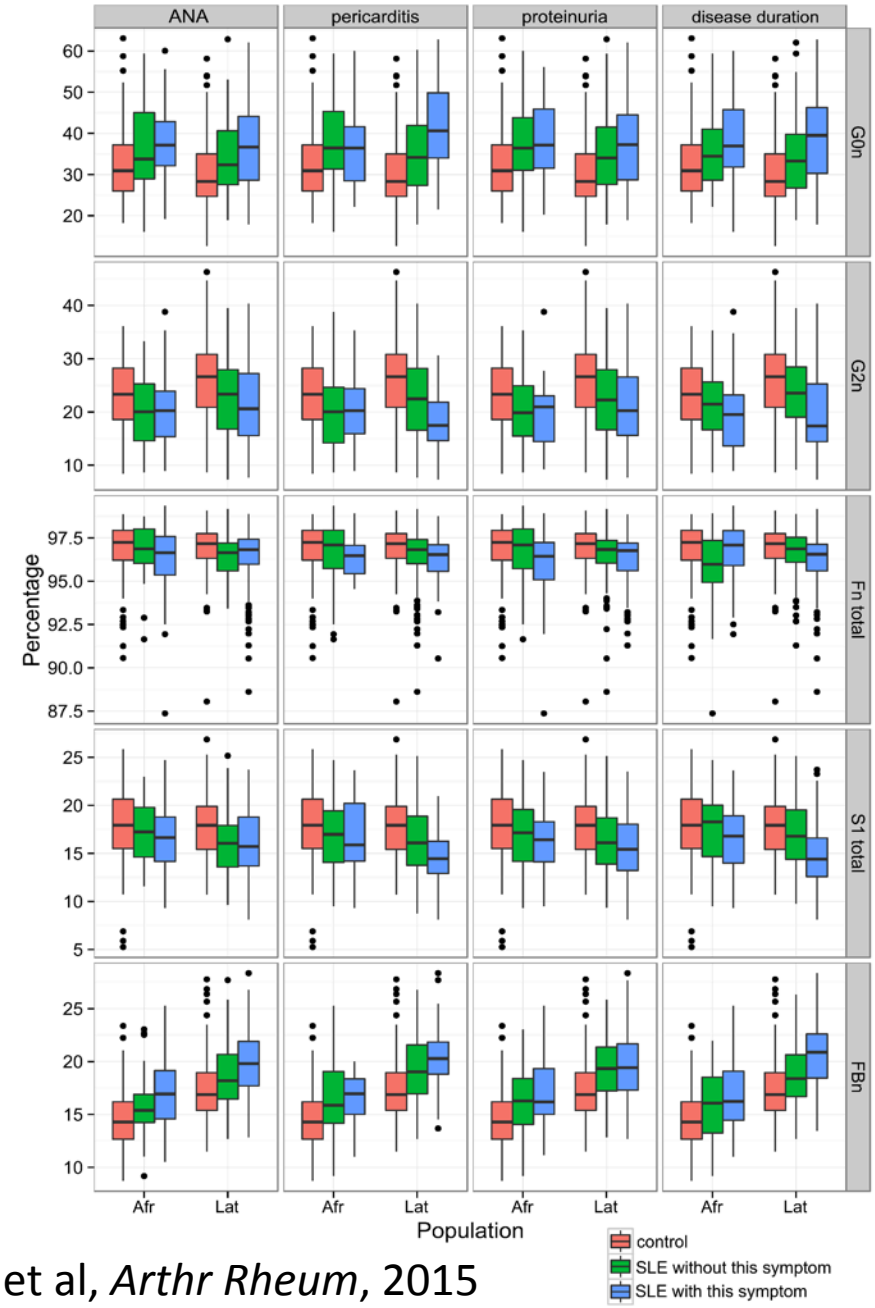
Michael J. Kemna [a,b,1], Rosina Plomp [d,1], Pieter van Paassen [a,b], Carolien A.M. Koeleman [c], Bas C. Jansen [c], Jan G.M.C. Damoiseaux [d], Jan Willem Cohen Tervaert [a,*,2], Manfred Wuhrer [c,2]

