Novel Findings in Genomics and Metabolomics in the ARIC study

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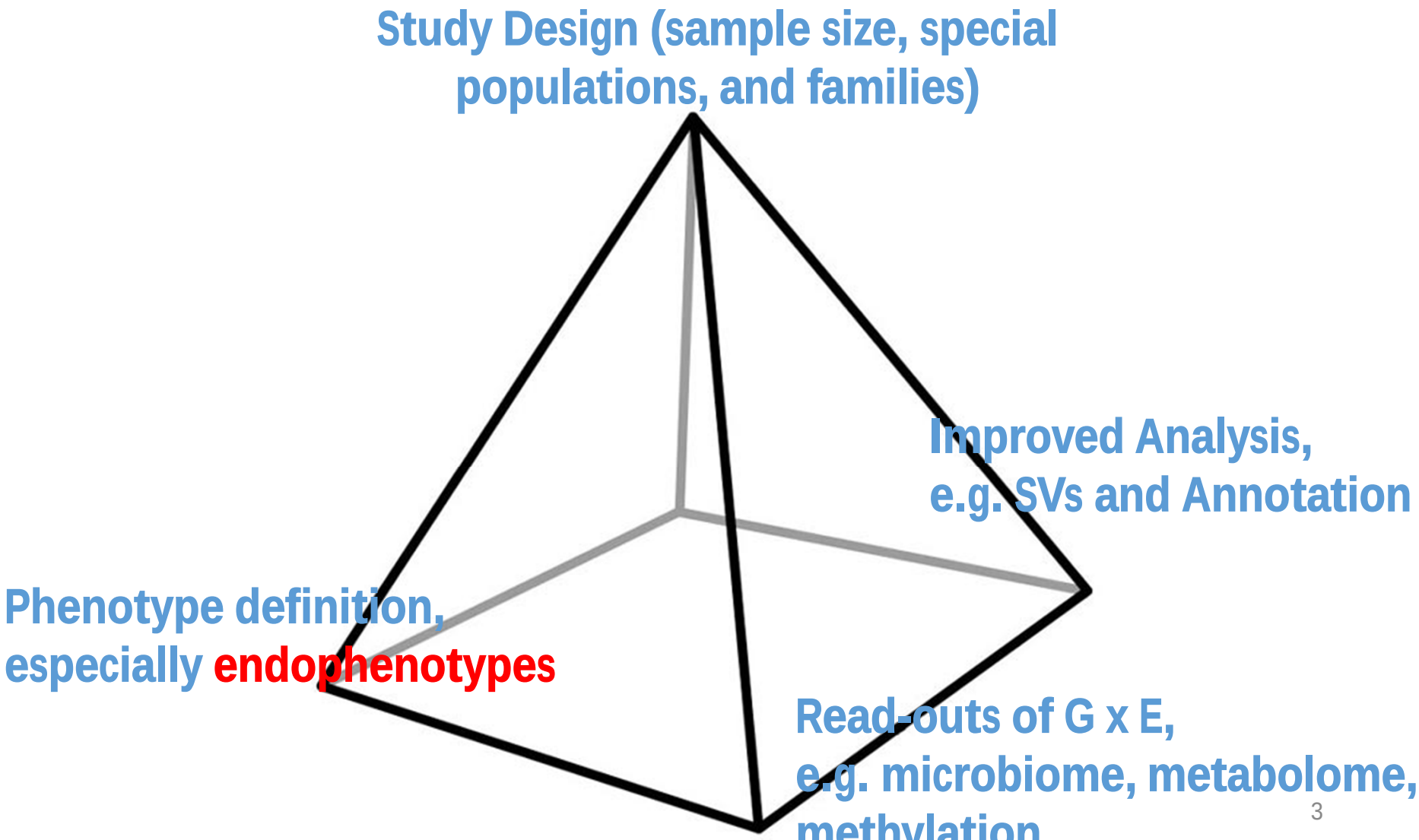
HGSC
HUMAN GENOME SEQUENCING CENTER

Goals of Genetic Studies
(of the Metabolome)

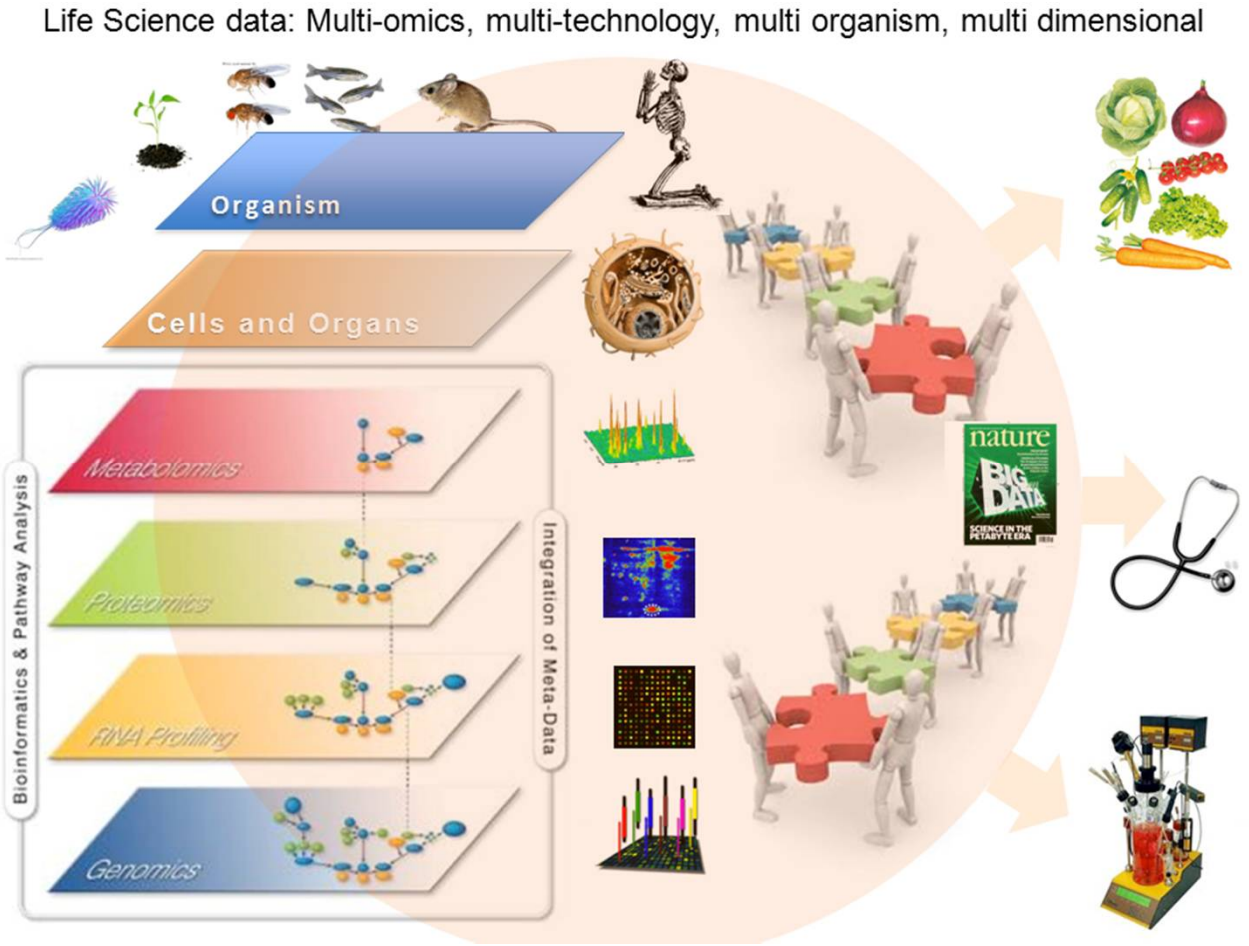
- Genes being novel predictors of disease
- Predictors vs Biomarkers and the principal of Mendelian Randomization
- Biology of the human metabolome
- Drug Target Discovery
- Gene x Environment Interaction

Maximizing Opportunity for Discovery

↑ Power, while controlling costs



Multi-Omics Integration

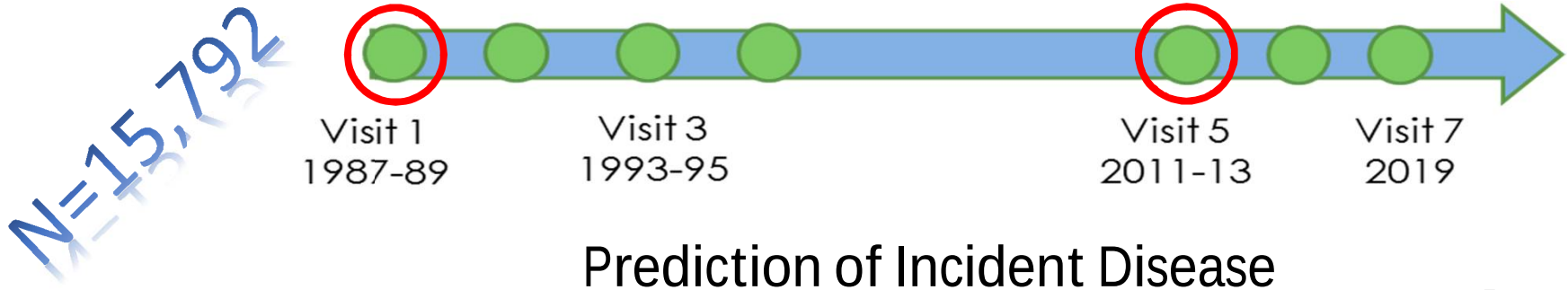


Achieving this vision, requires delivering large amounts of high quality data to the community in a timely manner.

