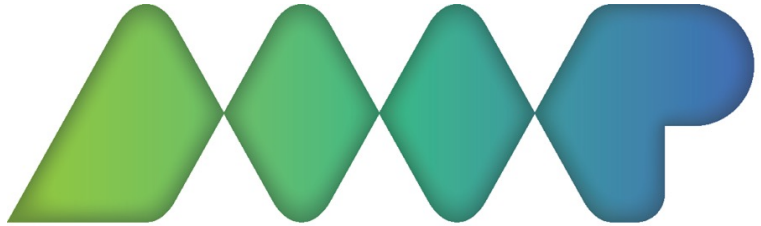
Knowledge Portal Network Webinar & Workshop

December 9, 2021

[kp4cd.org](kp4cd.org)

AMP Accelerating Medicines Partnership®
Common Metabolic Disease

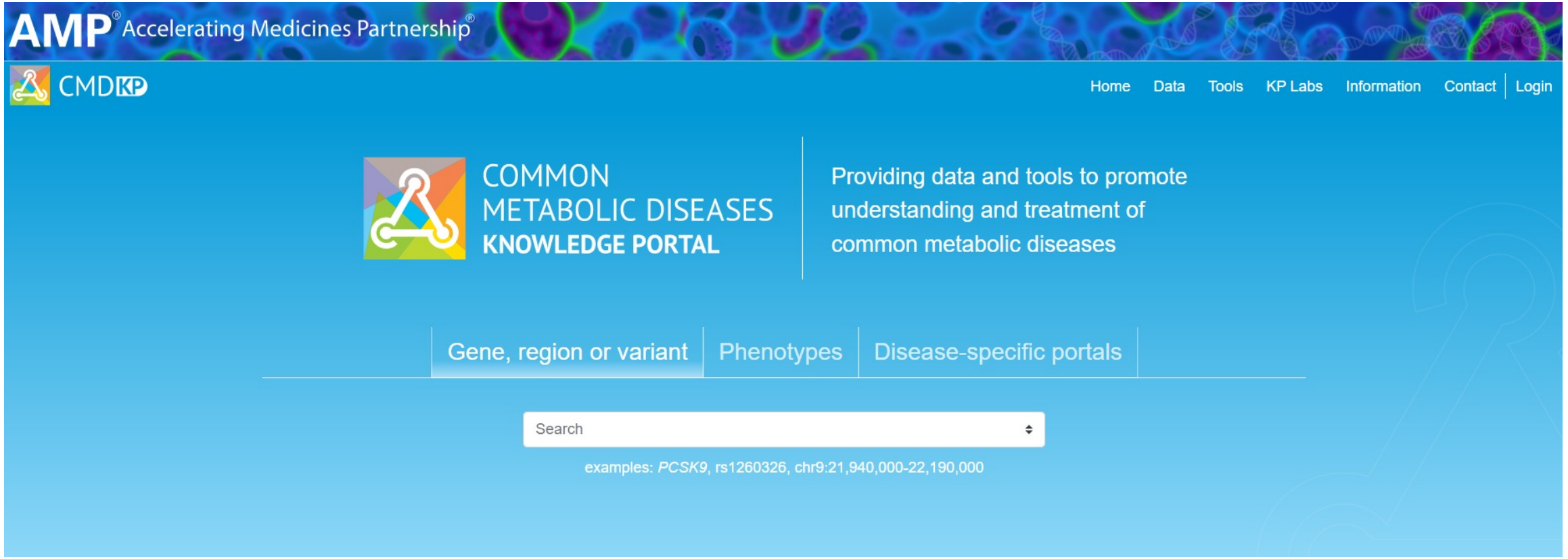
A new research product



HuGeAMP

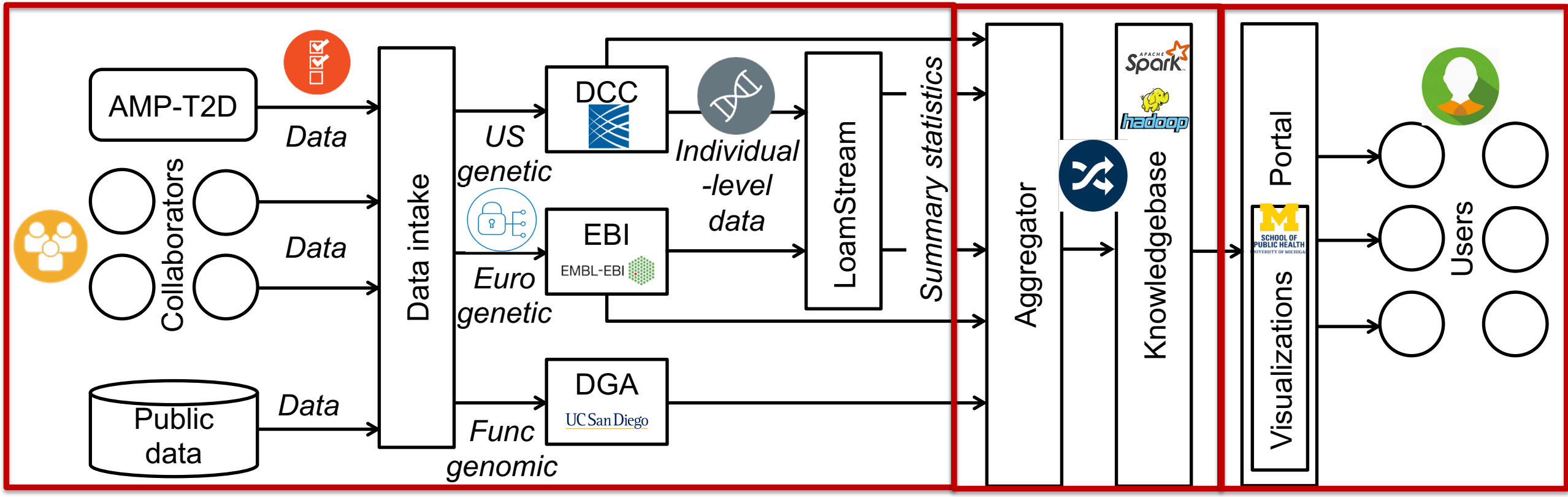
HUMAN GENETICS AMPLIFIER

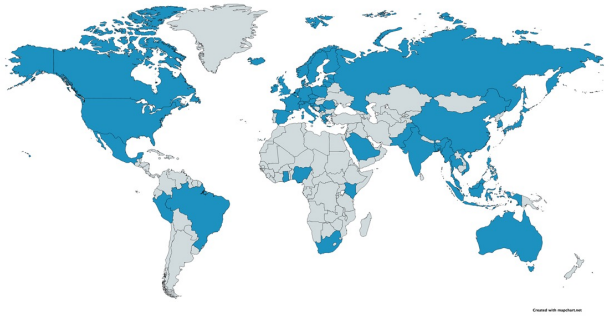
Knowledge Portals for Common Diseases



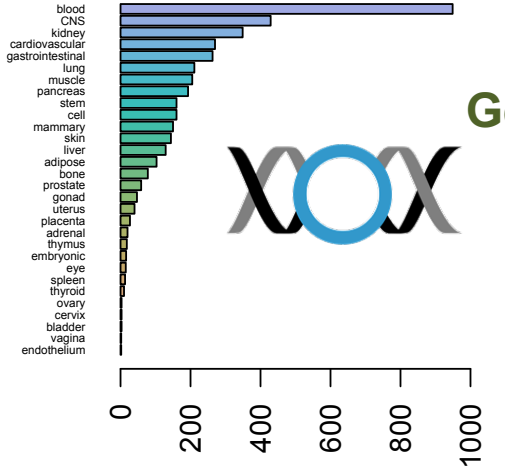