IgG glycosylation changes in RA are present years before diagnosis



Gudelj et al, BBA Mol Bas Dis, 2018

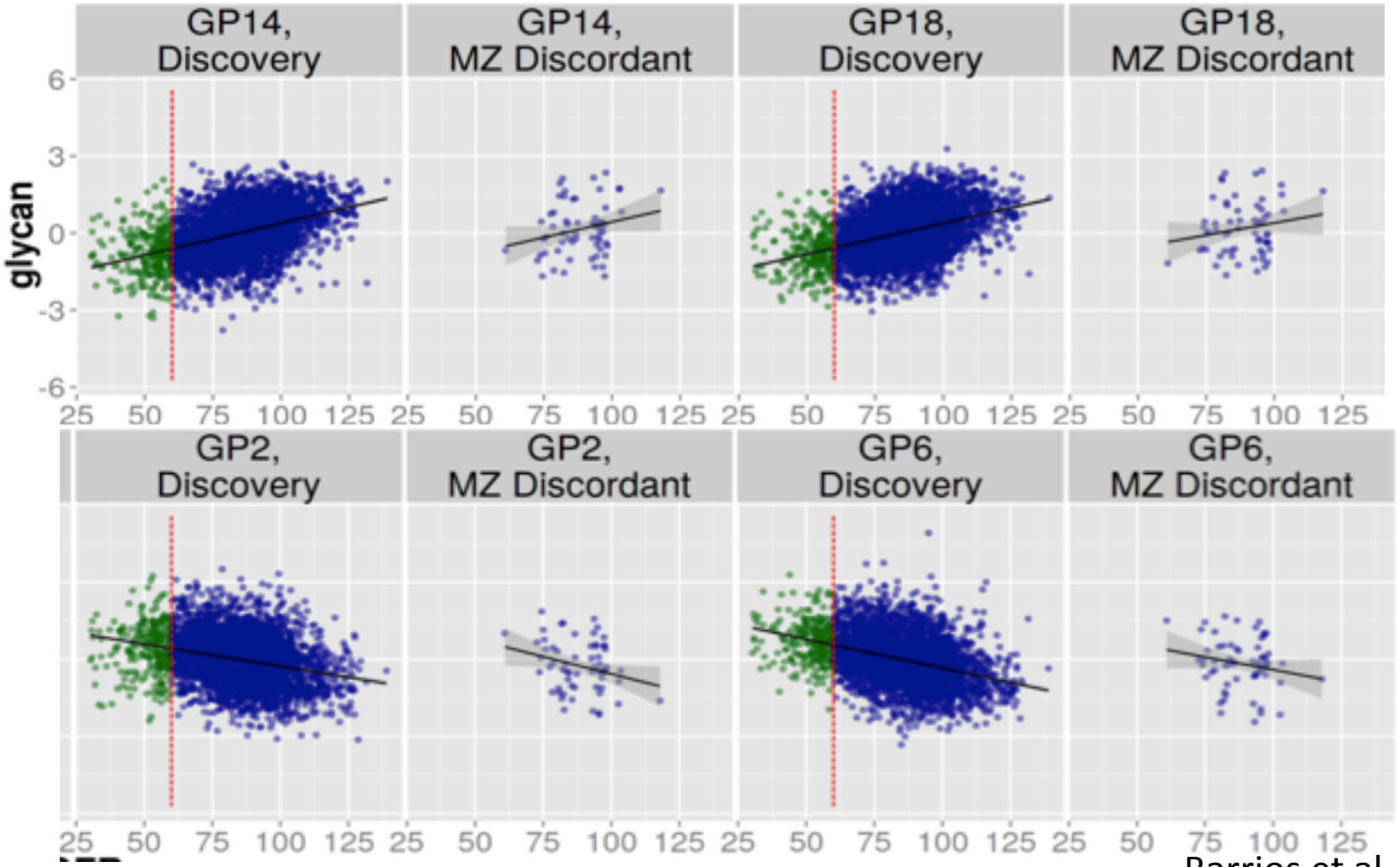
Sialylation, galactosylation, and bisecting GlcNAc on IgG associate with loss of kidney function in SLE