The Atherosclerosis Risk in Communities (ARIC) Study

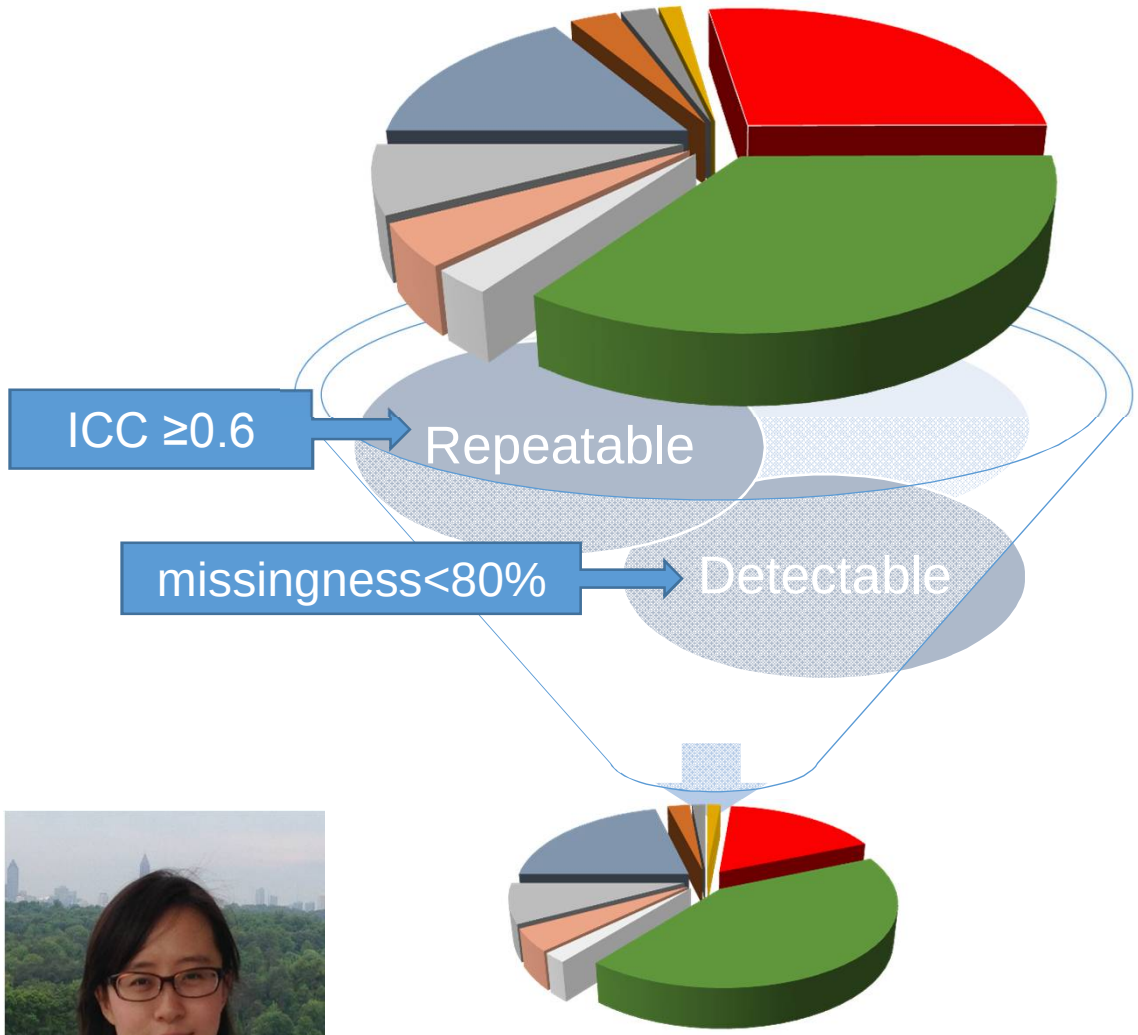
- 1,679 African-Americans (AAs) among the ARIC study
- 1,458 ARIC European Americans (EAs)

Having metabolomics data



Prediction of Incident Disease

Metabolomics in the ARIC study



METABOLON
SOLUTIONS BEYOND THE DATA...™

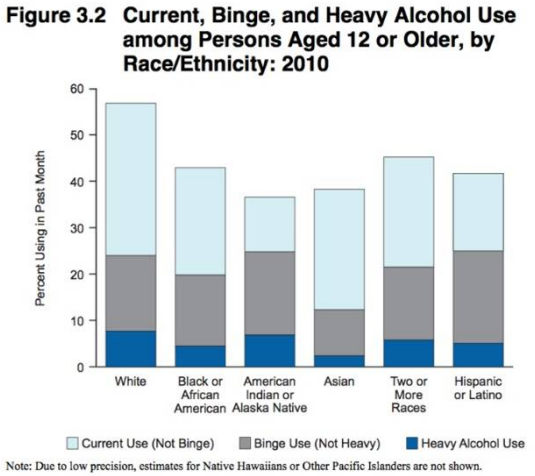
COMPOUND TYPE	COUNT
Named Metabolites	361
Unnamed Metabolites	241
Total Number of Measured Metabolites	**602**

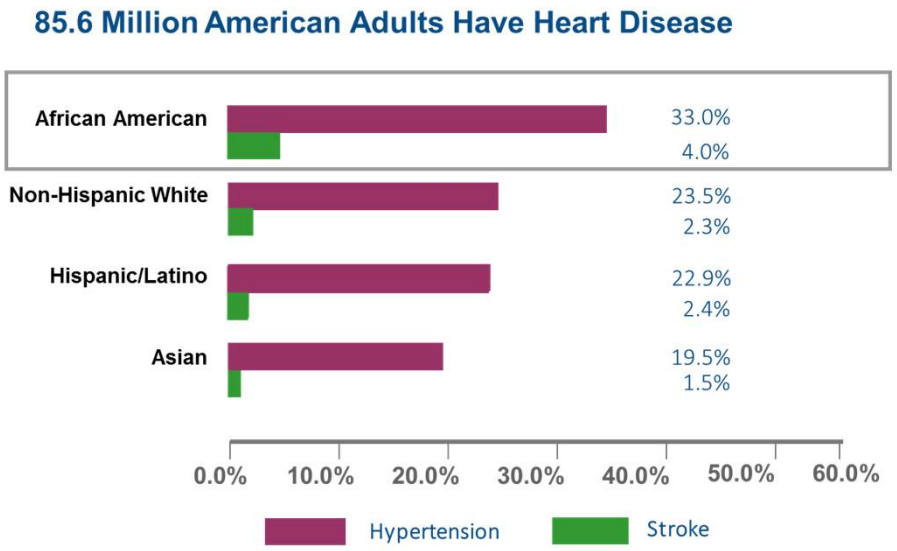
- Amino acid
- Carbohydrate
- Cofactors and vitamins
- Energy
- Lipid
- No Super Pathway
- Nucleotide
- Peptide
- Xenobiotics

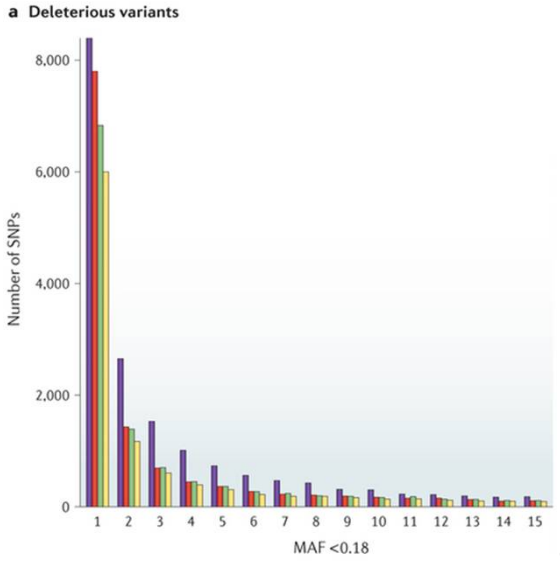
COMPOUND TYPE	COUNT
Named Metabolites	118
Unnamed Metabolites	86
Total Number	**204**

Why Multi-Ethnic Studies?

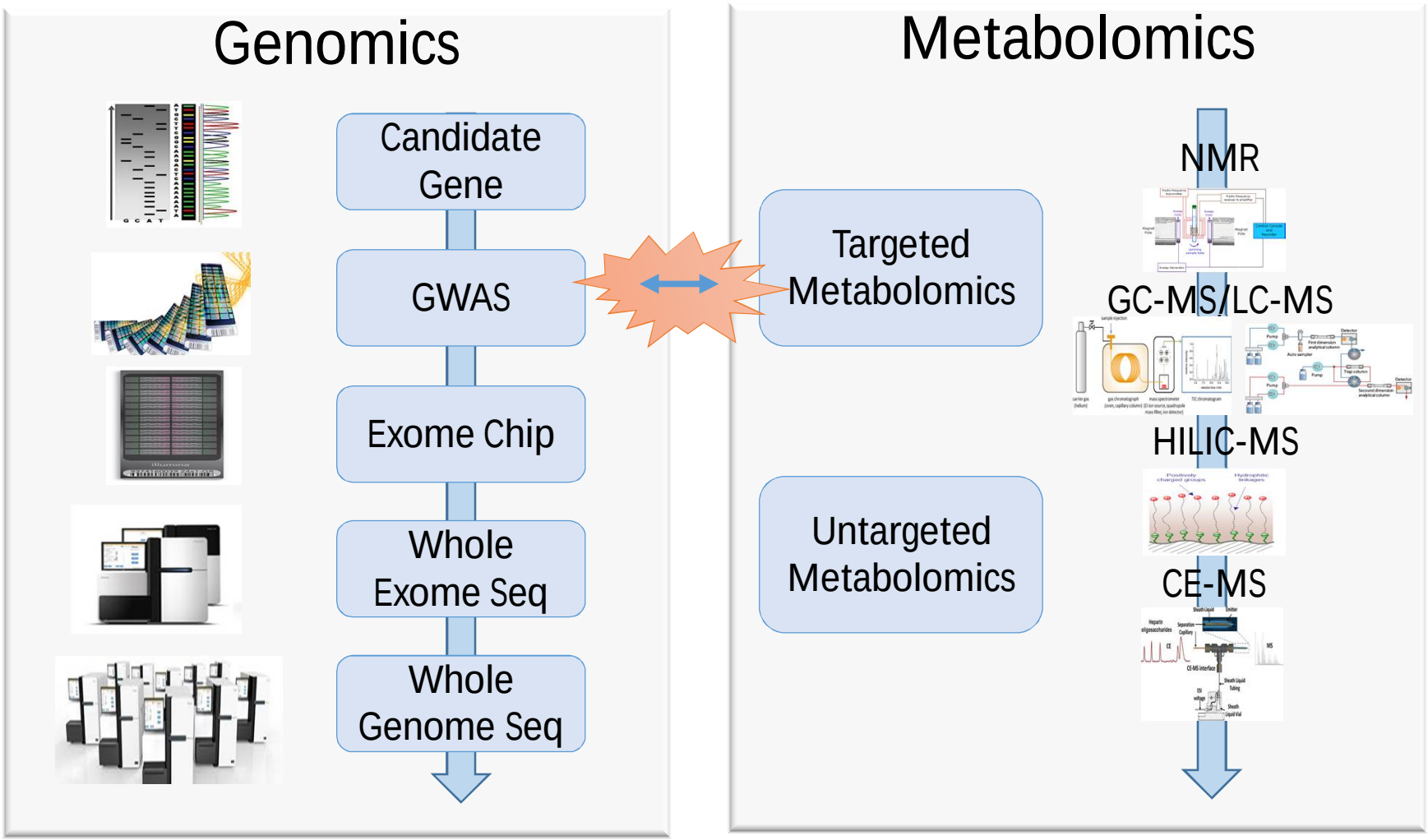
- Differences in Environment
- Differences in site frequency spectrum
- G x E
- Epidemiology of Disease