The data & software platform

HuGeAMP
HUMAN GENETICS AMPLIFIER

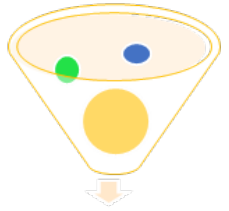




Genetic Data



Functional Genomics Data

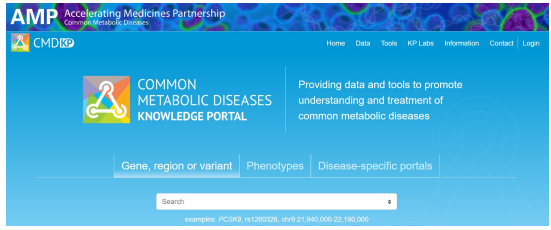


Aggregator

bioIndex

Access

Bioinformatic Methods & Approaches



The product

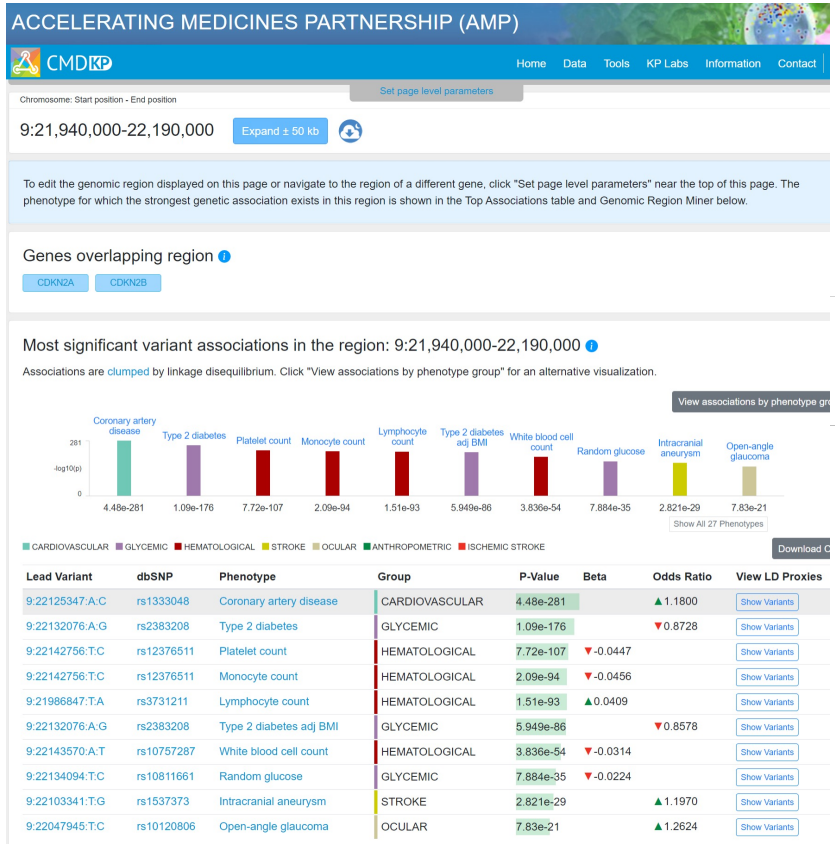
~77M variants

- 304 genetic datasets
- 4193 Genomic annotations
- 40 Curated credible sets
- 10 Bioinformatic methods
- 3 gene prediction approaches