Vučković et al, *Arthr Rheum*, 2015

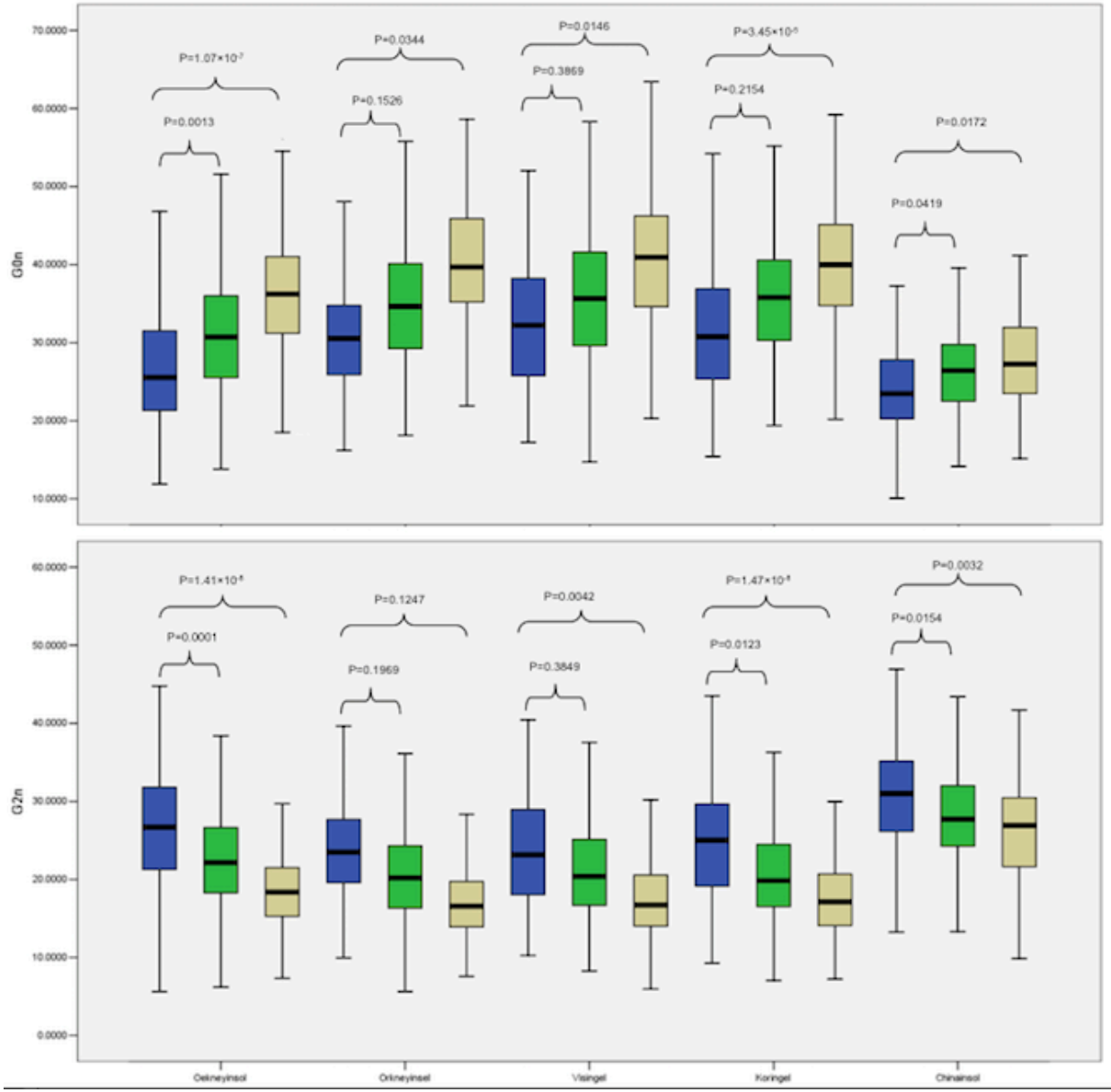
Sialylation, galactosylation, and bisecting GlcNAc on IgG associate with decreased kidney function in general population