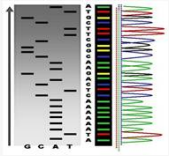


Advances in Genomics & Metabolome



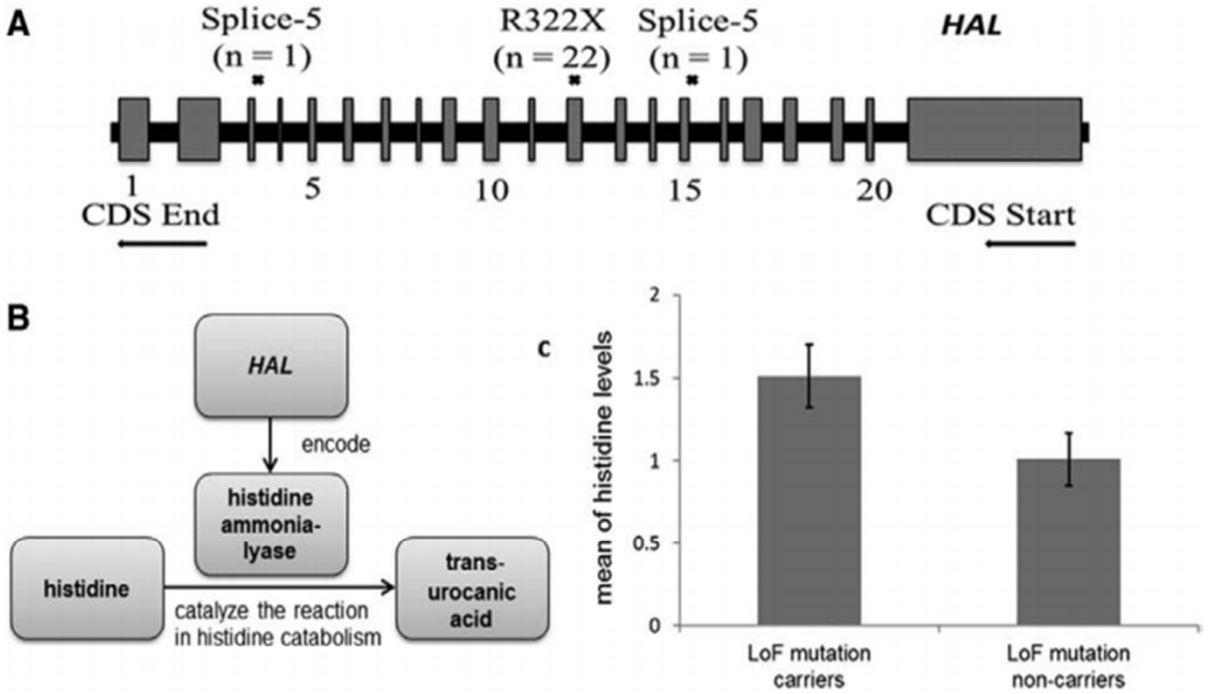
Advances in Genomics & Metabolome

Genomics



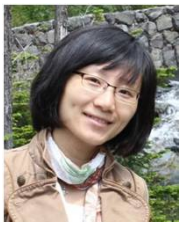
Candidate Gene

HAL, Histidine and Coronary Heart Disease



African Americans in ARIC

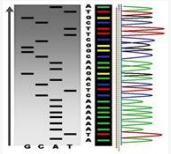
European Americans in FHS

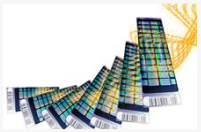


Yu, *Circ Cardiovasc Genet*, 2015

Advances in Genomics & Metabolome

Genomics





Candidate Gene

GWAS

GWAS on Metabolomics

A Genome-wide Association Study of the Human Metabolome in a Community-Based Cohort

Eugene P. Rhee,[1,6,18] Jennifer E. Ho,[8,11,18] Ming-Huei Chen,[9,1]
Martin G. Larson,[11,14] Anahita Ghorbani,[3] Xu Shi,[2] Iiro T. Helen
Amy Deik,[6] Kerry A. Pierce,[6] Kevin Bullock,[6] Geoffrey A. Walfo
Clary Clish,[6] J.-R. Joanna Yeh,[2] Thomas J. Wang,[16,17,19,*] and

ARTICLE

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Genetics Meets Metabolomics: A Genome-Wide Association Study of Metabolite Profiles in Human Serum

Christian Gieger[1,2], Ludwig Geistlinger[1], Elisabeth Altmaier[3,4], Martin Hrabé de Angelis[5,6], Florian Kronenberg[7], Thomas Meitinger[8,9], Hans-Werner Mewes[3,10], H.-Erich Wichmann[1,2], Klaus M. Weinberger[11], Jerzy Adamski[5,6], Thomas Illig[1], Karsten Suhre[3,4]*

Human metabolic individuality in biomedical and pharmaceutical re

Karsten Suhre[1,2,3], So Youn Shin[4,*], Ann Kristin Petersen[5,*], Robert P. Mohney[6], David Meredith[7], Brigitu

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Genetic Determinants Influencing Human Serum Metabolome among African Americans

Bing Yu[1], Yan Zheng[1], Danny Alexander[2], Alanna C. Morrison[1], Josef Coresh[3], Eric Boerwinkle[1,4]*

1 Human Genetics Center, University of Texas Health Science Center at Houston, Houston, Texas, United States of America, 2 Metabolon, Inc., Durham, North Carolina, United States of America, 3 Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland, United States of America, 4 Human Genome Sequencing Center, Baylor College of Medicine, Houston, Texas, United States of America

A genome-wide association study in human urine

Karsten Suhre[1,2,18], Henri Wallaschofski[3], Johannes Raffler[1,2], Nele

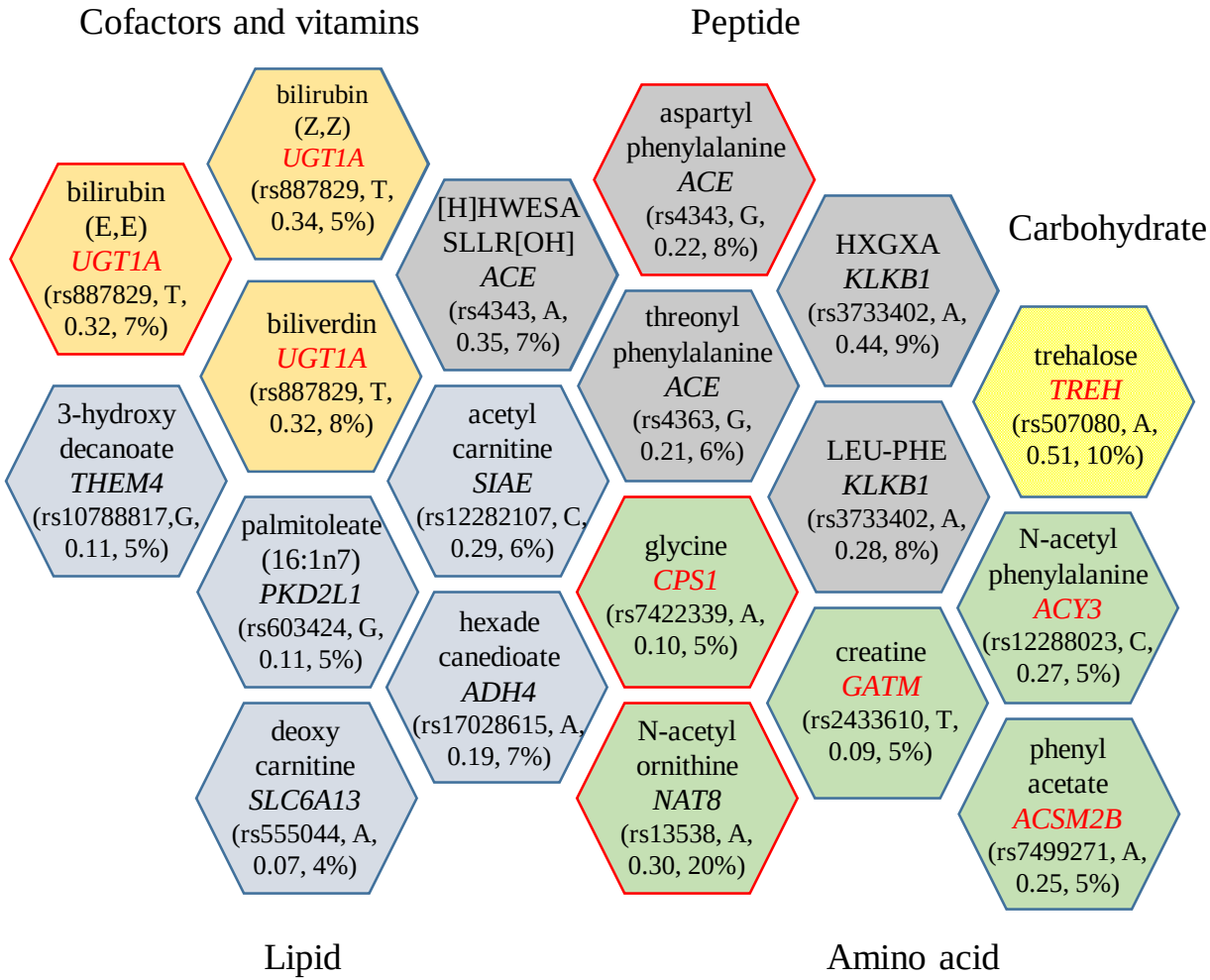
Genome-wide association study identifies multiple loci influencing human serum metabolite levels

Taru Tukiainen[1,3–5,37], Antti-Pekka Sarin[1,2], Alfredo Ortega-Alonso[1,6], Emmi Tikkanen[1,2], Antti J Kangas[5], Pasi Soininen[5,6], Peter Würtz[1,3,5], Kaisa Silander[1,2], Danielle M Dick[9], u J Savolainen[11,12], Jorma Viikari[13], Mika Kähönen[14], Terho Lehtimäki[7], Michael Inouye[17,18], Mark I McCarthy[19,20], Antti Jula[2], Johan Eriksson[21–24], ko Salomaa[2], Jaakko Kaprio[1,6,27], Marjo-Riitta Järvelin[3,12,28–30], Leena Peltonen[36], n B Freimer[32], Mika Ala-Korpela[5,6,11,12], Aarno Palotie[1,33–35] & Samuli Ripatti[1,2,33]

An atlas of genetic influences on human blood metabolites

So-Youn Shin[1,21,23], Eric B Fauman[2,23], Ann-Kristin Petersen[3,23], Jan Krumsiek[4,23], Rita Santos[5], Jie Huang[1], Matthias Arnold[6], Idil Erte[7], Vincenzo Forgetta[8], Tsun-Po Yang[1], Klaudia Walter[1], Cristina Menni[7], Lu Chen[1,9], Louella Vasquez[1], Ana M Valdes[7,10], Craig L Hyde[11], Vicky Wang[2], Daniel Ziemek[2], Phoebe Roberts[2,22], Li Xi[2], Elin Grundberg[6,12], The Multiple Tissue Human Expression Resource (MuTHER) Consortium[13], Melanie Waldenberger[14], J Brent Richards[7,8,15], Robert P Mohney[16], Michael V Milburn[16], Sally L John[17], Jeff Trimmer[18,21], Fabian J Theis[4,19], John P Overington[5], Karsten Suhre[6,20,24], M Julia Brosnan[11,24], Christian Gieger[3,24], Gabi Kastenmüller[6,24], Tim D Spector[7,24] & Nicole Soranzo[1,9,24]

