



Common  
Metabolic  
Diseases  
Genome  
Atlas



UC San Diego

EMBL-EBI



# Knowledge Portal Network Webinar & Workshop

*December 9, 2021*  
[kp4cd.org](http://kp4cd.org)



**AMP**

Accelerating Medicines Partnership®  
Common Metabolic Disease

# A new research product

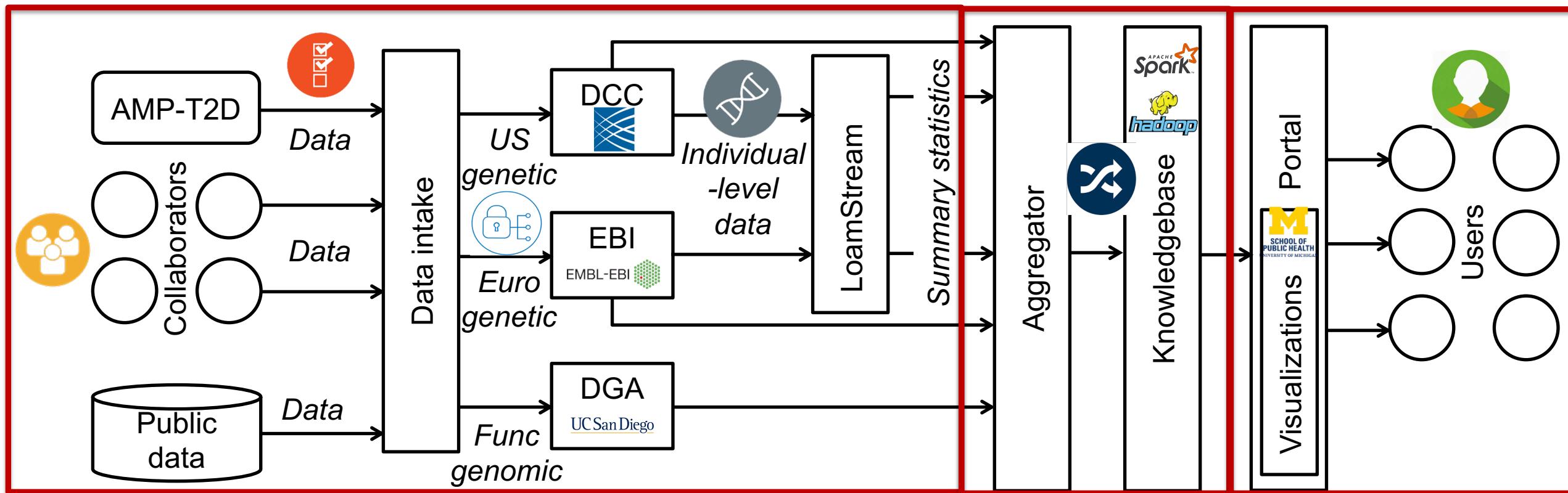


# Knowledge Portals for Common Diseases

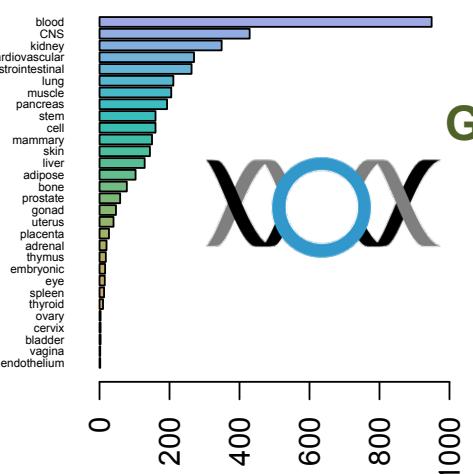
The screenshot shows the homepage of the Common Metabolic Diseases Knowledge Portal (CMDKP). At the top left is the AMP Accelerating Medicines Partnership logo. To its right is the CMDKP logo, which consists of a stylized DNA helix icon followed by the text "CMDKP". On the far right of the header are links for "Home", "Data", "Tools", "KP Labs", "Information", "Contact", and "Login". Below the header, there is a large banner featuring a blue background with a faint illustration of a brain and DNA helices. In the center of this banner is the text "COMMON METABOLIC DISEASES KNOWLEDGE PORTAL" next to a logo of three overlapping colored triangles (orange, green, and blue) forming a network-like structure. To the right of this text is a descriptive paragraph: "Providing data and tools to promote understanding and treatment of common metabolic diseases". Below the banner is a search bar with the placeholder text "Search" and a dropdown arrow, followed by the text "examples: PCSK9, rs1260326, chr9:21,940,000-22,190,000". Below the search bar are three navigation tabs: "Gene, region or variant", "Phenotypes", and "Disease-specific portals".