Prof. Tim Spector



Barrios et al, JASN, 2015

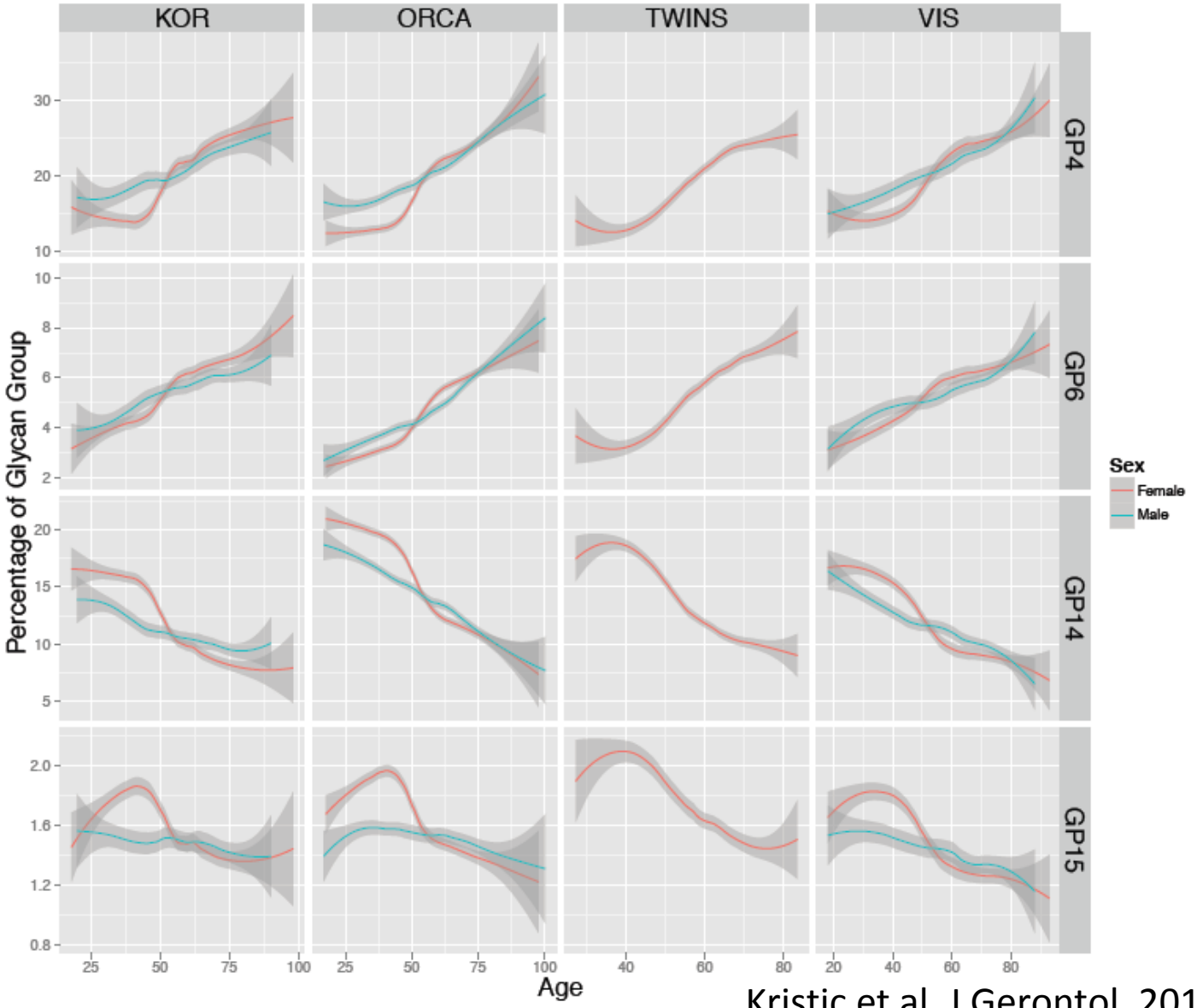
IgG glycome associates with hypertension