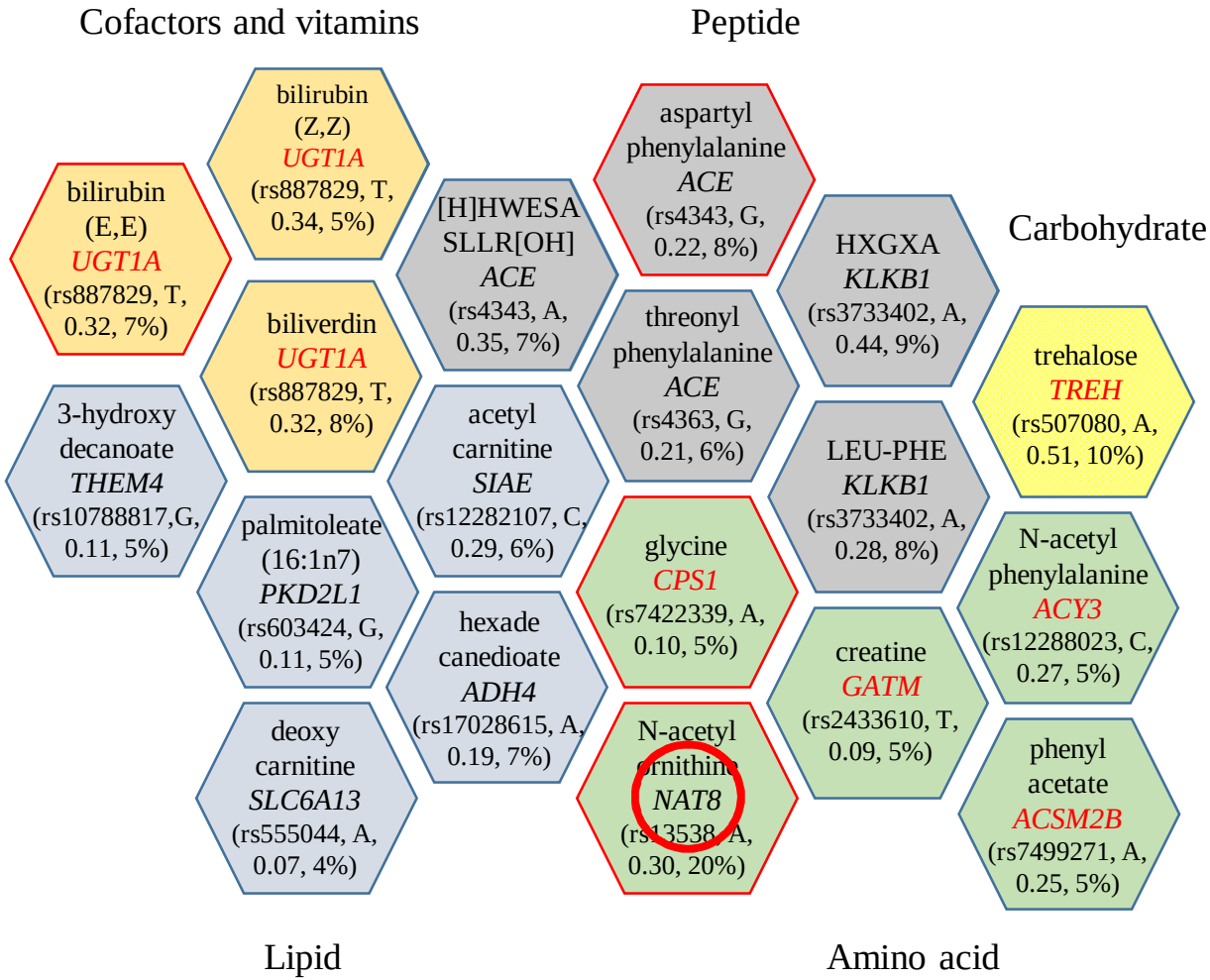
Genome-wide Significant Gene-Metabolite Pairs in 1,679 ARIC African Americans



Common variants with p-value < 1.6×10^{-10}

Yu, *PLoS Genet*, 2014

Genome-wide Significant Gene-Metabolite Pairs in 1,679 ARIC African Americans

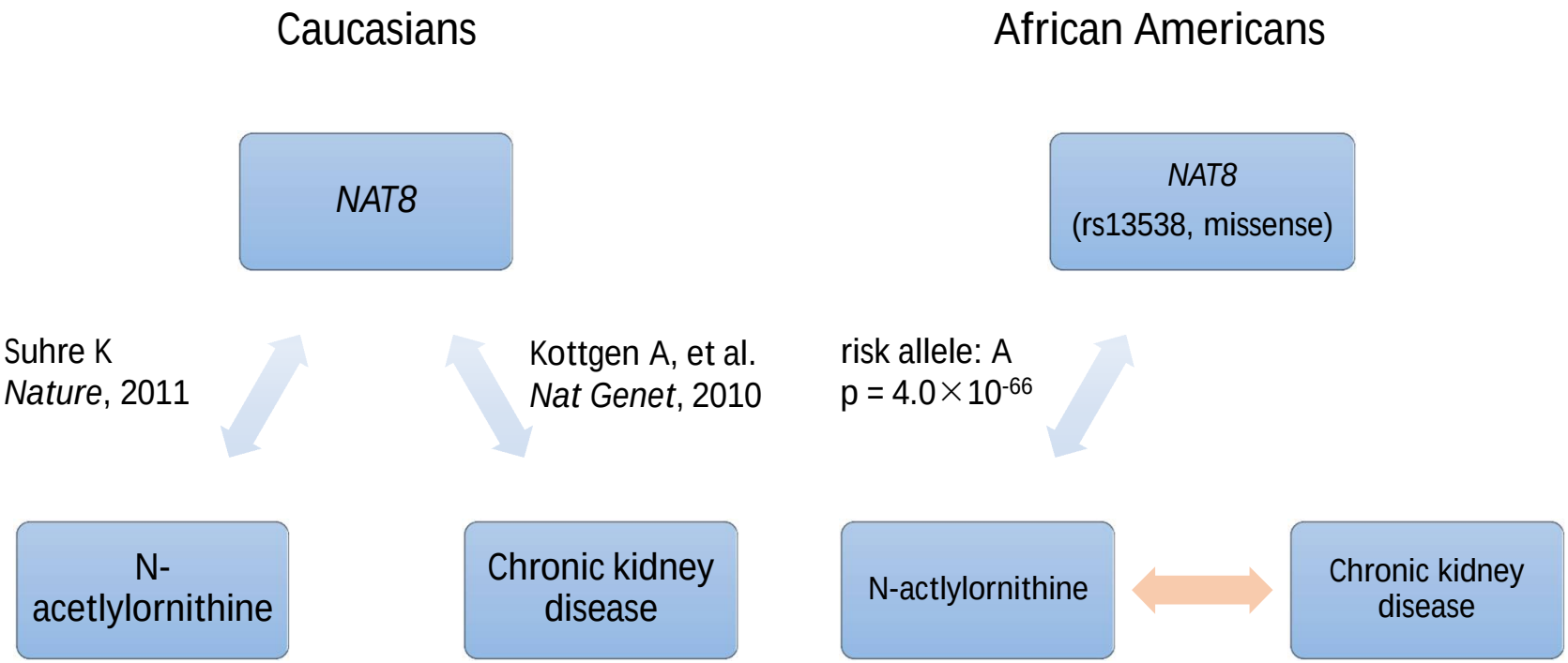


Common variants with p-value < 1.6×10^{-10}

Yu, *PLoS Genet*, 2014

NAT8 and Chronic Kidney Disease

Hypothesis 1: *NAT8* – N-acetlyornithine – chronic kidney disease?