HuGeAMP
HUMAN GENETICS AMPLIFIER

Data
&
Software
platform

Open Access Web Portal & Visualizations



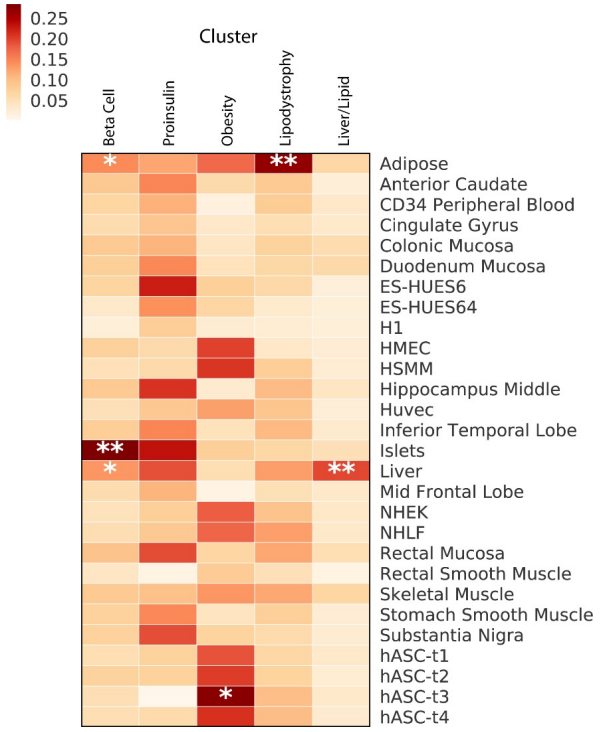
Fast tracking access to results

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 [1 2 3 4], Jaegil Kim [3], Marcin von Grotthuss [3], Sílvia Bonàs-Guarch [5], Joanne B Cole [2 3], Joshua Chiou [6], Christopher D. Anderson on behalf of METASTROKE and the ISGC; Michael Boehnke [7], Markku Laakso [8], Gil Atzmon [9 10 11], Benjamin Glaser [12], Josep M Mercader [1 2 3 5], Kyle Gaulton [6], Jason Flannick [3 13], Gad Getz [3], Jose C Florez [1 2 3 4]

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	**0.021**	**$2.08E^{-12}$**	−0.003	0.67	0.016	0.04	**0.021**	**2.5×10^{-8}**	−0.009	0.27	0.017	**1.2×10^{-15}**
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	**−0.002**	**1.2×10^{-6}**	0.000	0.07
UACR	0.001	0.42	0.003	0.27	0.003	0.32	**0.006**	**9.0×10^{-5}**	−0.010	3.7×10^{-3}	0.002	0.01
Stroke_IS	**0.016**	**2.0×10^{-4}**	0.009	0.37	0.022	0.03	0.014	9.1×10^{-3}	−0.002	0.84	**0.013**	**1.3×10^{-5}**
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	**0.032**	**5.6×10^{-5}**	−0.006	0.73	0.020	0.31	0.026	0.01	−0.017	0.46	**0.023**	**5.1×10^{-5}**
Stroke_SVD	**0.032**	**2.6×10^{-4}**	0.029	0.17	0.027	0.22	0.036	1.5×10^{-3}	−0.007	0.79	**0.028**	**7.3×10^{-6}**
SBP	0.035	0.09	−0.014	0.76	−0.088	0.07	**0.149**	**4.9×10^{-9}**	−0.041	0.45	0.048	9.3×10^{-4}
DBP	0.014	0.30	−0.027	0.36	−0.046	0.14	**0.073**	**6.4×10^{-6}**	0.0005	0.99	0.023	0.01

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

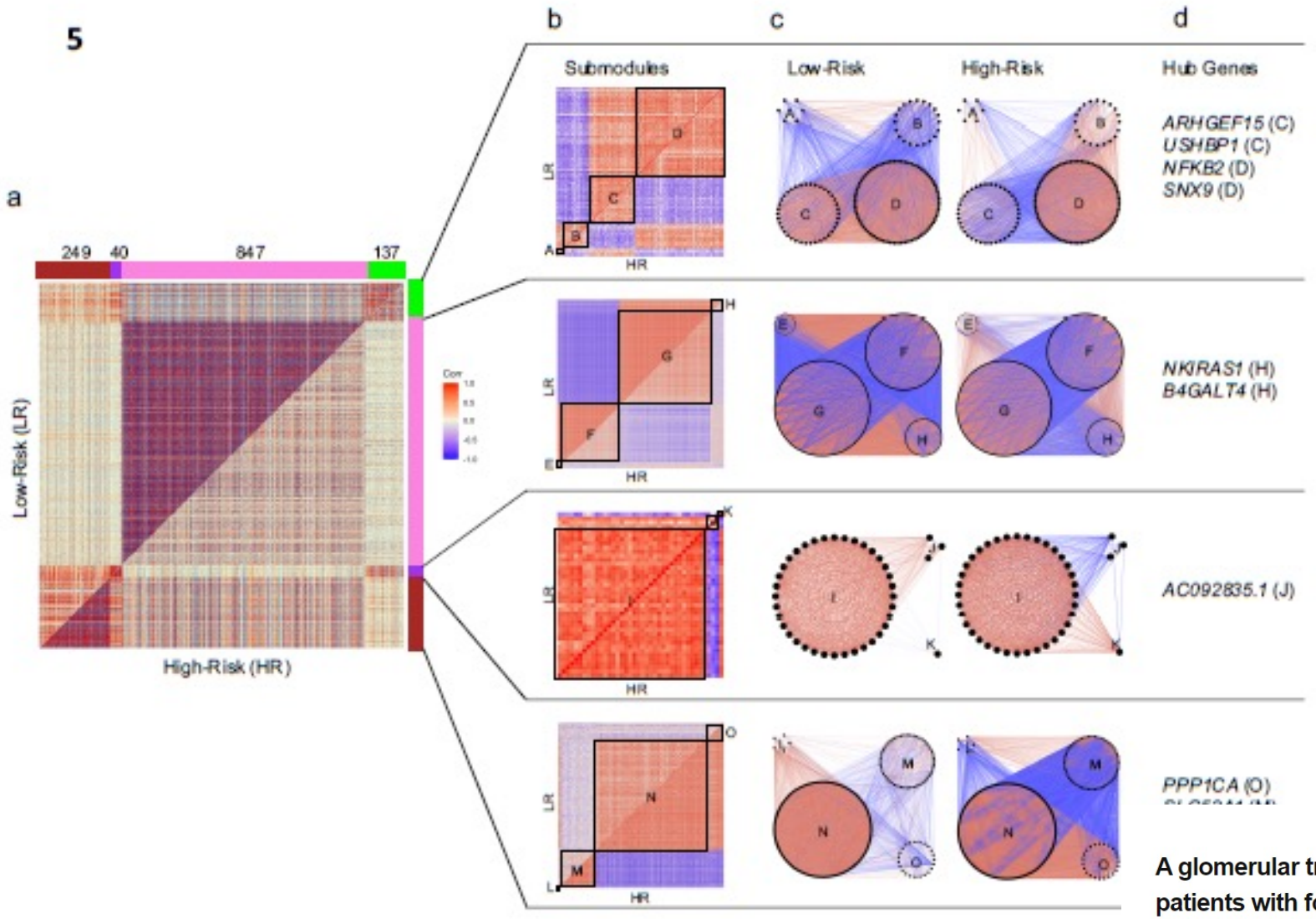
Abbreviations: CAD, coronary artery disease; CE, cerebroembolic; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IS, ischemic stroke all subtypes; LVD, large vessel disease; SBP, systolic blood pressure; SVD, small vessel disease; UACR, urine albumin-creatinine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