Prof. Wei Wang

Yu et al, *Medicine*, 2016

Age is a very strong confounder for IgG glycome



Jasminka Krištić

Toma Keser

Frano Vučković

Kristic et al, J Gerontol, 2014

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

Ivan Gudelj

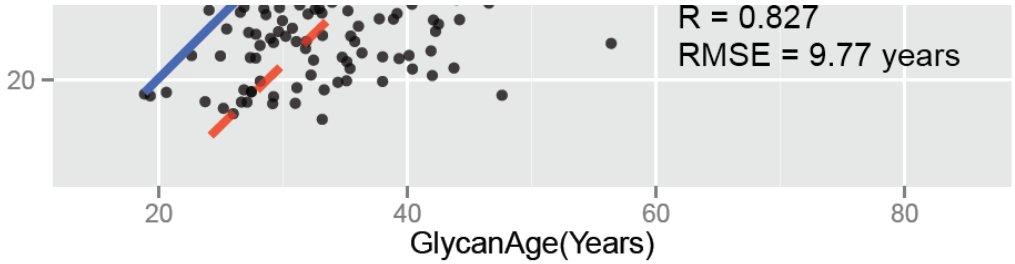
Jasminka

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

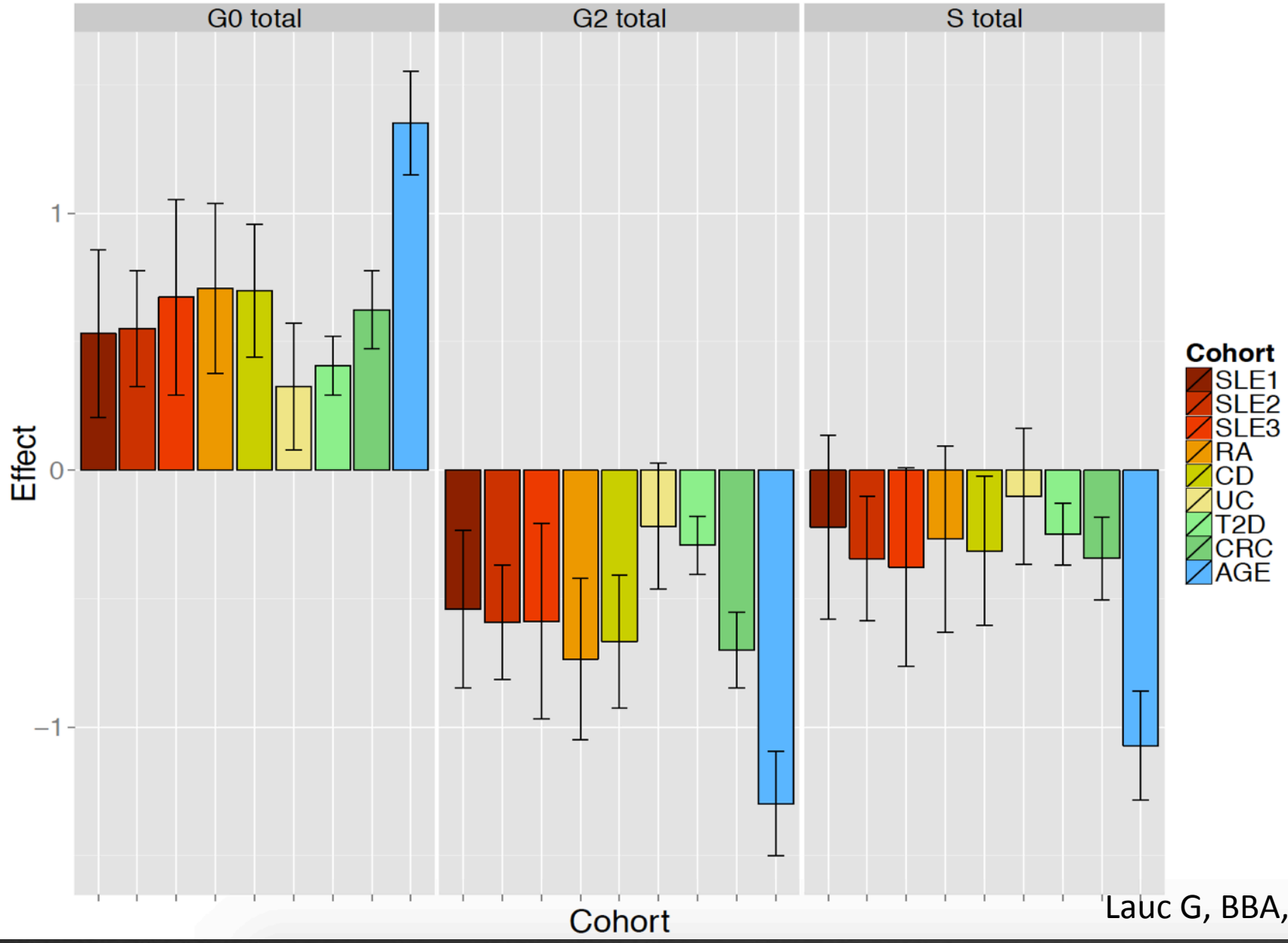
After correcting for chronological age, glycan age index associates with “unhealthy” life