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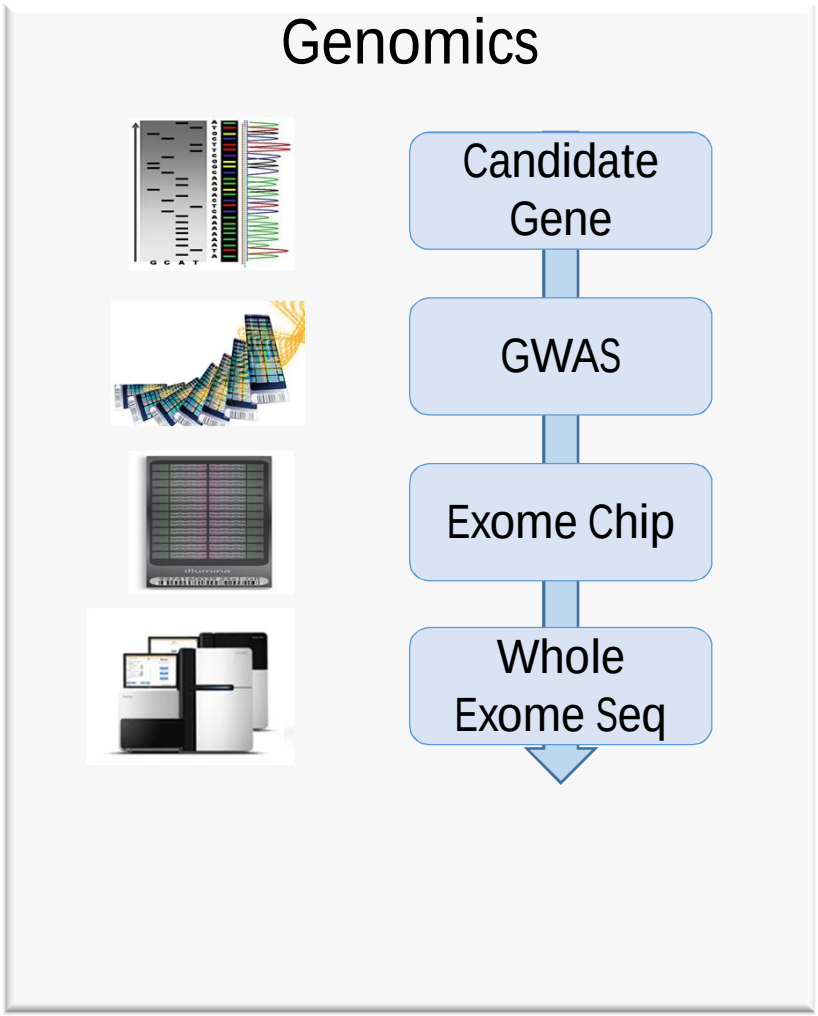
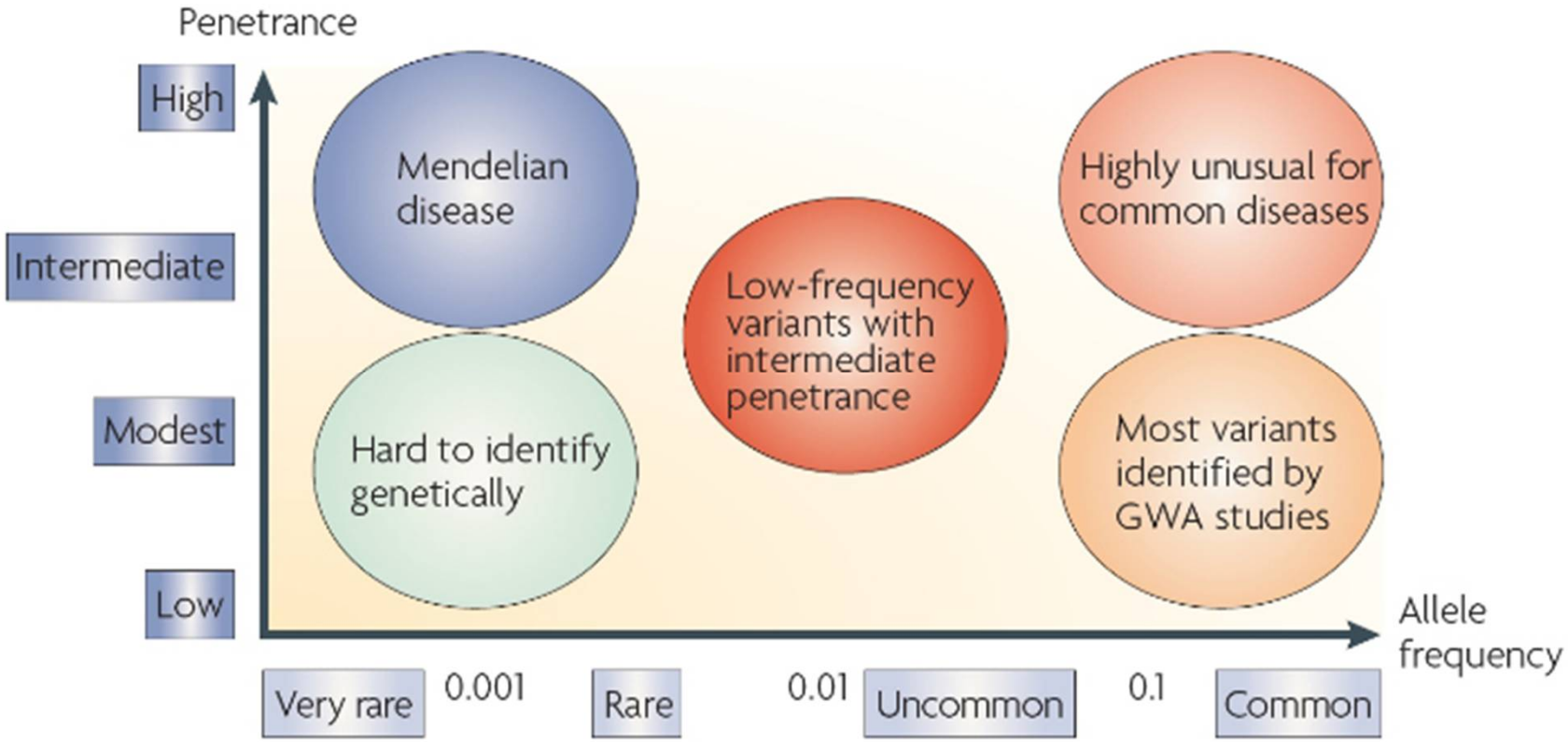


Why Sequencing?



McCarthy, *Nat Reviews Genet*, 2009

Defining LOF

- Variants predicted to trigger nonsense-mediated decay (NMD)

- Categories:
  1) Premature stop codon-introducing
  2) Disrupt essential splice site
  3) Insertion/deletion frameshifts (indel)

- Additional Subdivision:
  - Full: all known protein coding transcripts
  - Partial: affecting only a fraction of known coding transcripts

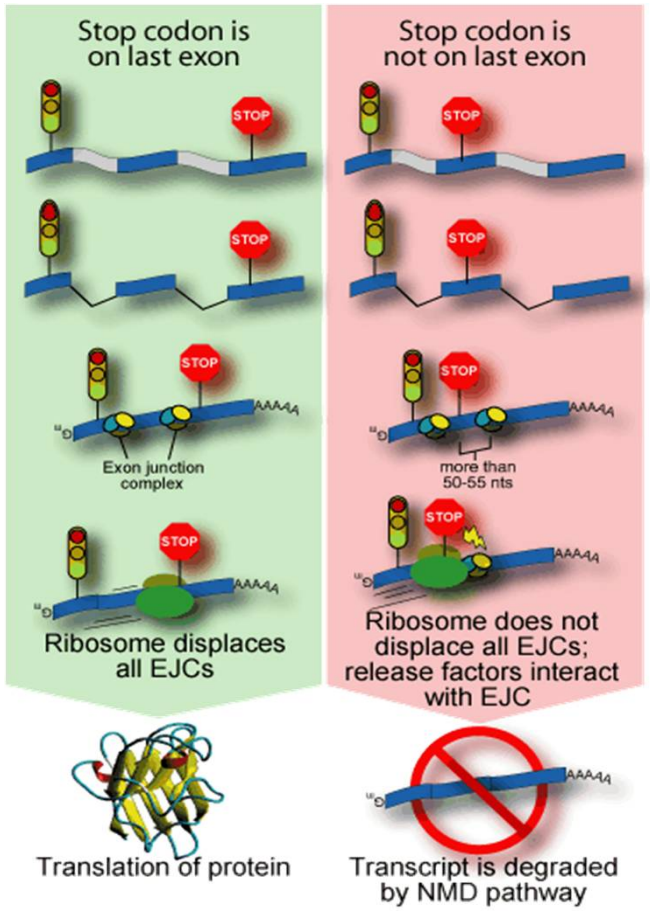


Image via: http://compbio.berkeley.edu/people/ed/rust/

Annotating LOF

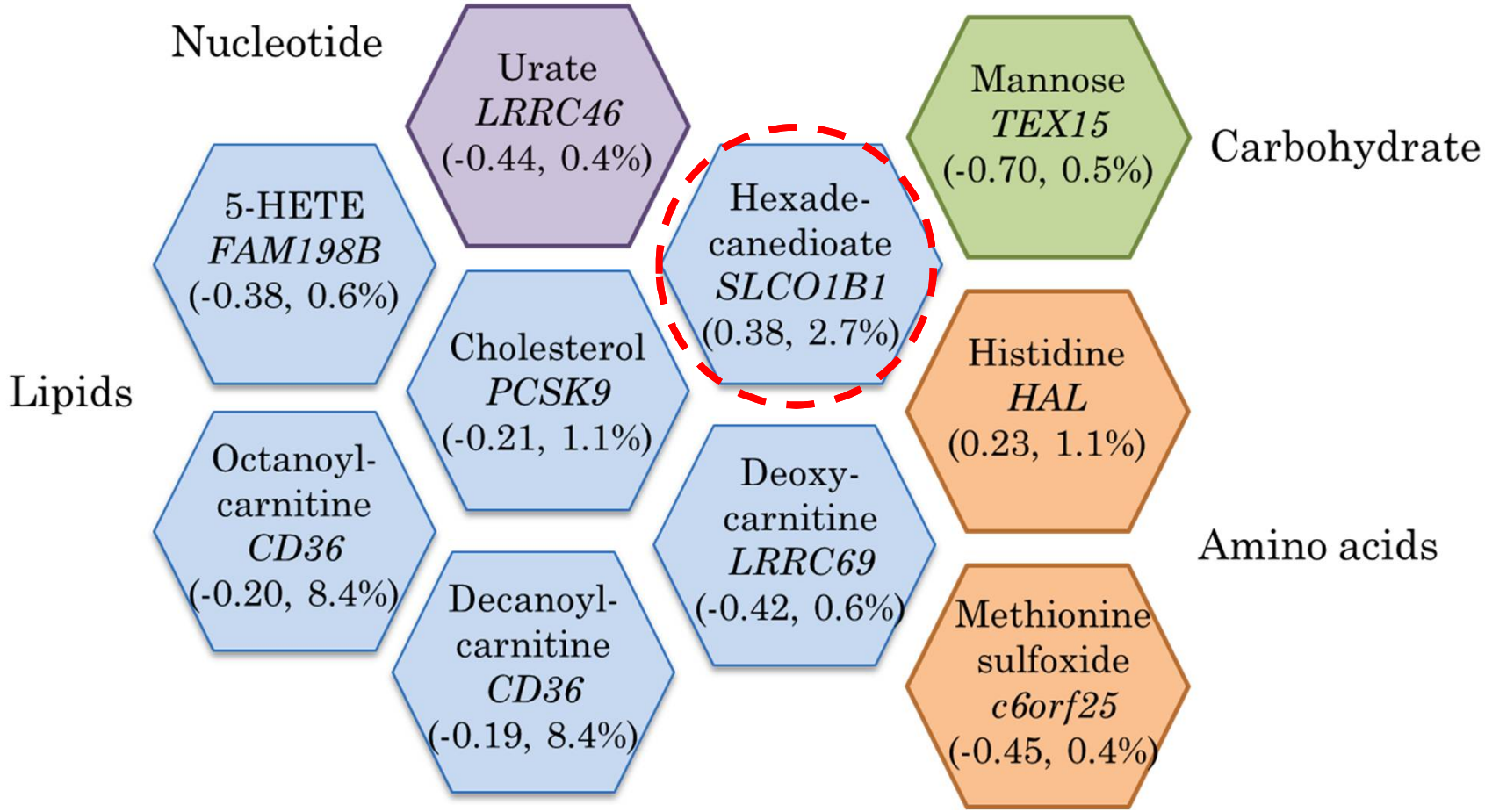
- 8,554 ARIC Study participants
  - 5,718 EA and 2,836 AA
  - (4,277 disc and 4,277 repl)
- Variant filtering:
  - Single-exon genes
  - Non protein-coding genes
  - Affect all gene isoforms
  - Terminal gene exon
- 36,787 LOF sites in 11,922 genes
- Average per individual:
  - Heterozygous (homozygous)

LOF type	Initial	After filtering	% Filtered out (Low-Confidence)
Stop gain	19,759	14,076	28.7%
Splice	10,634	8,843	16.8%
Frame Shift	33,703	13,868	58.8%
Total	**64,096**	**36,787**	

LOF type	AA	EA
Stop gain	27.3 (2.1)	21.1 (2.2)
Splice	16.7 (1.9)	9.6 (1.8)
Frame Shift	36.1 (4.4)	22.6 (3.1)
Total	**80.1 (8.4)**	**53.3 (7.1)**