https://doi.org/10.1371/journal.pmed.1002654.t002

Complex distilled lists of genes & supportive evidence

	A	B	C	D	E	F	G	H	I	J	K	L
1								Locus				GENETI
		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*	TTLL6		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*				

Mahajan et al



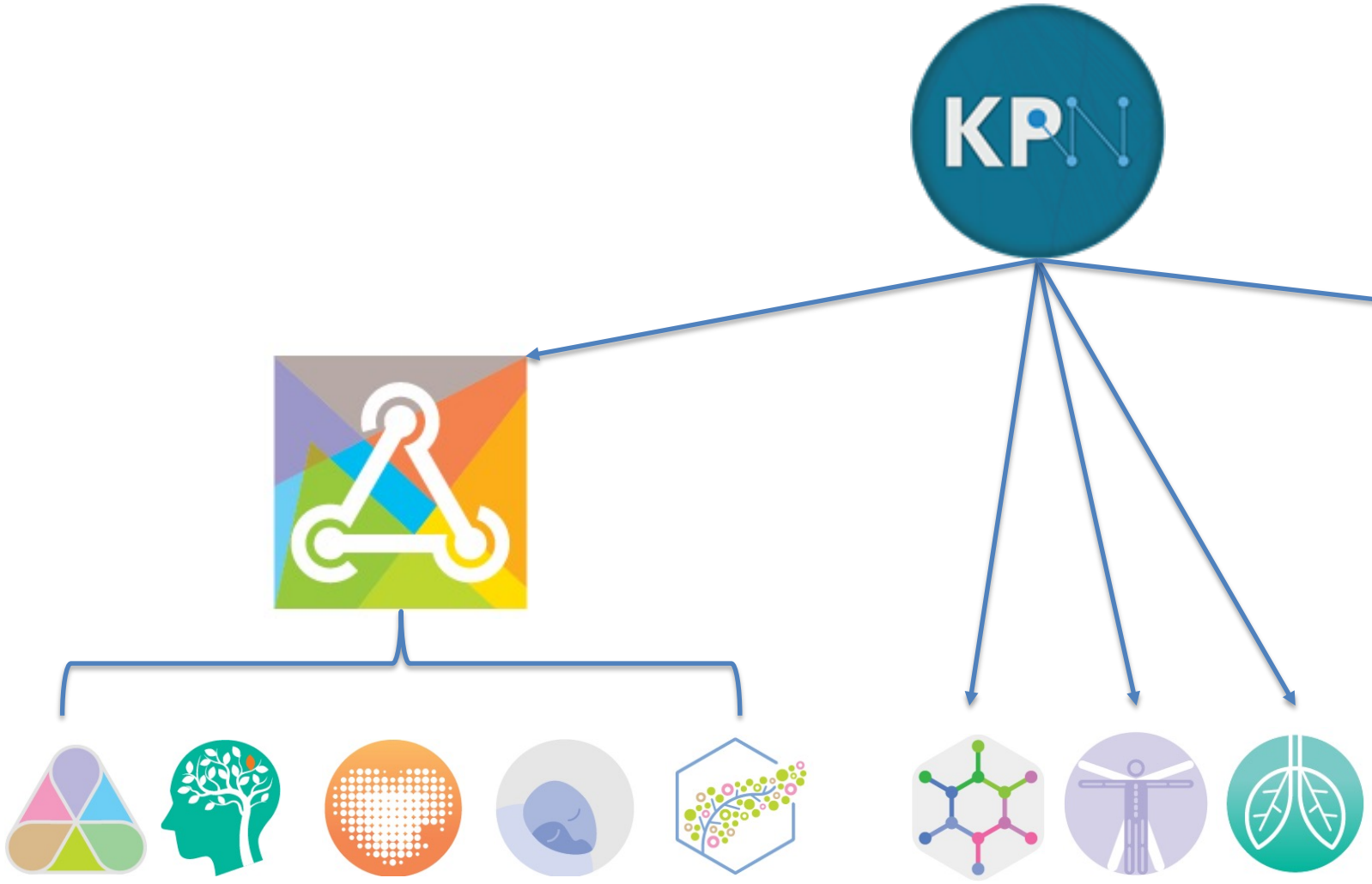
Static figures from manuscripts converted into interactive visualizations