# The data & software platform



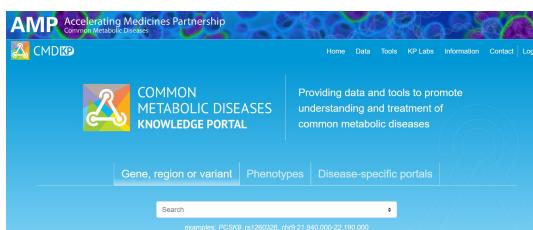
Genetic Data



Functional Genomics Data



Bioinformatic Methods & Approaches



Access



# The product

~77M variants

304 genetic datasets

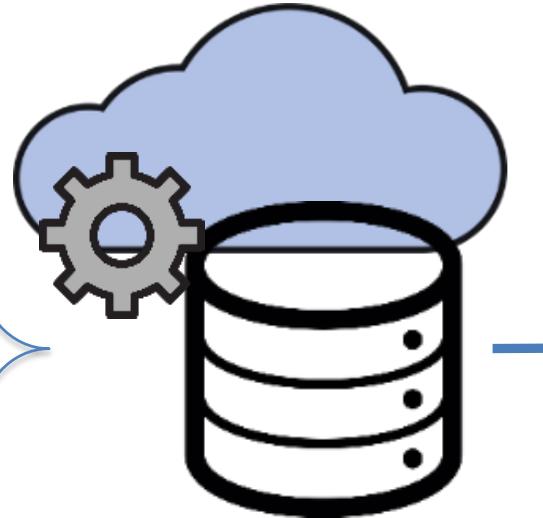
4193 Genomic annotations

40 Curated credible sets

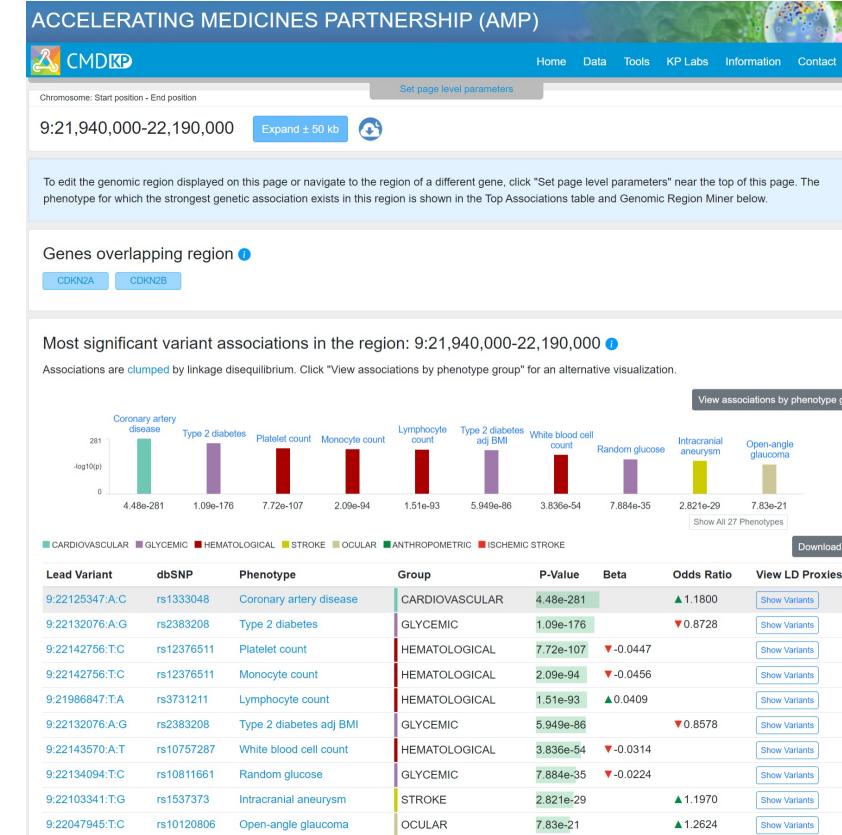
10 Bioinformatic methods

3 gene prediction approaches

Data  
&  
Software  
platform



Open Access Web  
Portal &  
Visualizations



# Fast tracking access to results



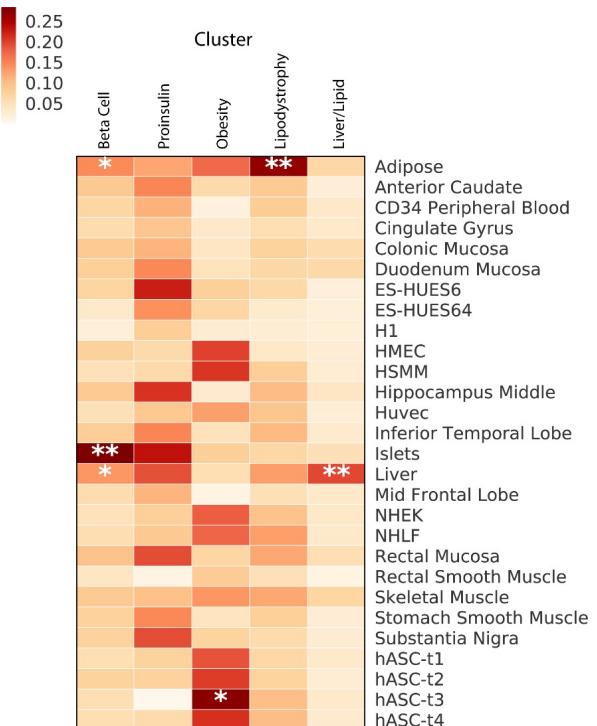
Novel approaches to make accessible

# Type 2 diabetes genetic loci informed by multi-trait associations point to disease mechanisms and subtypes: A soft clustering analysis