FHS: phs000651.v4.p9; CHS: phs000667.v1.p1; ARIC phs000668.v1.p1

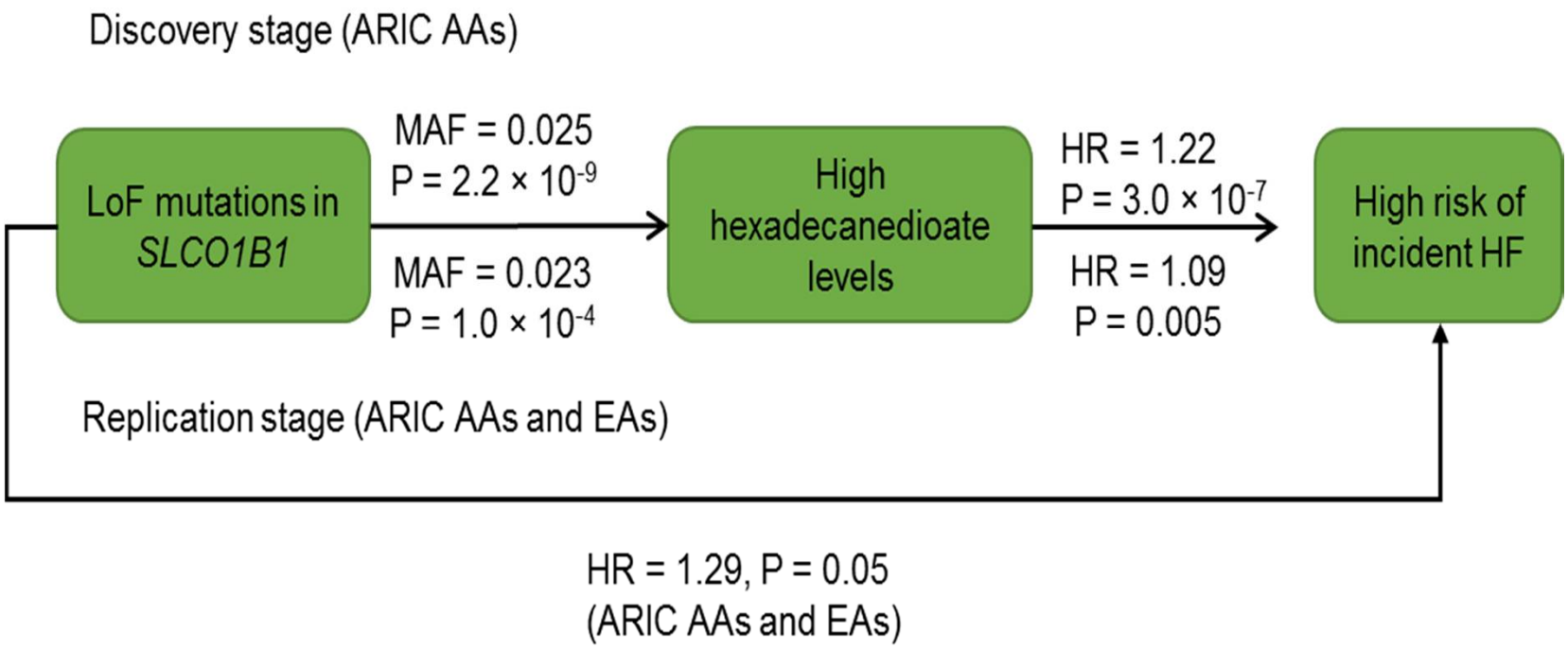
Significant LoF mutation metabolite pairs



324 single LoF varaints (MAF ≥ 5%),
1285 genes with cMAC ≥ 7 included,
p-value < 1.3×10^{-7}

Yu, *Sci Adv*, 2016

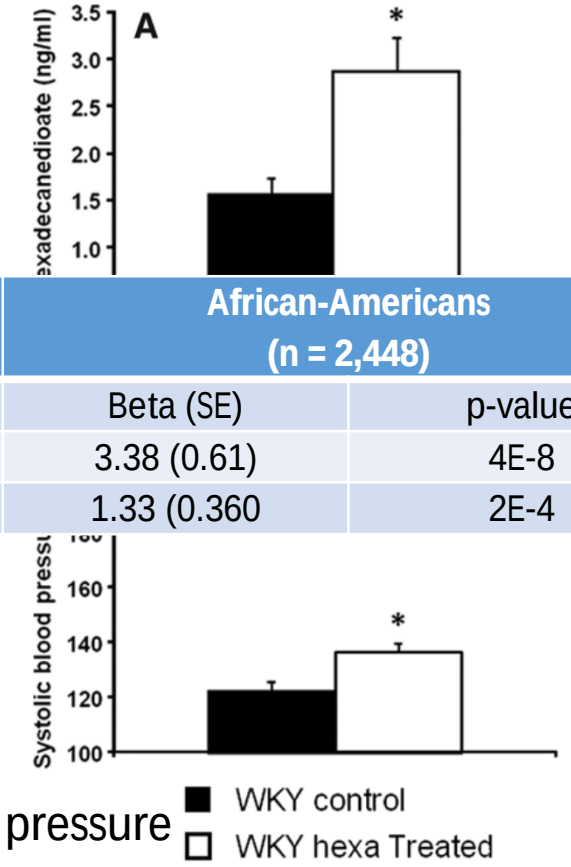
SLCO1B1, Hexadecanedioate & Heart Failure



Yu, *Sci Adv*, 2016

Possible Mechanism of the Association

250 mg/kg/day hexadecanedioate feeding



	European-Americans (n = 1,551)		African-Americans (n = 2,448)	
	Beta (SE)	p-value	Beta (SE)	p-value
Systolic BP	1.30 (0.43)	0.002	3.38 (0.61)	4E-8
Diastolic BP	0.74 (0.26)	0.004	1.33 (0.360	2E-4

C. Menni *et al.*,
Metabolomic identification of a novel pathway of blood pressure regulation involving hexadecanedioate.
Hypertension **66**, 422 (Aug, 2015).

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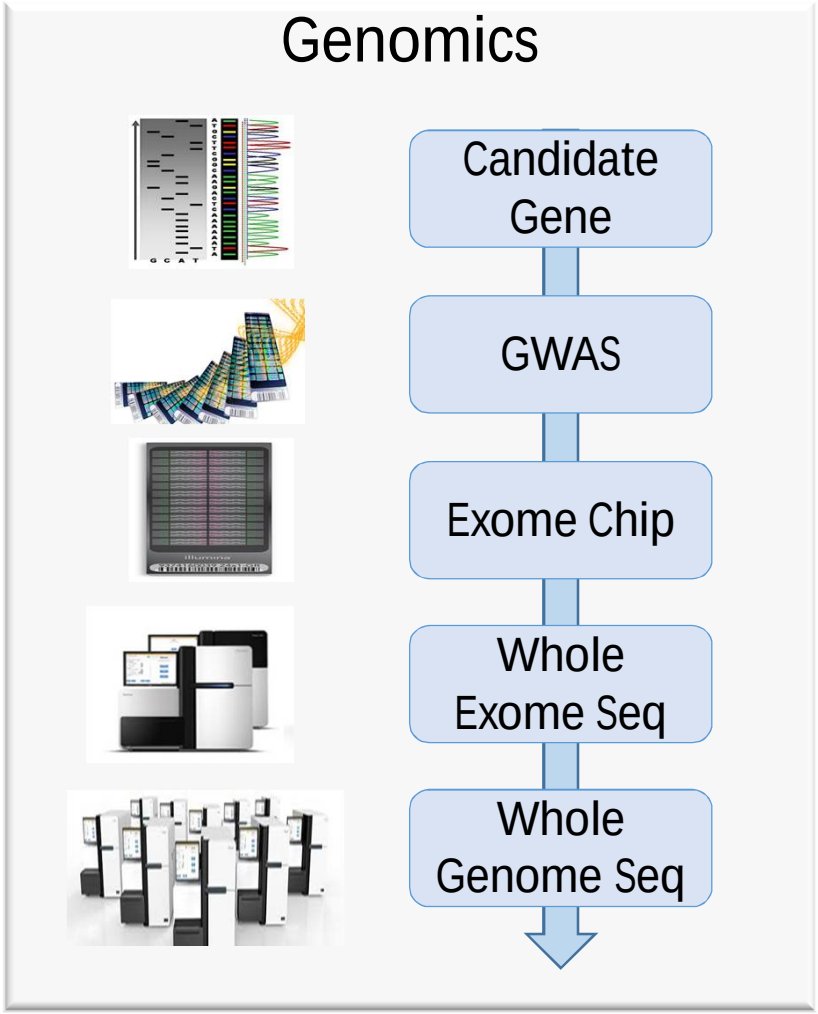
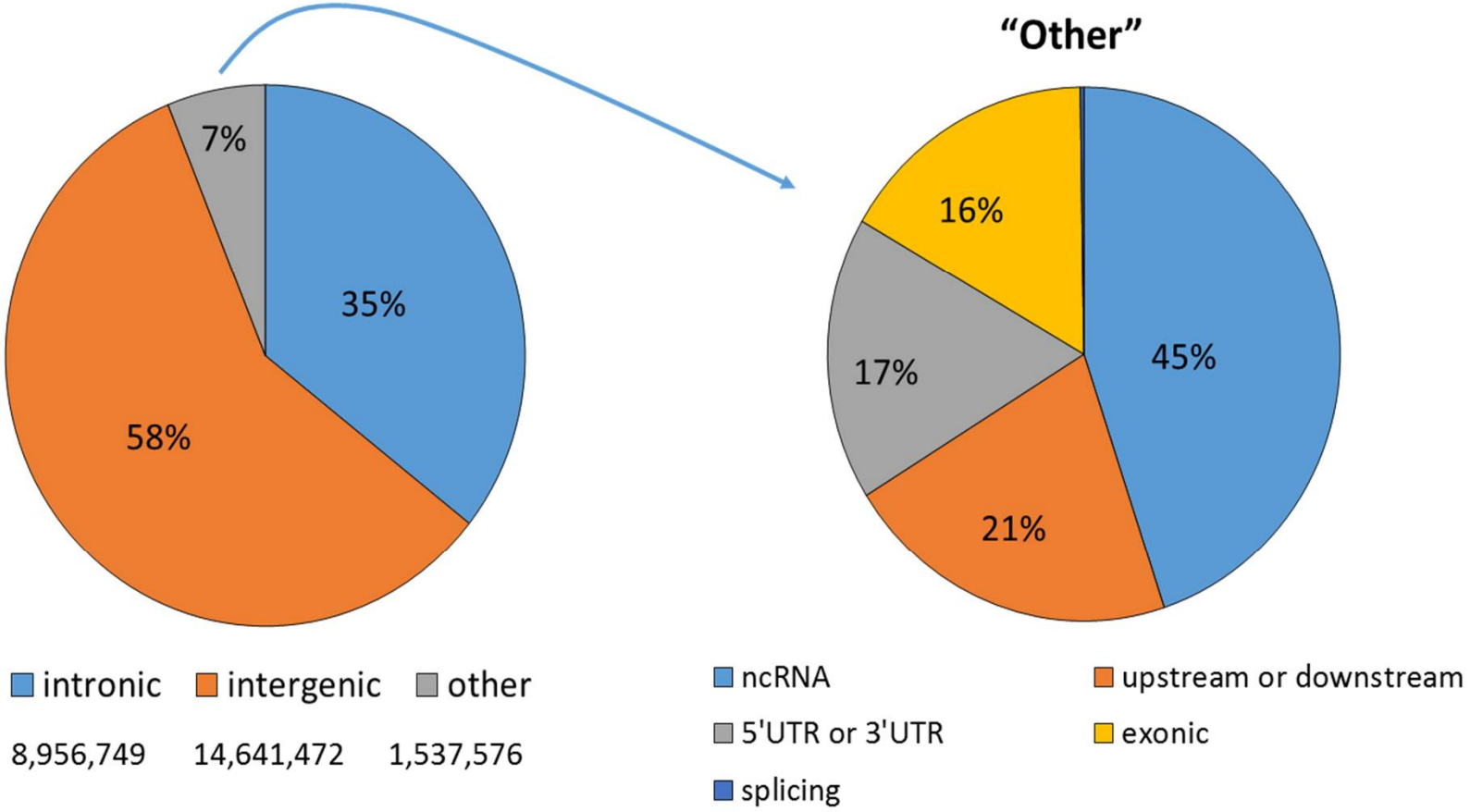