Comment on this paper

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

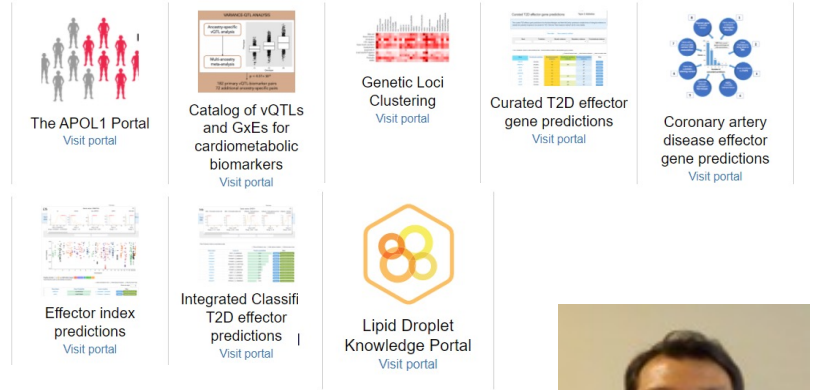
Michelle M. McNulty, Damian Fermin, Felix Eichinger, Dongkeun Jang, Matthias Kretzler, Noel Burtt, Martin R. Pollak, Jason Flannick, David J. Friedman, Nephrotic Syndrome Study Network (NEPTUNE), Matthew G. Sampson

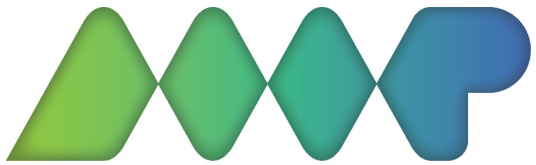
doi: https://doi.org/10.1101/2021.02.18.21251945