Miriam S Udler <sup>1 2 3 4</sup>, Jaegil Kim <sup>3</sup>, Marcin von Grothuss <sup>3</sup>, Sílvia Bonàs-Guarch <sup>5</sup>, Joanne B Cole <sup>2 3</sup>, Joshua Chiou <sup>6</sup>,

Christopher D. Anderson on behalf of METASTROKE and the ISGC; Michael Boehnke <sup>7</sup>, Markku Laakso <sup>8</sup>, Gil Atzmon <sup>9 10 11</sup>, Benjamin Glaser <sup>12</sup>, Josep M Mercader <sup>1 2 3 5</sup>, Kyle Gaulton <sup>6</sup>, Jason Flannick <sup>3 13</sup>, Gad Getz <sup>3</sup>, Jose C Florez <sup>1 2 3 4</sup>

# Unique genetic & genomic study results



	Beta Cell N Loci = 30		Proinsulin N Loci = 7		Obesity N Loci = 5		Lipodystrophy N Loci = 20		Liver/Lipid N Loci = 5		Loci Combined N Loci = 62	
Outcome	beta	P-value	beta	P-value	beta	P-value	beta	P-value	beta	P-value	Beta	P-value
CAD	<b>0.021</b>	<b>2.08E<sup>-12</sup></b>	-0.003	0.67	0.016	0.04	<b>0.021</b>	<b>2.5×10<sup>-8</sup></b>	-0.009	0.27	0.017	<b>1.2×10<sup>-15</sup></b>
CKD	0.003	0.35	0.009	0.22	0.015	0.04	0.0002	0.97	0.011	0.18	0.004	0.06
eGFR	0.000	0.87	0.0002	0.70	-0.0008	0.06	-0.00003	0.89	<b>-0.002</b>	<b>1.2×10<sup>-6</sup></b>	0.000	0.07
UACR	0.001	0.42	0.003	0.27	0.003	0.32	<b>0.006</b>	<b>9.0×10<sup>-5</sup></b>	-0.010	$3.7\times10^{-3}$	0.002	0.01
Stroke_IS	<b>0.016</b>	<b>2.0×10<sup>-4</sup></b>	0.009	0.37	0.022	0.03	0.014	$9.1\times10^{-3}$	-0.002	0.84	<b>0.013</b>	<b>1.3×10<sup>-5</sup></b>
Stroke_CE	0.004	0.59	-0.001	0.94	0.048	0.01	0.005	0.62	0.002	0.93	0.007	0.20
Stroke_LVD	<b>0.032</b>	<b>5.6×10<sup>-5</sup></b>	-0.006	0.73	0.020	0.31	0.026	0.01	-0.017	0.46	<b>0.023</b>	<b>5.1×10<sup>-5</sup></b>
Stroke_SVD	<b>0.032</b>	<b>2.6×10<sup>-4</sup></b>	0.029	0.17	0.027	0.22	0.036	$1.5\times10^{-3}$	-0.007	0.79	<b>0.028</b>	<b>7.3×10<sup>-6</sup></b>
SBP	0.035	0.09	-0.014	0.76	-0.088	0.07	<b>0.149</b>	<b>4.9×10<sup>-9</sup></b>	-0.041	0.45	0.048	$9.3\times10^{-4}$
DBP	0.014	0.30	-0.027	0.36	-0.046	0.14	<b>0.073</b>	<b>6.4×10<sup>-6</sup></b>	0.0005	0.99	0.023	0.01