	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.

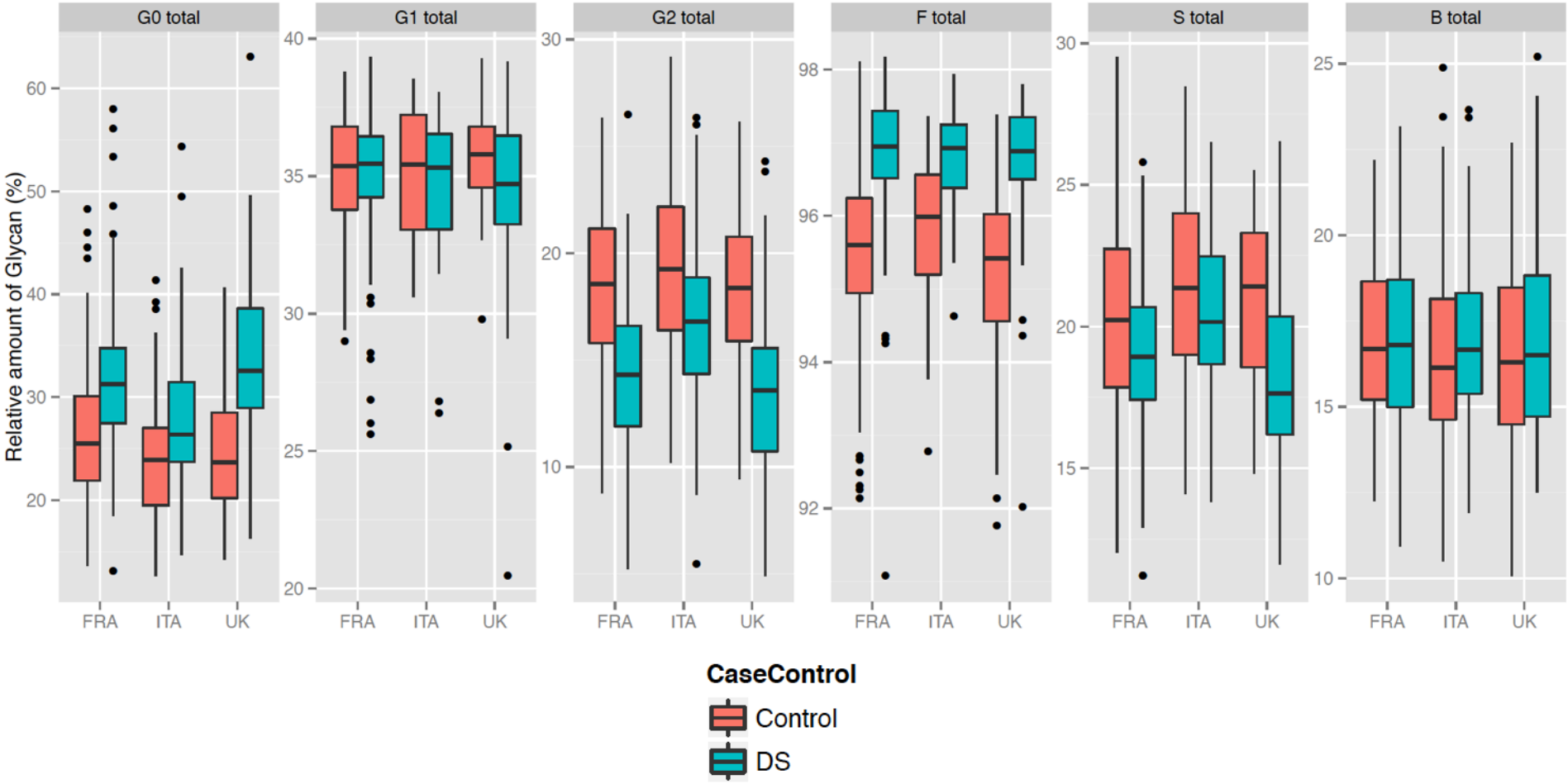
Kristic et al, J Gerontol, 2014

Changes of IgG glycome in many diseases resemble ageing

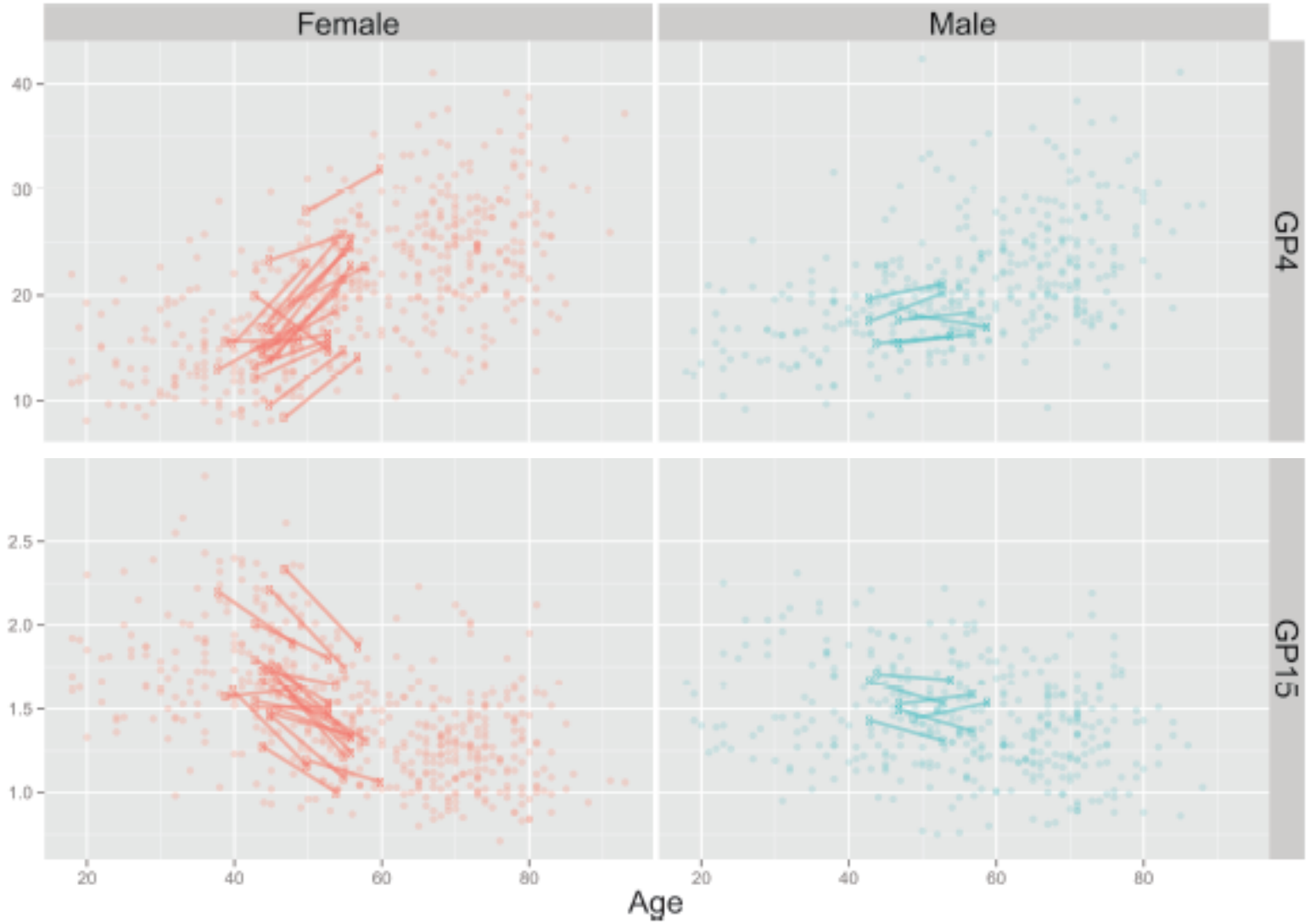


Lauc G, BBA, 2016

IgG glycome in Down syndrome reflects accellerated ageing



Changes within an individual generally follow trends observed in a population

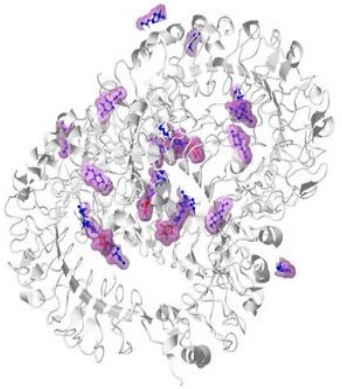


Cohort	Plasma glycome	IgG Glycome
10001 Dalmatian	2,000	4,000
Orcades	2,000*	2,000
TwinsUK	4,000	4,500
KORA	–	2,000
SABRE	2,000	–
Global population study	–	2,700
FINNRISK	–	1,200
Estonian biobank	–	1,300
China	1,000	1,000
CRC	2,000*	2,000
IBD	3,000	5,700
SLE	–	1,200
Type 1 Diabetes	1,000	1,000
Type 2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

* Analysed in NIBRT

Mining the gold from big glycomics datasets

Take-home message



1. **The majority of proteins are glycoproteins**
   - Nearly all secreted and membrane proteins
2. **Glycans are integral part of protein structure**
   - Glycans affect both structure and function of proteins
3. **Inter-individual variation in glycosylation is large**
   - Alterantive glycosylation can have same functional consequences as coding mutations
4. **Glycomic data should be combined with other omics data**
   - We need methods for multi-omic data analysis

2nd GlycoCom and 1st Human Glycome Project Meeting

October 3-6, 2018 Dubrovnik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University of


Kiyoko F. Aoki-Kinoshita


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Abstract deadline for oral presentations: April 15th