Whole Genome Composition

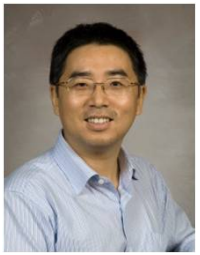
The genomes were annotated by ANNOVAR based on the RefSeq database



2.0×10^{15} sequenced bases

US corn production in 2014: 1.3×10^{15} kernels

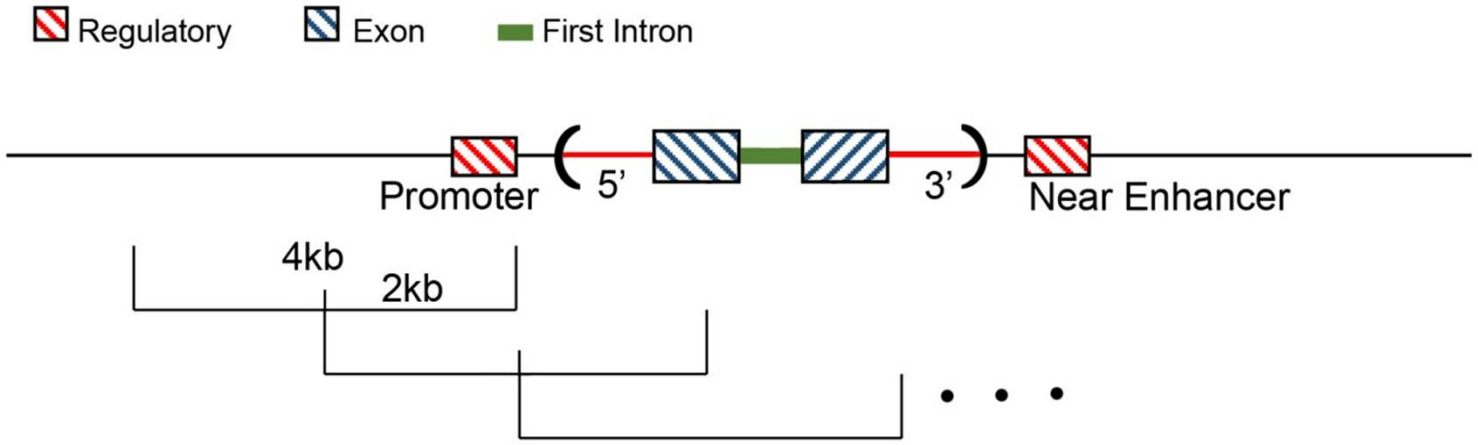
From G. Abecasis



Analytic Approach
WGS Annotation is Key

Aggregate by annotated functional motif for low frequency and rare SNVs (MAF ≤ 5%):

- Sliding window
- Regulatory domain
- First intron



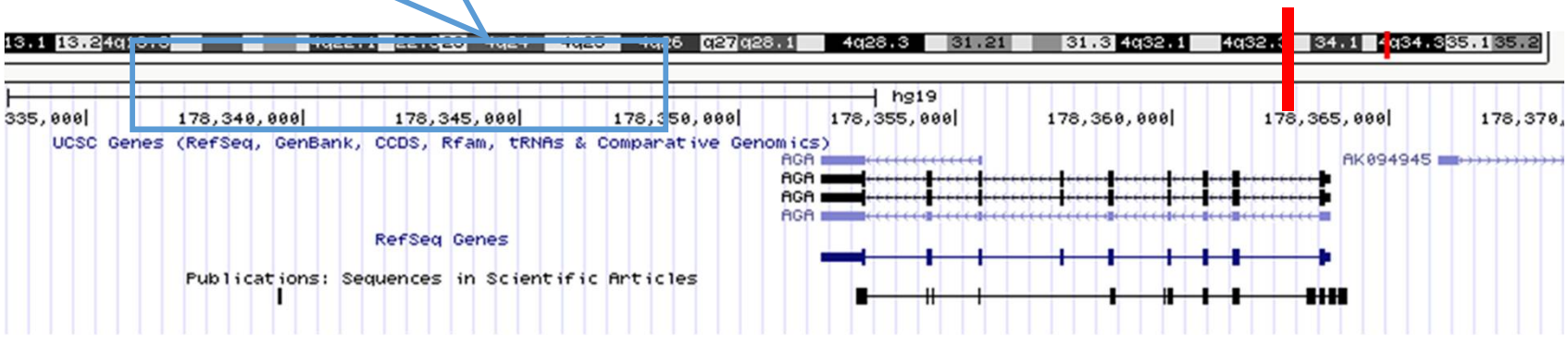
WGS Annotation Tool: WGSA (Liu et al, *J Med Genet*, 2015)

Asparagine:

- o A non-essential amino acid;
- o Biosynthesis/diet intake;
- o Required for development and function of the brain.

2 significant sliding windows (p < 4e-8), 6kb downstream of *AGA*

rs11131799, the most significant common variant



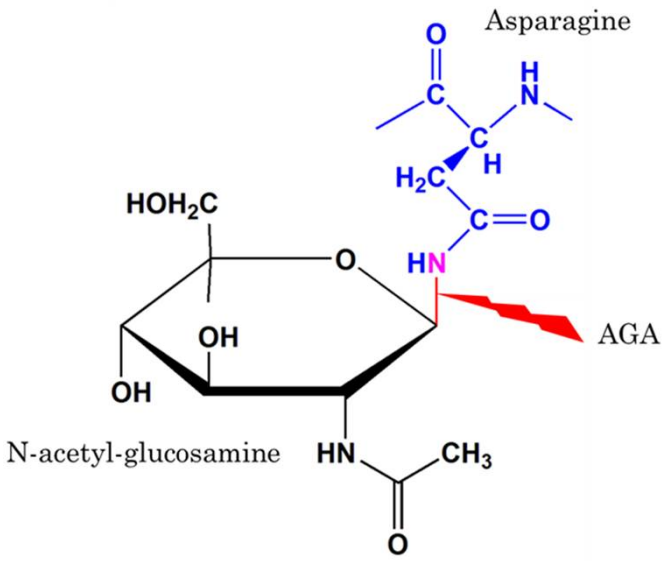
Functional coding variants (MAF < 5%) in *AGA* aggregately affect asparagine levels

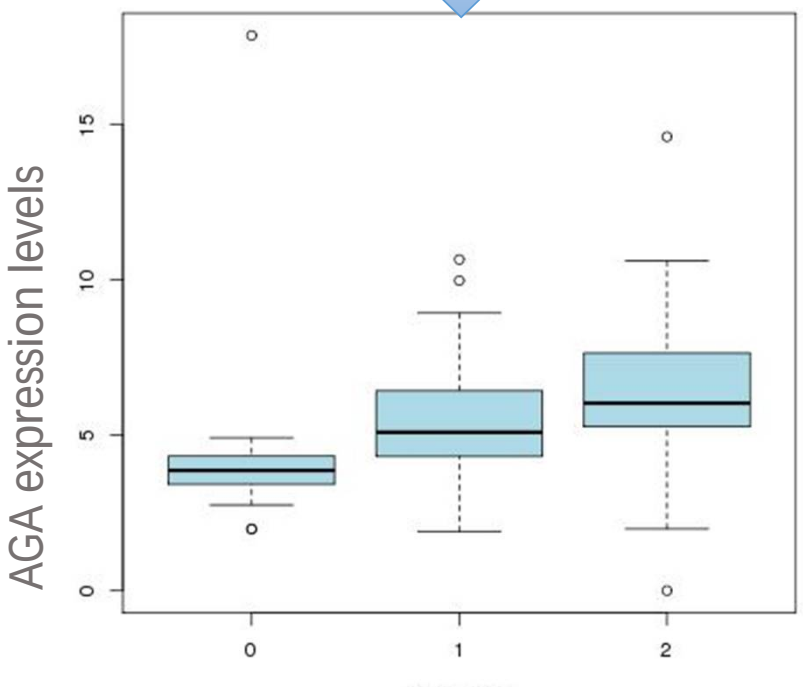
***AGA* gene:**

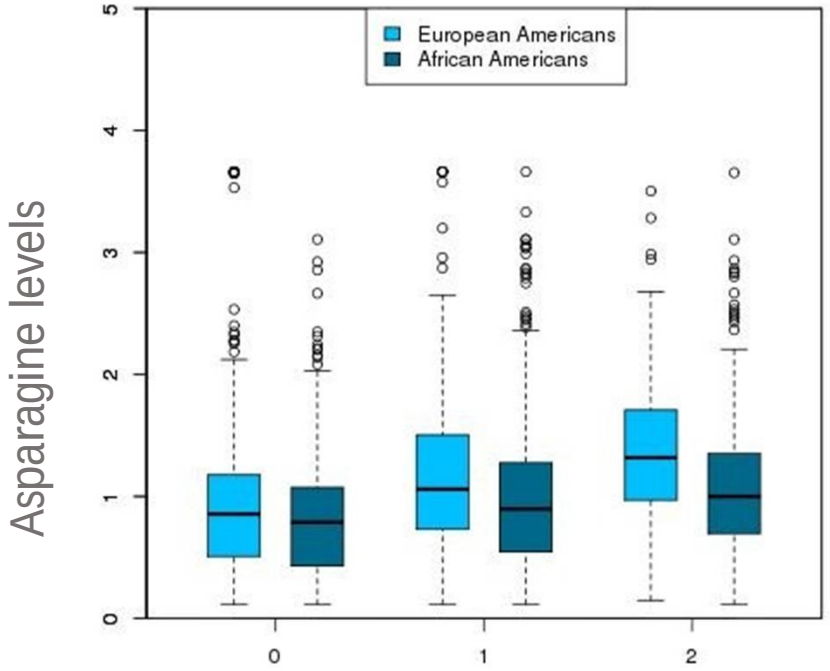
- Aspartylglucosaminidase
- cleaves *asparagine* from N-acetylglucosamine.

rs11131799 (1st intron of *AGA*):