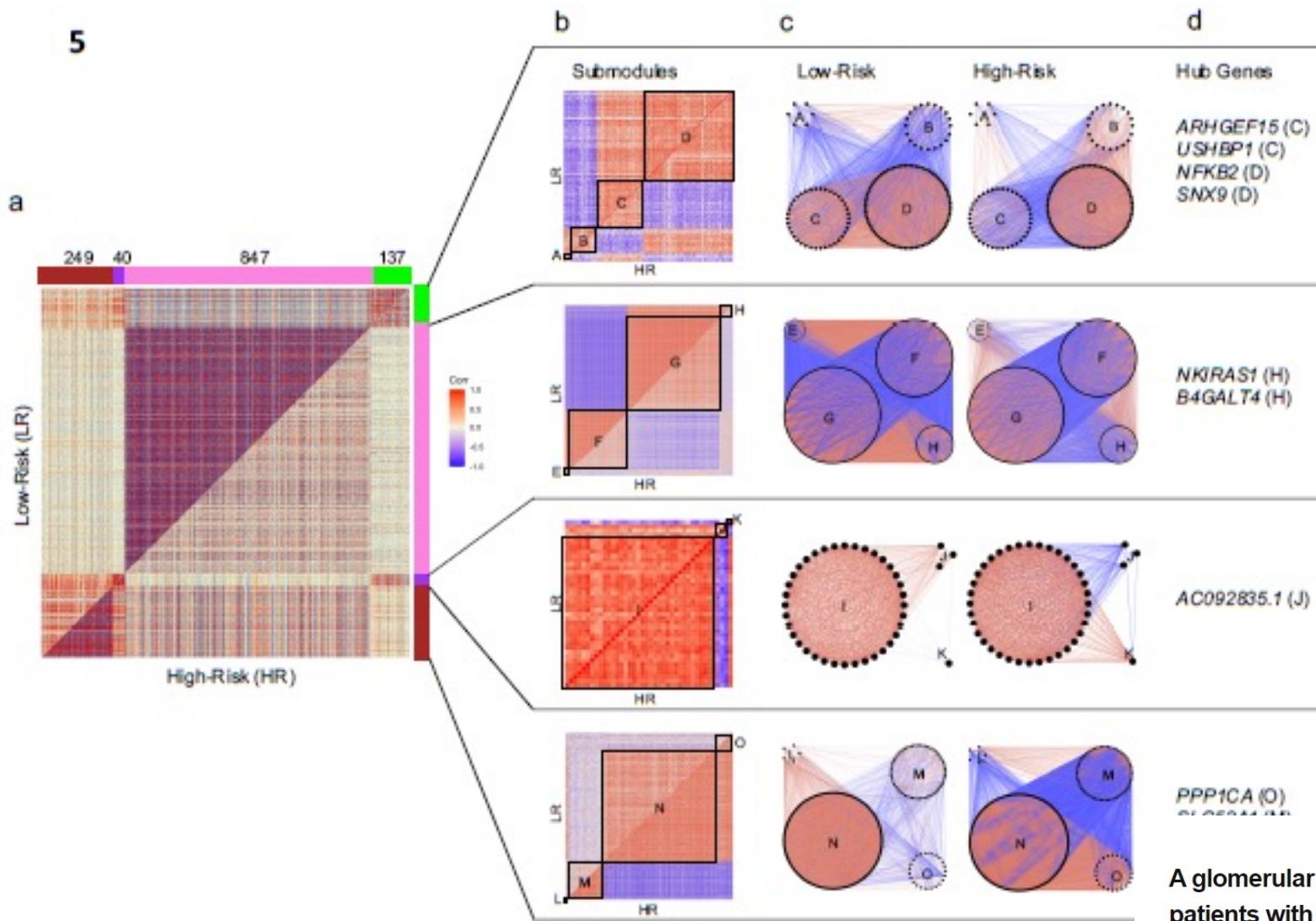
P-values  $< 8 \times 10^{-4}$  and corresponding betas are bolded, representing a Bonferroni correction of 10 outcomes  $\times$  6 groups.

Abbreviations: CAD, coronary artery disease; CE, cerebroembolic; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IS, ischemic stroke all subtypes; LVD, large vessel disease; SBP, systolic blood pressure; SVD, small vessel disease; UACR, urine albumin-creatinine ratio.

# Complex distilled lists of genes & supportive evidence

A	B	C	D	E	F	G	H	I	J	K	L
	Combined category	Combined category_noNames	EXTRA_NonT2D_regions	Perturbation combined	Genomic combined	Genetic Combined	Gene name	Locus name	GWAS coding (causal)	Exome array coding (causal)	Exome sequence
3	STRONG	B		3P	2R	2C	ABCB9	MPHOSPH9			Medium
4	CAUSAL	A		2P		1C	ABCC8				
5	WEAK	E			3R		ABO				
6	MODERATE	C		3P	2R		ADCY5				
7	(T2D_related)	Extra	GLYCEMIC	2P	2R		ADRA2A				
8	MODERATE	C		3P		2C	AGPAT2	GPSM1			
9	MODERATE	C		2P	3R		AGTR2				
10	(T2D_related)	Extra	GLYCEMIC   Lipodystrophy	2P		1C	AKT2			Strong for glycemic	Medium for glycemic
11	CAUSAL	A		2P	3R	1C	ANGPTL4				
12	POSSIBLE	D		3P	3R		ANK1	ANK1			
13	CAUSAL	A		3P		1C	ANKH		Strong	Strong	
14	MODERATE	C		3P	2R		AP3S2	AP3S2			
15	CAUSAL	A		2P		1C	APOE		Strong		
16	(T2D_related)	Extra	MODY	3P		2C	APPL1				
17	POSSIBLE	D				2C	ASCC2	MTMR3		Medium	
18	STRONG	B		2P	2R		BCAR1				
19	MODERATE	C		3P		2C	BCL11A				Medium
20	(T2D_related)	Extra	MODY   Familial early onset diabetes		3R	2C	BLK				
21	(T2D_related)	Extra	Lipodystrophy	3P		2C	BSCL2				
22	STRONG	B		2P	2R		C2CD4B	C2CD4B/A			
23	POSSIBLE	D				2C	CALCOCO2	TTL6		Medium	
24	STRONG	B		2P	2R		CAMK1D				
25	WEAK	E			3R		CARD9	GPSM1			
26	(T2D_related)	Extra	Lipodystrophy	2P		2C	CAV1				
27	STRONG	B		2P	3R	2C	CCND2				Medium
28	WEAK	E			3R		CDK2AP1	MPHOSPH9			
29	CAUSAL	A		3P		1C	CDKN1B		Strong		
30	(T2D_related)	Extra	GLYCEMIC   MODY   Familial early onset diabetes			2C	CEL				
31	MODERATE	C		3P		2C	CISD2	SLC9B1			
32	WEAK	E			3R		CTNNAL1	IKBKAP			
33	STRONG	B		2P	2R		DGKB				
34	WEAK	E			3R		DNZL	GPSM1			
35	(T2D_related)	Extra	NDM	3P		2C	EIF2AK3				
36	(T2D_related)	Extra	GLYCEMIC		3R		ERAP2				