BYOR

Research Data Pages and Portals

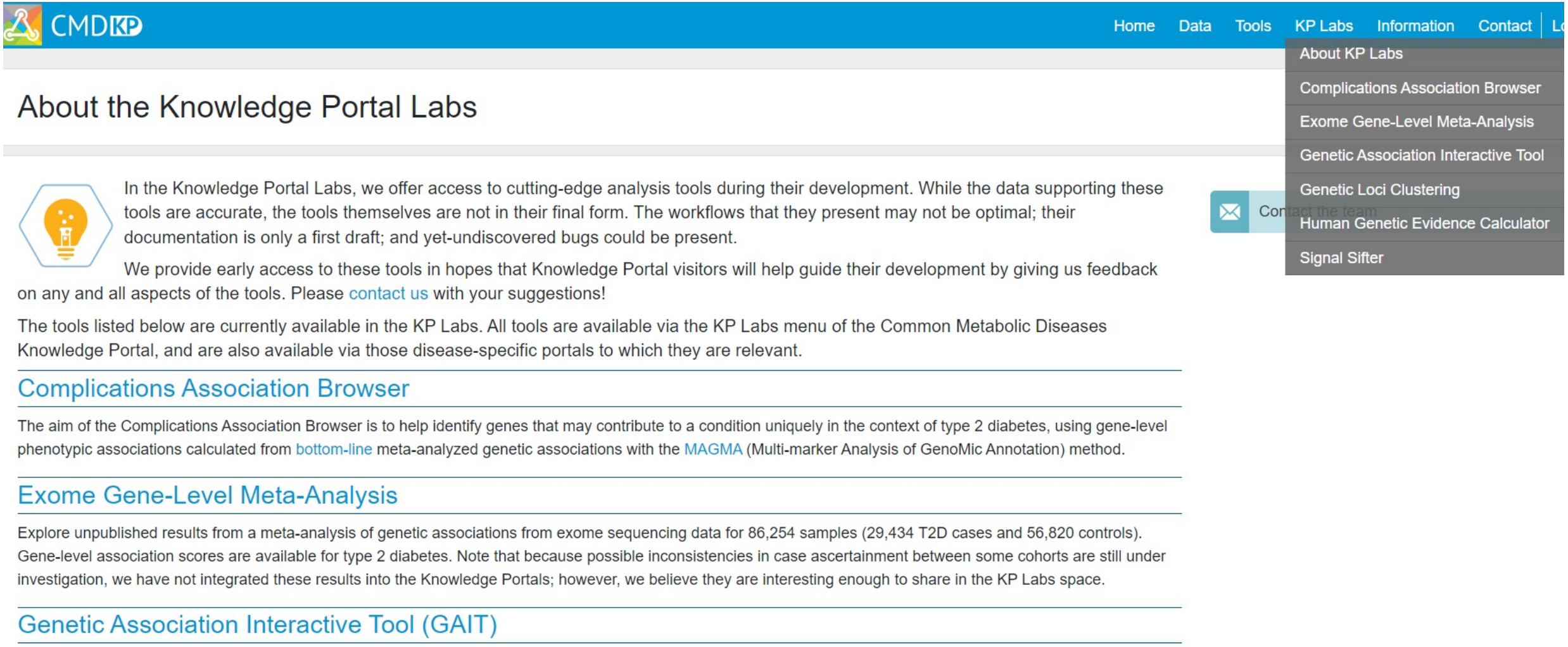




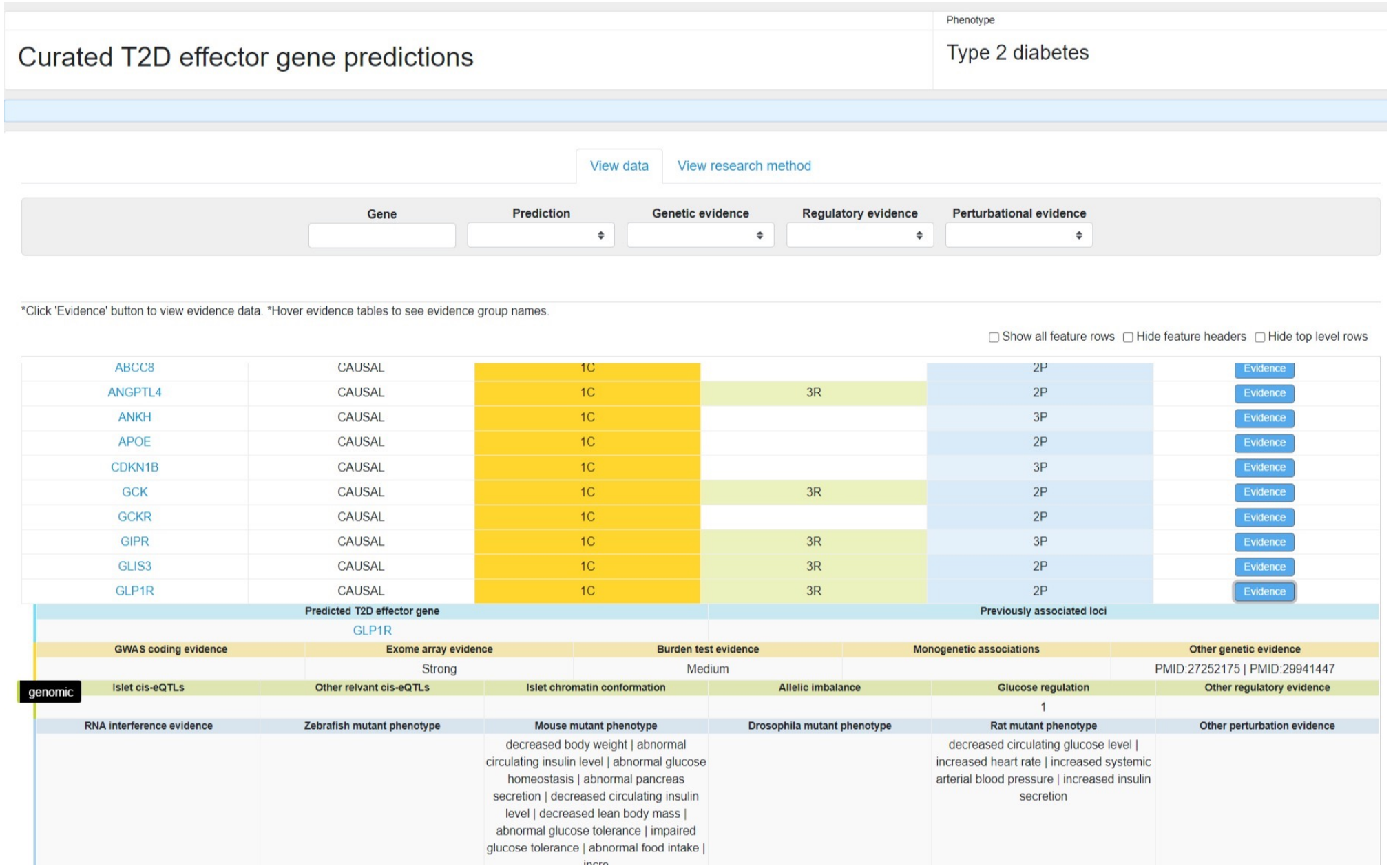
HuGeAMP

HUMAN GENETICS AMPLIFIER

Some currently part of CMD-KP



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

*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

ABCC8	CAUSAL	1C		2P	Evidence
ANGPTL4	CAUSAL	1C	3R	2P	Evidence
ANKH	CAUSAL	1C		3P	Evidence
APOE	CAUSAL	1C		2P	Evidence
CDKN1B	CAUSAL	1C		3P	Evidence
GCK	CAUSAL	1C	3R	2P	Evidence
GCKR	CAUSAL	1C		2P	Evidence
GIPR	CAUSAL	1C	3R	3P	Evidence
GLIS3	CAUSAL	1C	3R	2P	Evidence
GLP1R	CAUSAL	1C	3R	2P	Evidence