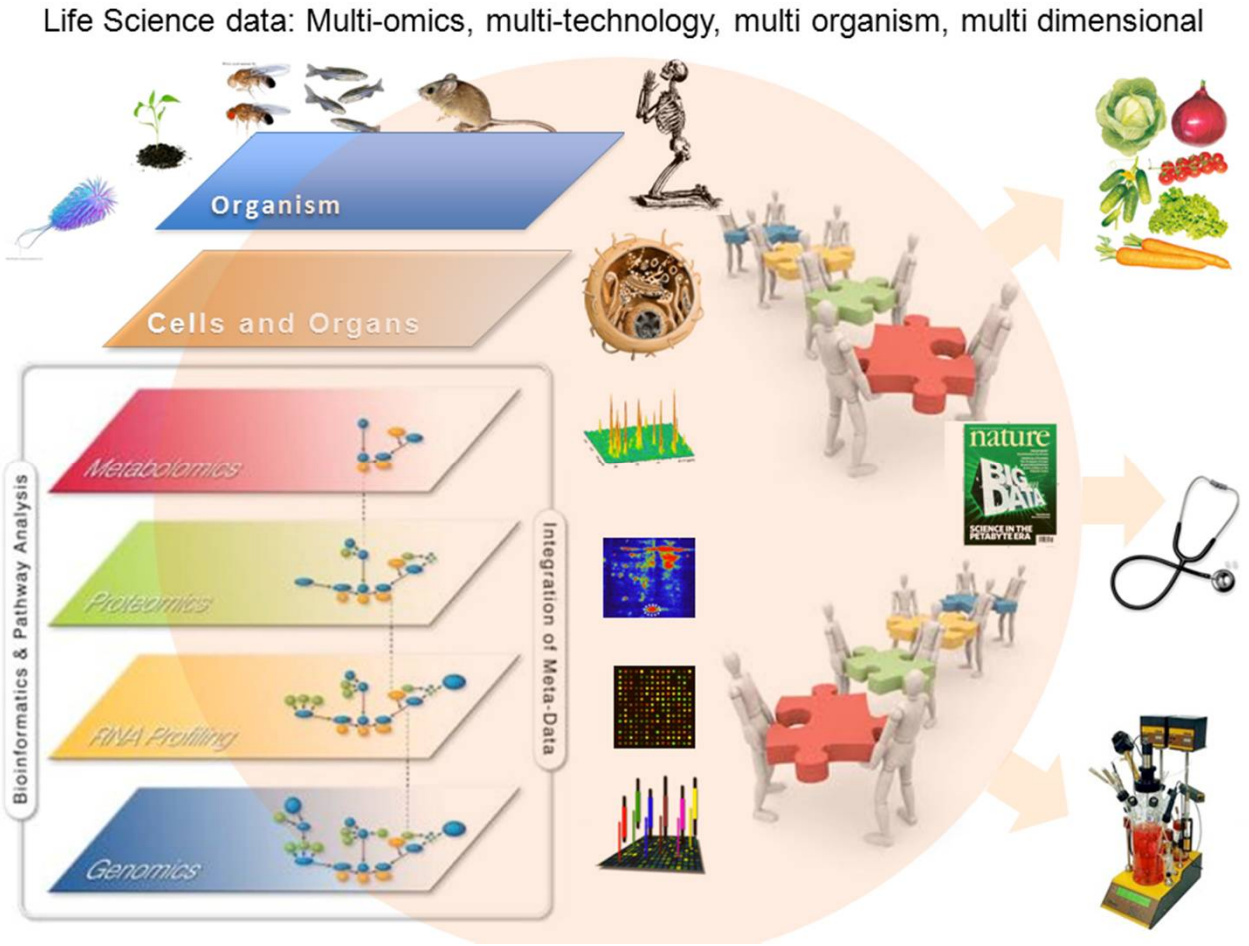
- Predicted promoter;
- Influences the expression levels of *AGA* ($p = 0.01$).







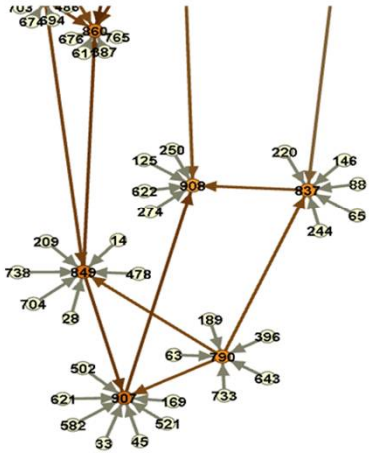
Multi-Omics Integration

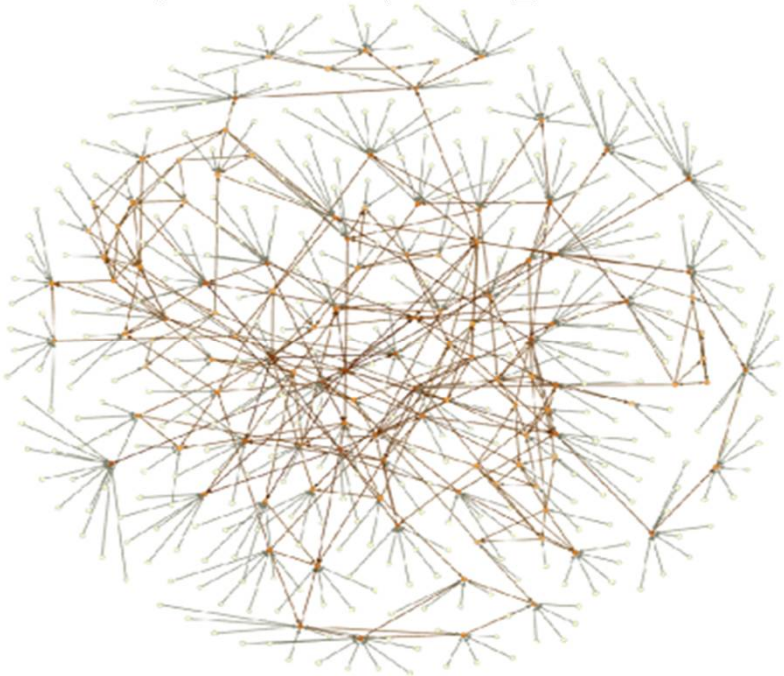


Achieving this vision, requires delivering large amounts of high quality data to the community in a timely manner.

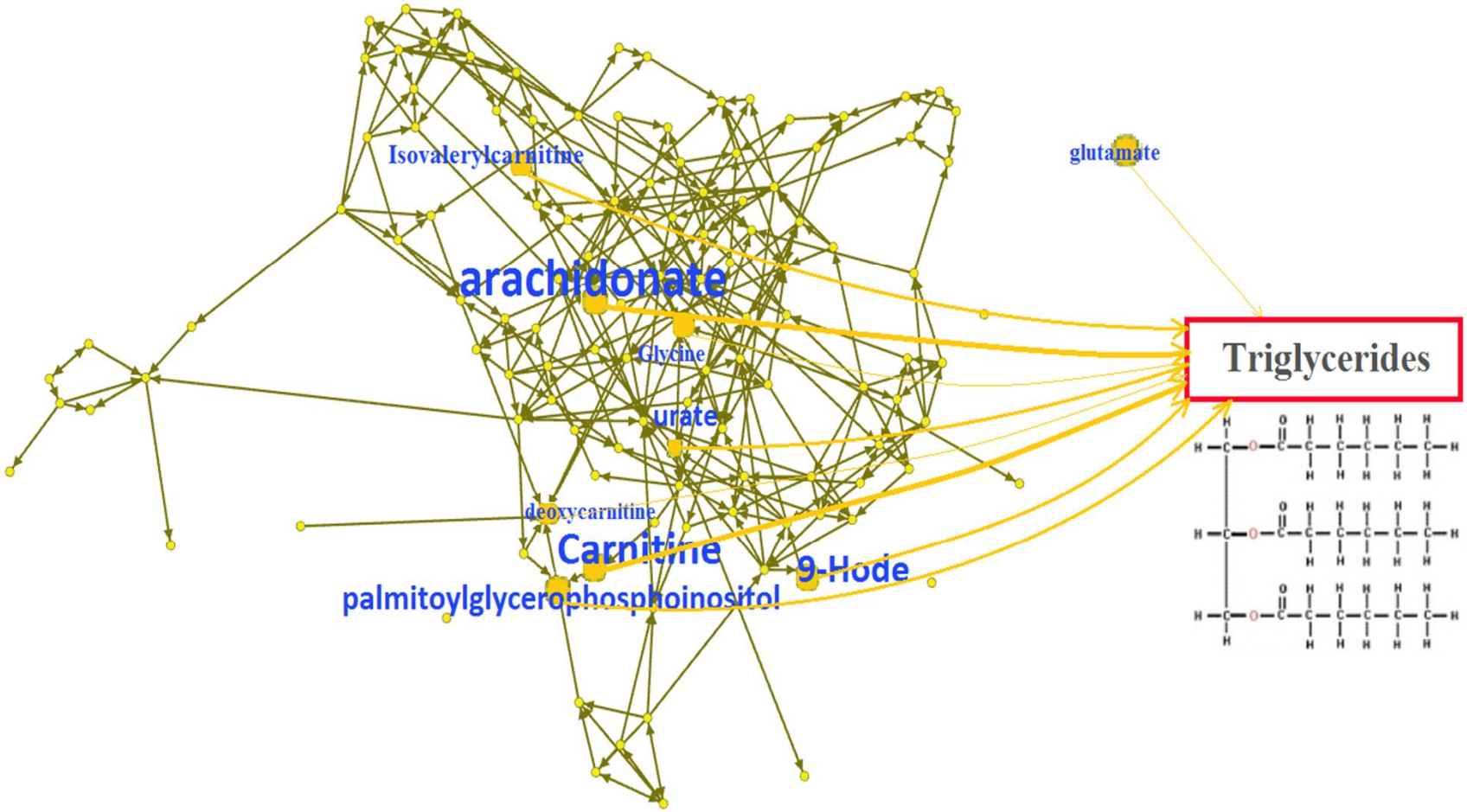
Identification of “Causal” Pathways among the Serum Metabolome

- As shown above, the principal of Mendelian randomization can lend credence to claims of causal inference.
- This principal of Mendelian randomization can extend to information across the genome.
- We (Yazdani, 2016) have combined the principal of genome-wide Mendelian randomization with Directed Acyclic Graph algorithms. (GDAG).





Metabolomic-Triglycerides Network



In total, 9 metabolites have direct a effect on triglyceride levels.

Yazdani et. al, (2016). Metabolomics

Acknowledgments

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Bing Yu
Mandana Yazdani
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Ginger Metcalf
Fuli Yu
Donna Muzny
Richard Gibbs

Framingham Heart Study
Robert Gerszten
Eugene Rhee
Dan Levy
Vasan Ramachandran

Atherosclerosis Risk in Communities Study
Christie Ballantyne
Josef Coresh

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SOLUTIONS BEYOND THE DATA...™