5



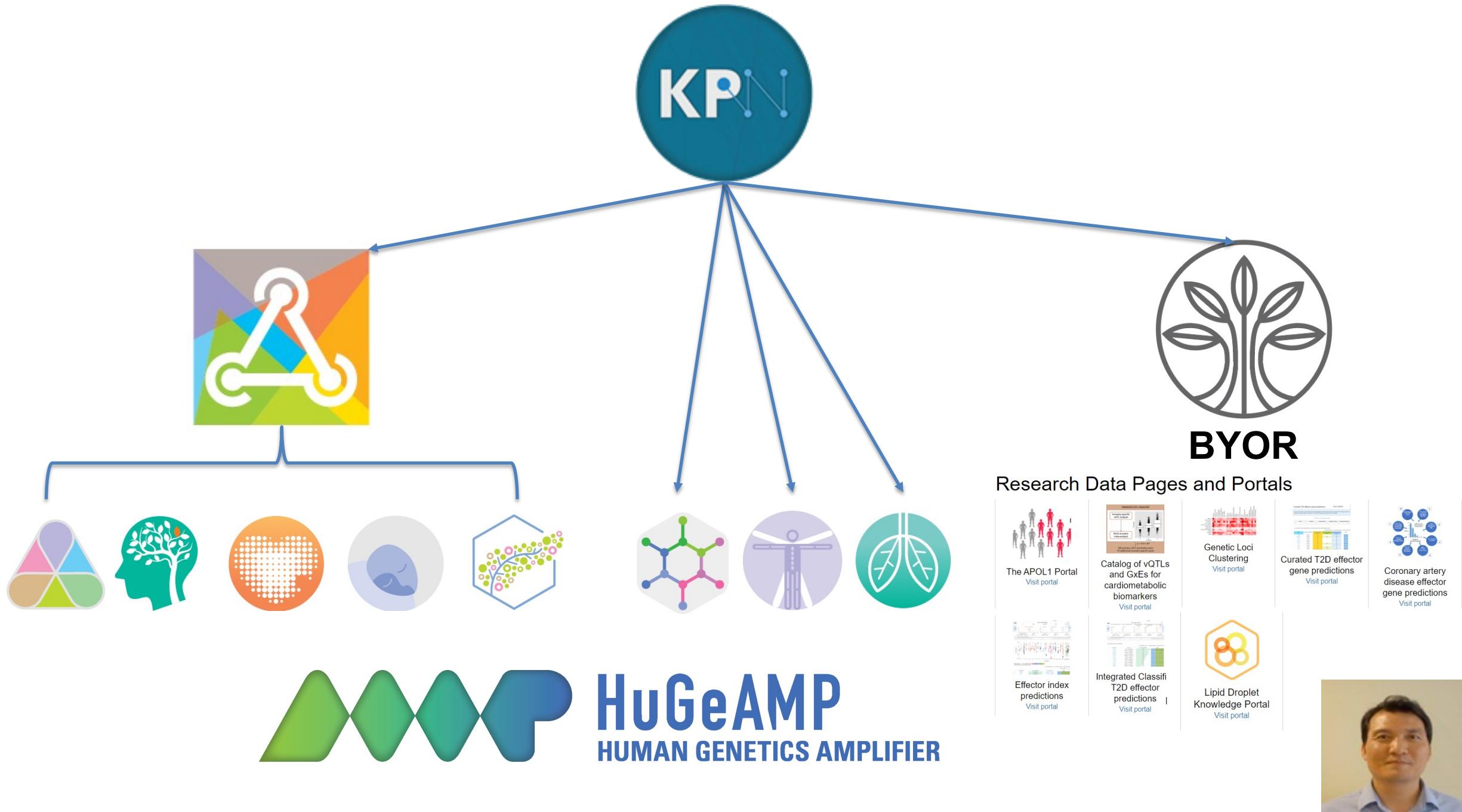
A glomerular transcriptomic landscape of *APOL1* in Black patients with focal segmental glomerulosclerosis

[Comment on this paper](#)

Michelle M. McNulty, Damian Fermin, Felix Eichinger, Dongkeun Jang, Matthias Kretzler, Noel Burtt, Martin R. Pollak, Jason Flannick, David J. Friedman, Nephrotic Syndrome Study Network (NEPTUNE),  
✉ Matthew G. Sampson

doi: <https://doi.org/10.1101/2021.02.18.21251945>

# Static figures from manuscripts converted into interactive visualizations



# Some currently part of CMD-KP

 CMDKP

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## About the Knowledge Portal Labs

In the Knowledge Portal Labs, we offer access to cutting-edge analysis tools during their development. While the data supporting these tools are accurate, the tools themselves are not in their final form. The workflows that they present may not be optimal; their documentation is only a first draft; and yet-undiscovered bugs could be present.

We provide early access to these tools in hopes that Knowledge Portal visitors will help guide their development by giving us feedback on any and all aspects of the tools. Please [contact us](#) with your suggestions!

The tools listed below are currently available in the KP Labs. All tools are available via the KP Labs menu of the Common Metabolic Diseases Knowledge Portal, and are also available via those disease-specific portals to which they are relevant.

### Complications Association Browser

The aim of the Complications Association Browser is to help identify genes that may contribute to a condition uniquely in the context of type 2 diabetes, using gene-level phenotypic associations calculated from bottom-line meta-analyzed genetic associations with the **MAGMA** (Multi-marker Analysis of GenoMic Annotation) method.