Predicted T2D effector gene	Previously associated loci
GLP1R	

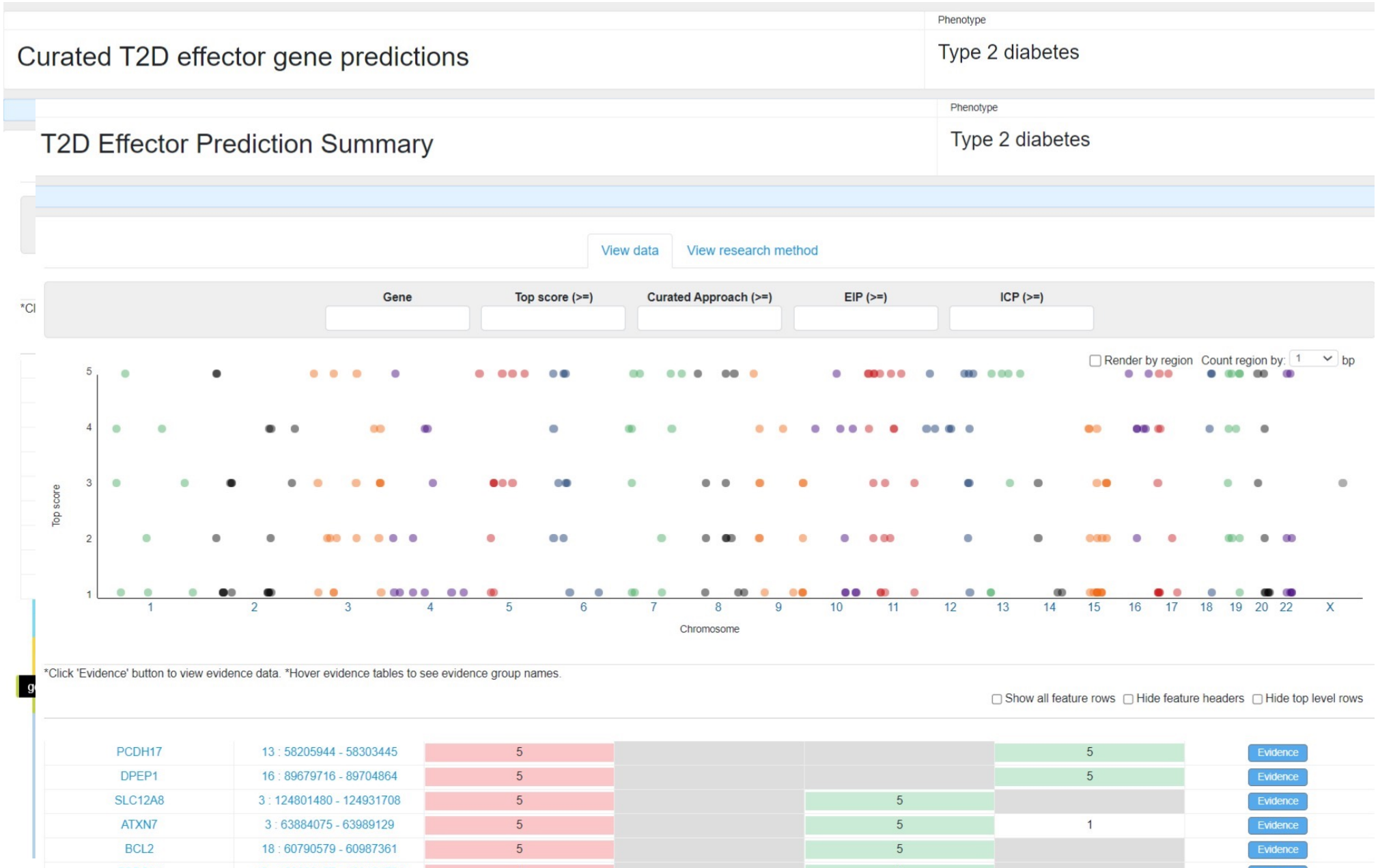
GWAS coding evidence	Exome array evidence	Burden test evidence	Monogenetic associations	Other genetic evidence
	Strong	Medium		PMID:27252175 | PMID:29941447

genomic

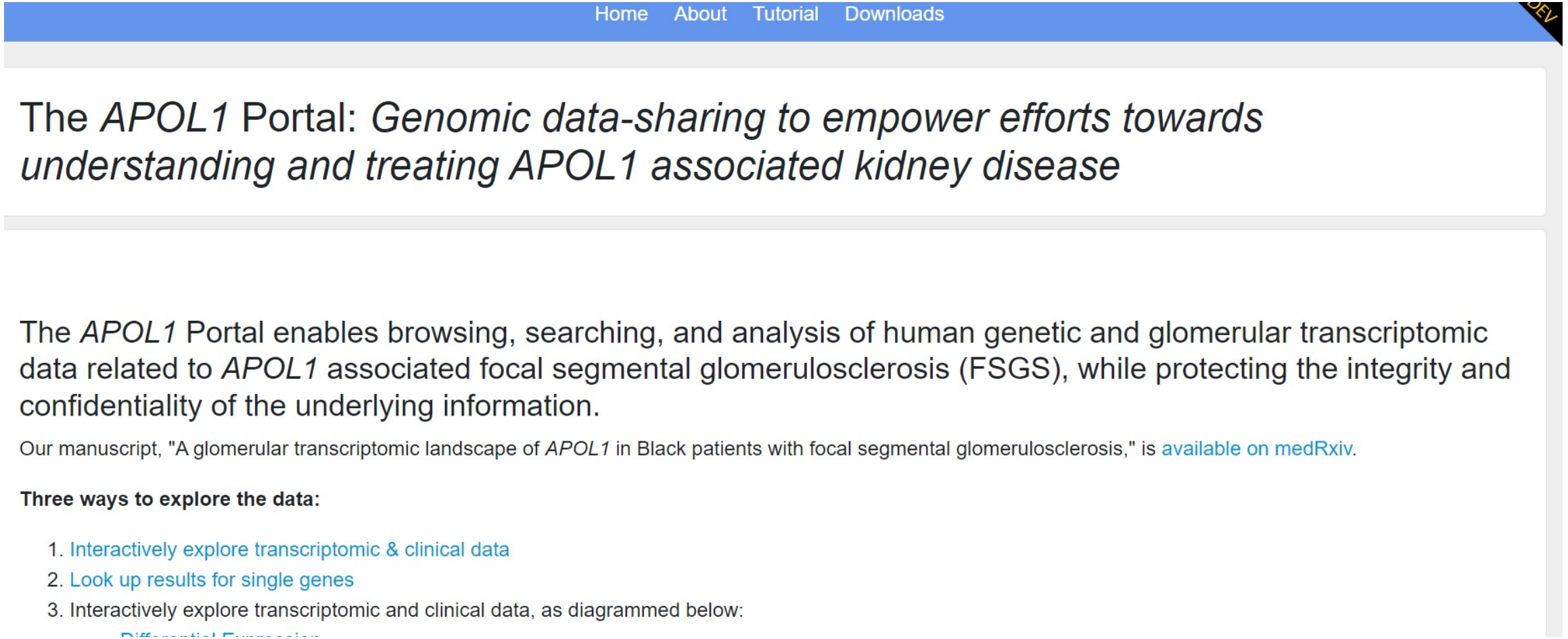
Islet cis-eQTLs	Other relvant cis-eQTLs	Islet chromatin conformation	Allelic imbalance	Glucose regulation	Other regulatory evidence
				1	