### Exome Gene-Level Meta-Analysis

Explore unpublished results from a meta-analysis of genetic associations from exome sequencing data for 86,254 samples (29,434 T2D cases and 56,820 controls). Gene-level association scores are available for type 2 diabetes. Note that because possible inconsistencies in case ascertainment between some cohorts are still under investigation, we have not integrated these results into the Knowledge Portals; however, we believe they are interesting enough to share in the KP Labs space.

### Genetic Association Interactive Tool (GAIT)

Contact the team  
[Human Genetic Evidence Calculator](#)

Signal Sifter

About KP Labs  
Complications Association Browser  
Exome Gene-Level Meta-Analysis  
Genetic Association Interactive Tool  
Genetic Loci Clustering  
[Human Genetic Evidence Calculator](#)

# T2D Effector Transcripts



Curated T2D effector gene predictions

Phenotype: Type 2 diabetes

[View data](#) [View research method](#)

Gene	Prediction	Genetic evidence	Regulatory evidence	Perturbational evidence	
ABCC8	CAUSAL	1C		2P	<a href="#">Evidence</a>
ANGPTL4	CAUSAL	1C	3R	2P	<a href="#">Evidence</a>
ANKH	CAUSAL	1C		3P	<a href="#">Evidence</a>
APOE	CAUSAL	1C		2P	<a href="#">Evidence</a>
CDKN1B	CAUSAL	1C		3P	<a href="#">Evidence</a>
GCK	CAUSAL	1C	3R	2P	<a href="#">Evidence</a>
GCKR	CAUSAL	1C		2P	<a href="#">Evidence</a>
GIPR	CAUSAL	1C	3R	3P	<a href="#">Evidence</a>
GLIS3	CAUSAL	1C	3R	2P	<a href="#">Evidence</a>
GLP1R	CAUSAL	1C	3R	2P	<a href="#">Evidence</a>

\*Click 'Evidence' button to view evidence data. \*Hover evidence tables to see evidence group names.

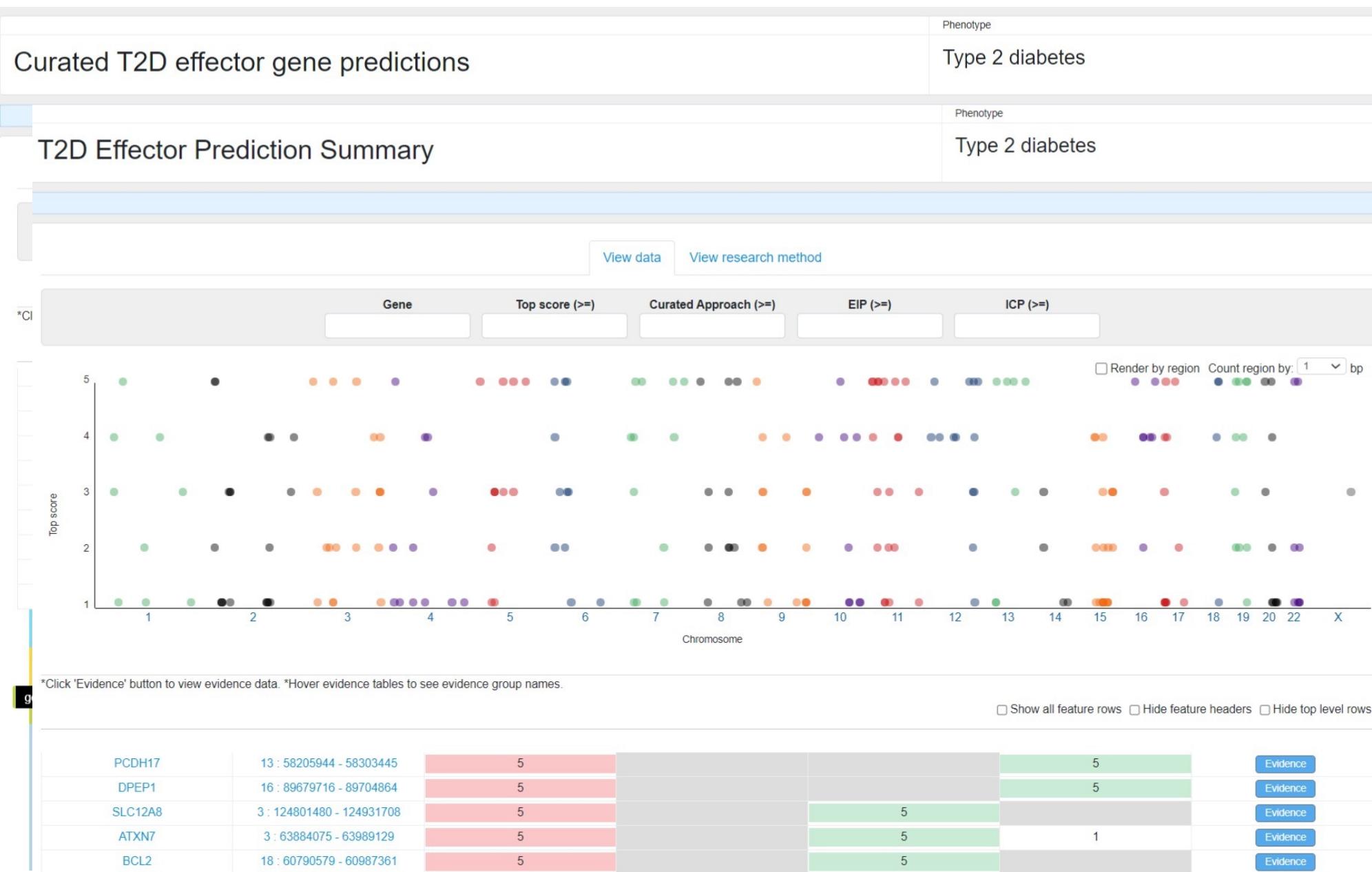
Show all feature rows  Hide feature headers  Hide top level rows