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



Differential Expression

View data | Method and supporting data

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

Functional Enrichment Analysis with DAVID

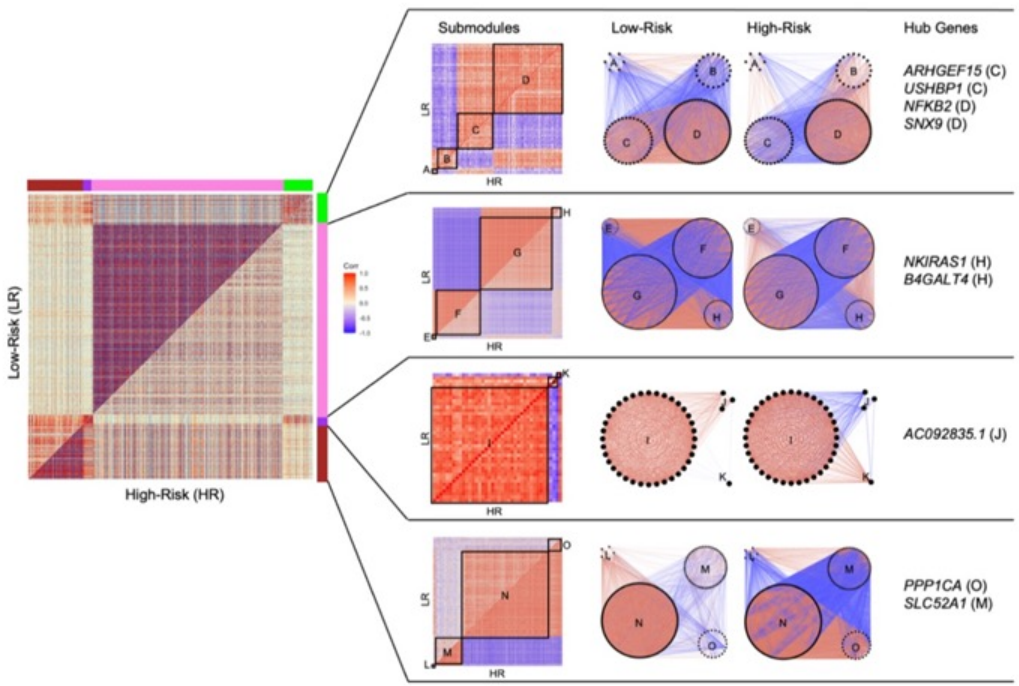
Differential Co-expression

View data | Method and supporting data

supporting data

dule

Gene Set Enrichment Analysis



Only annotations with enrichment scores > 1 are included. Submodules A, J, K, and L do

Show all feature rows | Hide feature headers | Hide top level rows

Rows per page:

3.13

Evidence

Pop Hits	Pop Total	Fold	Bonferroni	Benjamini	FDR
4480	15209	1.4	0.02	0.01	0.01
2010	15209	1.67	0.04	0.01	0.01

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

HuGeAMP
HUMAN GENETICS AMPLIFIER

KPN

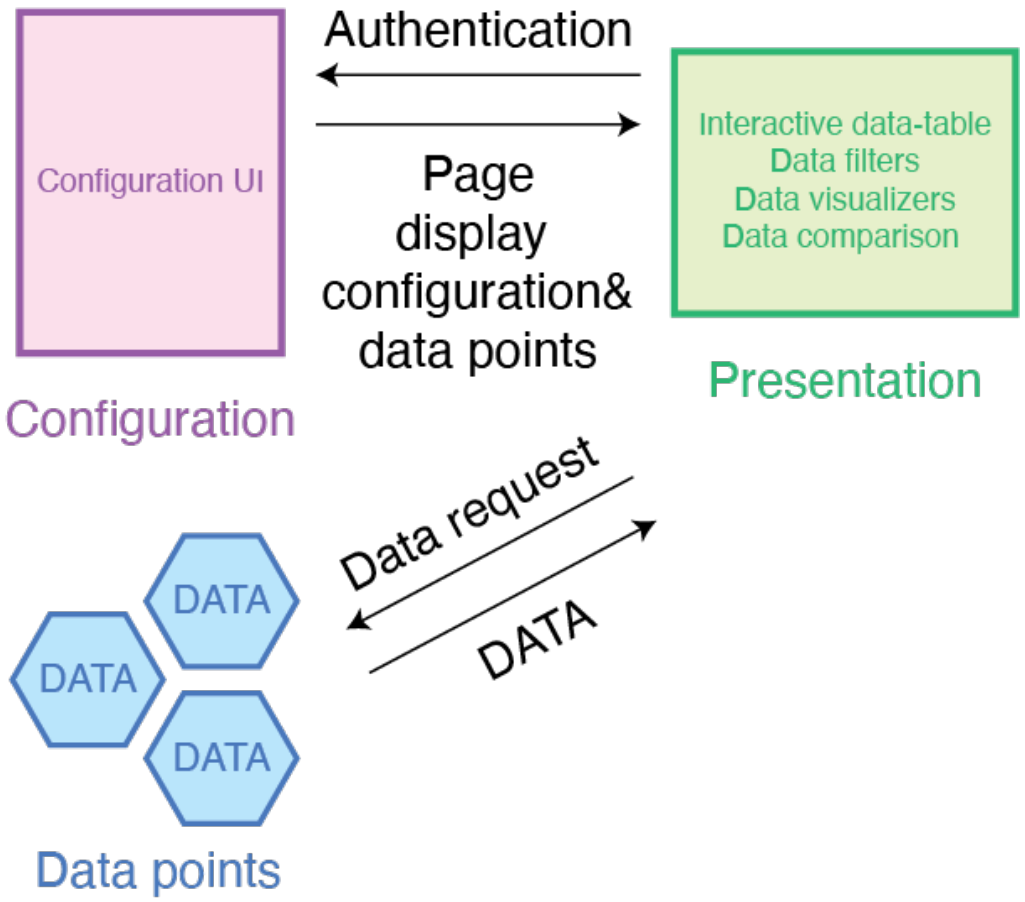
Bring Your Own Results (BYOR) Portal Service

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

HuGeAMP
HUMAN GENETICS AMPLIFIER

KPN

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

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