Gene	Prediction	Genetic evidence	Regulatory evidence	Perturbational evidence	
ABCC8	CAUSAL	1C		2P	<a href="#">Evidence</a>
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ANKH	CAUSAL	1C		3P	<a href="#">Evidence</a>
APOE	CAUSAL	1C		2P	<a href="#">Evidence</a>
CDKN1B	CAUSAL	1C		3P	<a href="#">Evidence</a>
GCK	CAUSAL	1C	3R	2P	<a href="#">Evidence</a>
GCKR	CAUSAL	1C		2P	<a href="#">Evidence</a>
GIPR	CAUSAL	1C	3R	3P	<a href="#">Evidence</a>
GLIS3	CAUSAL	1C	3R	2P	<a href="#">Evidence</a>
GLP1R	CAUSAL	1C	3R	2P	<a href="#">Evidence</a>

Predicted T2D effector gene		Previously associated loci				
GLP1R						
GWAS coding evidence		Exome array evidence		Burden test evidence	Monogenetic associations	Other genetic evidence
genomic	Islet cis-eQTLs	Strong		Medium		PMID:27252175   PMID:29941447
	Other relevant cis-eQTLs		Islet chromatin conformation	Allelic imbalance	Glucose regulation	Other regulatory evidence
					1	
	RNA interference evidence	Zebrafish mutant phenotype	Mouse mutant phenotype	Drosophila mutant phenotype	Rat mutant phenotype	Other perturbation evidence
			decreased body weight   abnormal circulating insulin level   abnormal glucose homeostasis   abnormal pancreas secretion   decreased circulating insulin level   decreased lean body mass   abnormal glucose tolerance   impaired glucose tolerance   abnormal food intake   incre		decreased circulating glucose level   increased heart rate   increased systemic arterial blood pressure   increased insulin secretion	



# T2D Effector Transcripts



# Complete stand alone portal

The APOL1 Portal: *Genomic data-sharing to empower efforts towards understanding and treating APOL1 associated kidney disease*

The APOL1 Portal enables browsing, searching, and analysis of human genetic and glomerular transcriptomic data related to APOL1 associated focal segmental glomerulosclerosis (FSGS), while protecting the integrity and confidentiality of the underlying information.

Our manuscript, "A glomerular transcriptomic landscape of APOL1 in Black patients with focal segmental glomerulosclerosis," is [available on medRxiv](#).

**Three ways to explore the data:**

1. [Interactively explore transcriptomic & clinical data](#)
2. [Look up results for single genes](#)
3. Interactively explore transcriptomic and clinical data, as diagrammed below:

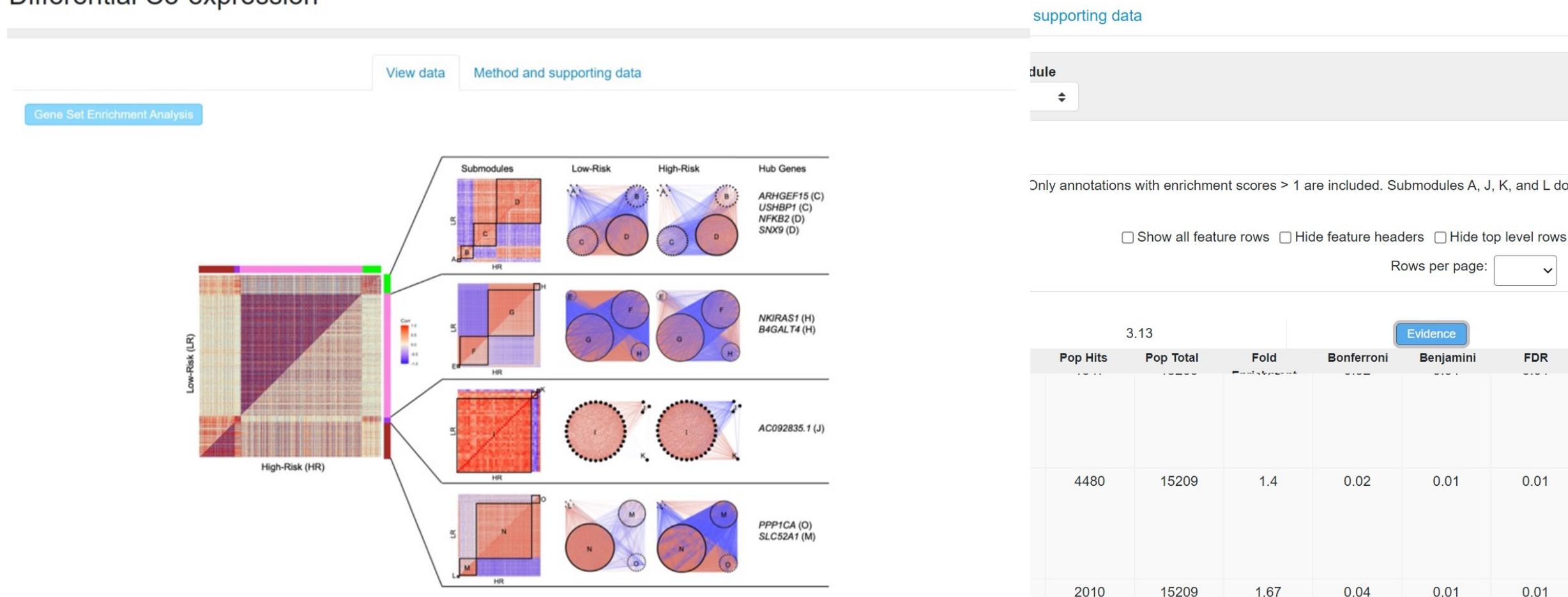


# Differential Expression

Gene Symbol	Ensembl Gene ID	P-value (<=)	Log2 Fold Change: N1, N2(<= OR >=)

## Functional Enrichment Analysis with DAVID

### Differential Co-expression



# Guiding Principles

- Your results the way you intend
- A set of core capabilities
- Collaborate to construct
- Easy to use & update
- Stage access
- Leverage the HuGeAMP resource

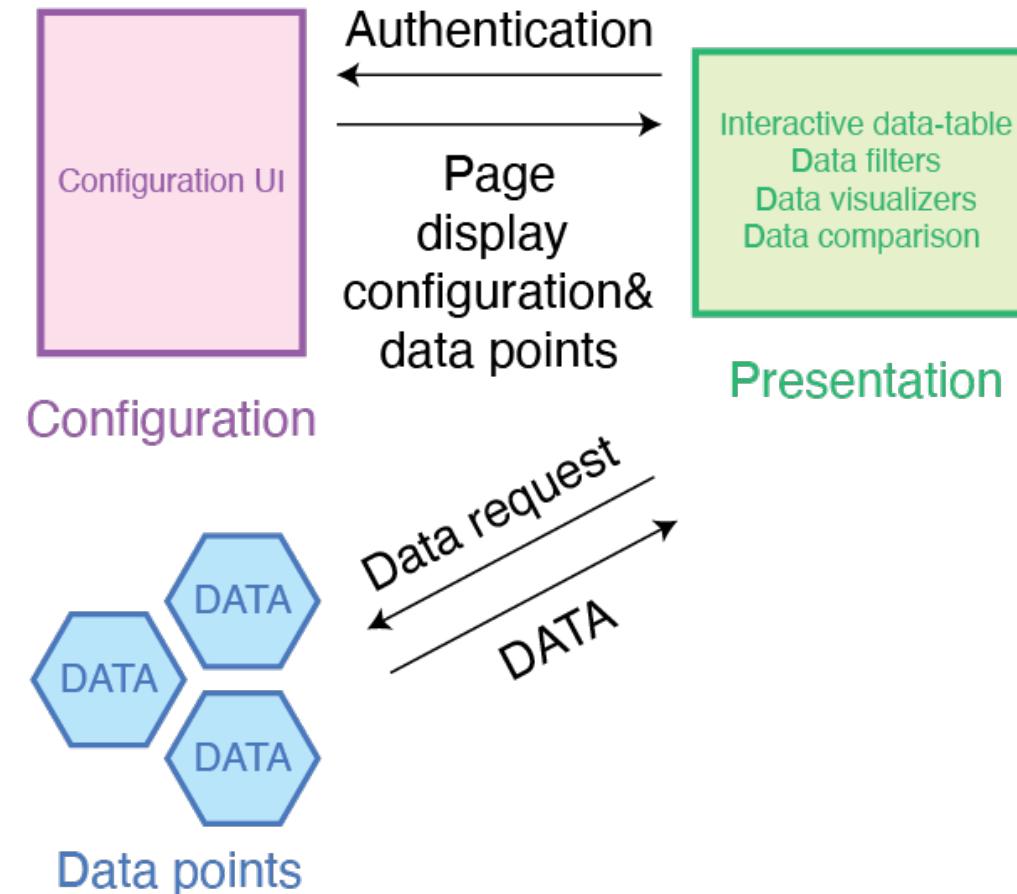


# Bring Your Own Results (BYOR) Portal Service

- Framework- DK Jang
- Capabilities- Maria Costanzo
- Demonstration- Kenny Westerman
- Outlook-all



## The Bring Your Own Results (BYOR) platform



## **Demonstrations**

Maria Costanzo demonstrated how to use the BYOR interface and showed examples of Research Pages and Portals created using the BYOR framework.

Getting started with BYOR: [https://kp4cd.org/research\\_portals](https://kp4cd.org/research_portals)

Examples of Research Pages and Portals: <https://kp4cd.org/>

Kenny Westerman demonstrated the portal that he created using the BYOR framework and discussed its implementation.

The vQTL-GxE Portal: <https://hugeamp.org/research.html?pageid=UKB-vQTL-GxE>